

ABSTRACTS

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Stem cell mobilisation and Graft engineering

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Abstract Content

Transplantation with 2-5 *106 mobilizedCD34+ cells/kg body weight lowers transplantation costs and mortality. To maximize HSC harvest in poor mobilizers the clinician needs to optimize current mobilization protocols, These include when to mobilize in relation to chemotherapy, how to schedule and perform apheresis, how to identify poor mobilizers, and what are the criteria for preemptive and immediate salvage use of plerixafor.

Material (or patients) and methods: 12 patients with different hematologic malignancy consist of NHL 4, MM 5, AML 1, HD 2 in common mobilization protocol (cyclophosphamide ,Erythropoietin ,GCSF) treated in our new center in west of Iran.WIth optima machine for separation ,our protocol consist cyclophosphamide 3 gr/m2, erythropoietin 4000 unit three /week with 5 days of GCSF twice daily.

Results: Engraftment was done before 10 days of stem cell infusion without significant grade 3-4 side effect. In all cases witht one stem cell collection ,we can accepted to more than 5*106 CD 34 stem cell. Most side effect be catheter infection and UTI .in one HD case grade 4 pneumonia that resolved with broad coverage antibiotic.

Conclusion: Despite of new effective druge like plerixafor in mobilization protocol always also old drugs with combination with growth factor can been effective in malignant hematologic disorders ,specially in low economic country with decreased the cost of transplant.

Keywords: Mobilization, engraftment



Next-generation sequencing-based characterization of the invasion by anatomical contiguity in a primary osseous diffuse large B-cell lymphoma. Correlation between the genetic profile of the malignancy and the clinical outcome of the patient

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Abstract Content

Introduction.

Primary bone lymphoma is now a well-known entity, described in the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone as a malignancy of the lymphoid tissue with at least one mass within bone, without involvement of supraregional lymph nodes or other extranodal sites. In the current paper, we describe the complete characterization of the mutational landscape of a diffuse large B cell non-Hodgkin's lymphoma (DLBLCL) of the tibial plateau.

Methods.

Currently, there is very little data about the genetic landscape of primary osseous lymphomas and about the genetic background of this type of malignancy while it becomes resistant to chemotherapy and invades the surrounding tissues. In the current paper, we and describe the complete characterization of the mutational landscape of a DLBCL of the tibial plateau.

Results.

Our data is consistent with already published data, that have shown that MKI67 activation is correlated with lymphoma progression. Along with a high Ki67 index, resistance to chemotherapy occurs with neurogenic locus notch homolog protein 1 (Notch) and KRAS activation.

Conclusion.

This is the first molecular characterization for the invasion by anatomical contiguity for a primary bone lymphoma and while we only characterized one case and further deep sequencing analyses are required, we can explain the clinical dismal evolution of the patient by correlating them with the genetic landscape of this type of lymphoma.





DELETION 7q31 MYELODYSPLASTIC SYNDROME EVOLVING AFTER A PREVIOUSLY DIAGNOSED SECONDARY PURE RED CELL APLASIA: A CASE REPORT

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Abstract Content

ABSTRACT

Introduction

The blood and bone marrow represent an intricate biological blackbox where diagnosis of anemia remains to be the hematologists' most overwhelming challenge to identify the source of pathology.

Pure red cell aplasia (PRCA) is relatively characterized by anemia, reticulocytopenia and evidence of erythroid hypoplasia of bone marrow. It is associated with a continuum of both diverse clinical syndromes such as thymoma, and, an underlying pathogenetic heterogeneity. Conversely, myelodysplastic syndrome (MDS) is a group of clonal myeloid disorders defined by dysplastic changes in hematopoietic precursors and abnormal cellular proliferation and maturation.

The association of PRCA and MDS has not been clearly elucidated; moreover, the condition evolving into the latter has remained a conundrum. The paucity of satisfactory clinical literatures and epidemiologic data has put interest in the review of this case.

Case Report

A 59-year-old male patient with previous history of transfusion-dependent anemia was referred for an evaluation of newly developed anemia. Five years prior, he was diagnosed with PRCA by laboratory findings of isolated anemia, reticulocytopenia and marked erythroid hypoplasia on bone marrow examinations. Cytogenetic studies showed a normal 46XY chromosome. Consequently, he underwent thymectomy after a thymoma was seen on screening CT. Slight hematologic improvement was noted thereafter but it was non-sustained. Cyclosporine was initiated which rendered protracted clinical and laboratory outcomes.

After years of remission from PRCA, severe anemia reappeared. Subsequent peripheral blood and trephine marrow examinations now revealed marked cellular dyspoiesis consistent with MDS-multilineage dysplasia. Deletion of chromosome 7q31 was also detected on fluorescence in-situ hybridization. Based on the Revised International Prognostic Scoring System (R-IPSS), a poor prognostic risk score was obtained which warranted subsequent chemotherapy with Decitabine.

Conclusion

We report a case of complex hematologic disorder with multi-step pathogeneses which post a formidable diagnostic and therapeutic challenge. The presence of clonal and inherent stem cell abnormalities, autoimmune etiologies and drug-induced mechanisms were proposed as plausible etiologies in the evolution of PRCA to MDS. Hence, in such rare instances, we highly recommend further analyses to resolve these dilemmas, and which may be utilized for future reference.

Keywords: pure red cell aplasia; myelodysplastic syndrome; thymoma; erythroid hypoplasia; dyspoiesis





Wnt/β-catenin Signaling Pathway Regulates Neural Differentiation of Mouse Induced Pluripotent Stem Cells in Vitro

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Abstract Content

Background: Increasing studies have demonstrated that induced pluripotent stem (iPS) cells have the capacity to differentiated into neural stem cells (NSCs), which are regarded as a more desirable cell resource for cell-therapy in degenerative diseases. However, the low differentiation efficiency of iPS cells' neural differentiation which hampers the cells' potential biomedical applications still need to be solve. Wnt/ β -catenin signaling pathway is crucial in regulating embryonic development, cell proliferation and cell fate determination. Here, we aimed to find the role of Wnt/ β -catenin signaling pathway in mouse iPS cells' neural differentiation in vitro.

Methods: The reprogrammed cells obtained by four factors method were identified their biological characteristics by AP staining, qRT-PCR, immunocytochemistry and EB forming experiments after . Then, iPS cells were induced into NSCs in vitro step by step. The changes of cell morphology were observed microscopically, and the expression levels of Nestin and β III Tubulin were detected by qRT-PCR and immunocytochemistry analysis. Western blotting was used to examine the the expression level of β -catenin, Nestin, β III Tubulin and Oct3/4 during neural differentiation. In order to determine the role of Wnt/ β -catenin signaling pathway in neural differentiation, exogenous recombinant protein Wnt3a and DKK-1, as well as small molecule inhibitors IWR-1 and CHIR99021 were added to regulate this signaling pathway, and the expression level of β -catenin, Nestin in the process of neural differentiation were measured by Western blotting as well. Meanwhile, the proliferation ability of NSCs derived from mouse iPS cells (iPS-NSCs) after regulating Wnt/ β -catenin signaling pathway during neural differentiation was evaluated using suspension culture method finally.

Results: The cells expressed AP and pluripotency factors, also maintained pluripotency and could differentiate into ectoderm (β III Tubulin), mesoderm (Smooth Muscle Actin, SMA) and endoderm (α -Fetoprotein) cells in vitro, which indicated that these cells was indeed mouse iPS cells. During neural differentiation, iPS cells shown the big changes of cell morphology and iPS-NSCs expressed both Nestin and β III Tubulin after neural induction. The expression of Nestin and β III Tubulin both increased in a time-dependent manner, and the pluripotency factor Oct3/4 decreased (P<0.05). Meantime, the expression of β -catenin decreased time dependently (P<0.01), demonstrating that Wnt/ β -catenin signaling pathway was inhibited during neural differentiation. After adding some regulators of Wnt/ β -catenin signaling pathway during neural differentiation, it also found this signaling pathway played a negative regulation role in neural differentiation. The proliferation ability of iPS-NSCs were down-regulated by the signaling pathway as well, which may account for its negative regulation on neural differentiation.

Conclusion: These data implicate that we could enhance the differentiation efficiency of mouse iPS cells by regulating Wnt/ β -catenin signaling pathway, and the researches of neural differentiation of the cells can provide a hopeful platform for regenerative medicine and so on.

Disclosures: No relevant conflicts of interest to declare.

Footnotes: Corresponding author: Qin Yu.

This work was financially supported by National Natural Science Foundation of China (No. 31570994).

Keywords: induced pluripotent stem cells; neural differentiation; neural stem cells; Wnt/β -catenin signaling pathway





Induction of hematopoietic cells from human embryonic stem cells using self-assembling peptide hydrogel

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Abstract Content

Introduction: Hematopoietic stem cells (HSCs) have been utilized to treat various hematological diseases. Embryonic stem cells (ESCs) are a potential source of HSCs. However, functional HSCs are difficult to obtain from ESCs using approaches being used. Here we address the effects of self-assembling peptide hydrogel on regulation the hematopoietic specification of human ESCs.

Methods: Hydrogel and cellular morphology were detected by scanning electron microscope. The expression of surface markers were evaluated by flow cytometry. Immunofluorescence staining was used to detect the CD34 expression. The expression of pluripotent genes, mesodermal genes and hematopoietic genes were assessed by quantitative real-time PCR. NOG mice were used to assess the engraftment potential of differentiated cells.

Results: Self-assembling peptide hydrogel was composed of nanofibers, the pore diameter of which ranged from 50 to 200 nm (Figure 1A). The hydrogel formed a three-dimensional (3D) scaffold for cell culture. Cell aggregates became progressively larger during differentiation, and many round cells appeared around the cell aggregate after differentiating 6 to 8 days. A number of CD34+ cells could be produced in 3D culture system. Compared to embryoid body (EB) culture system, ESCs in 3D culture system differentiated more potently. The expression of pluripotent genes were decreased more quickly. However, the expression of mesodermal genes and hematopoietic genes, such as GATA2 and HOXB4, were higher in 3D culture system (Figure 1B). In addition, the expression of KDR, CD31, CD144, CD34 and CD45 were also higher in 3D culture system. The engraftment was not obtained in differentiated cells from EB culture system. However, when the differentiated cells from 3D culture system were injected into the NOG mice, myeloid cells, B cells and T cells could be detected in peripheral blood three weeks after transplantation (Figure 1C).

Conclusion: 3D hydrogel culture system facilitates hematopoietic specification of ESCs, and the differentiated cells possess the short-term engraftment potential.

Keywords: Hydrogel; Nanofiber; Embryonic stem cells; Hematopoietic specification; Engraftment





PTPN21, a member of the protein tyrosine phosphatase family, participates in determining the fate of Human Bone Marrow-DerivedMesenchymal Stem Cells

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Abstract Content

Introduction:

Bone marrow-derived mesenchymal stem cells (BMSCs), as a crucial component of the bone marrow microenvironment, support the hematopoiesis of the bone marrow. Alterations in the characters of BMSCs, such as differentiation bias, are involved in many malignant hematological diseases.Previous studies have illustrated that protein tyrosine phosphatases (PTPs) act as key regulators in various cellular processes of stem cells including proliferation, differentiation etc. PTPN21, as a member of PTPs, however, the role in BMSCs remains unclear. The aim of this study is to clarify how PTPN21 regulate BMSCs and its potential mechanism.

Methods:

Lentiviral transfection was used to regulate the expression level of PTPN21 in BMSCs. Transwell migration assays, CCK8 kit and Annexin V/7AAD Apoptosis Kit were respectively used to assess the migration, proliferation and apoptosis of BMSCs. Senescence of BMSCs was assessed by Senescence β -Galactosidase Staining Kit. Senescence and differentiation associated markers were detected by real time PCR. The calcium and lipid accumulation were determined by alizarin red and oil red O staining. Western blot was used for evaluating the expression of STAT3 and pSTAT3.

Results:

There was no significant correlation between PTPN21 gene expression and senescence, motivation, apoptosis of BMSCs. PTPN21 overexpression would significantly inhibit the proliferation of BMSCs while the opposite result was observed when PTPN21 was knocked downby shRNA. PTPN21 overexpression can inhibit the expression of osteogenic makers and calcium accumulation but can enhance the expression of adipogenic markers and lipid accumulation during the differentiation of BMSCs. PTPN21 overexpression enhances the activation level of STAT3 thereby regulating differentiation.

Conclusions:

Senescence, motivation and apoptosis of BMSCs exist no difference between three groups.PTPN21 overexpression significantly affect the proliferation and differentiation balance of BMSCs which is related to STAT3 pathway. This phenomenon indicated that the PTPN21 may play as a negative regulators of haematopoietic microenvironment.

Figure 1. PTPN21 expression has no significant effect on the senescence, motivation and apoptosis of BMSCs. (a-b) β -galactosidase staining was used to visualize the senescence degree of BMSCs. (c) Detection of aging related genes p16, p21, p53 mRNA expression in BMSCs. (d-e) Cell migration assay of BMSCs using transwell chambers and DAPI staining. (f-g) Detection apoptosis rate in BMSCs.

Figure 2.PTPN21 significantly affect the proliferation and differentiation of BMSCs. (a) CCK8 assay reflected the proliferation of BMSCs. (b) Alizarin red staining was used to observe the mineralized nodes of BMSCs. (c) Detection of osteogenic related genes RUNX2, IBSP mRNA expression in BMSCs. (d) Oil red O staining was used to observe the lipid droplets in BMSCs. (e) Detection of adipogenic related genes FABP4, PPARγ mRNA expression in BMSCs. (f) Expression of STAT3 and pSTAT3 was confirmed by Western blot.



Keywords: PTPN21; Bone Marrow-Derived Mesenchymal Stem Cells; Differentiation

-Balans



Glia Maturation Factor-γ Regulates hematopoietictic stem cell development

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Abstract Content

Background and Aim:Hematopoietic stem cells (HSCs) emerge from aortic endothelium via a process known as the endothelial-to-hematopoietic transition during which hematopoietic endothelium(HE) bend, round up to transform to HSCs,then release from the aorta ventral wall and migrated to successive hematopoietic organs.Glia maturation factor γ (GMFG) functions to reorganize the actin cytoskeleton and has been implicated in mediating cell migration and adherence. Our previous secondary analysis of public mouse embryonic single cell RNA-seq data discovered that compared with endothelial cells,GMFG expression was much higher in HE and HSC,implying it a probable role in HSC development.

Methods: We injected GMFG antisense morpholinos (MOs) into zebrafish embryos at 1-2 cell stage or constructed a *GMFG* mutant embryo by CRISPR-Cas9 genome editing technique to knock down or knock out GMFG, respectively. Probes for the runx1, cmyb, gata1a,mpx, kdrl, and rag1 transcripts were generated and then were utilized for Whole-Mount RNA In Situ Hybridization(WISH). Fluorescence microscopy was performed on cmyb:eGFP, lck:GFP and fli1a:GFP transgenic animals.

Results: The number of HSCs in or near the floor of the dorsal aorta (DA) was significantly reduced in GMFGdeficient embryos at 26 hr post fertilization (26hpf) , 29hpf(Fig.1a) and 36hpf by WISH for the nascent HSC marker runx1 when compared with their standard MO(Std MO)siblings. This result was further supported when we visualized HSCs along the axial vessels by expression of cmyb at 36hpf. Moreover, GMFG morphants had sustained reductions of cmyb:GFP+HSCs colonizing the caudal hematopoietic tissue (CHT) at 75 -77hpf(Fig.1b) in the Tg(cmyb:eGFP) line, as determined by fluorescence microscopy.we also found that MO knockdown of GMFG impaired subsequent maintenance of HSC fate by monitoring the expression of rag1 and lck,two genes expressed in developing thymocytes.Besides,vascular development were unaffected in GMFG-depleted embryos when assayed by WISH for kdrl or using transgenic fli1a:eGFP animals, indicating GMFG regulate HSC development independently of its role in developing vasculature. In terms of primitive hematopoiesis, pimitive erythropoiesis appears to be unaffected but primitive neutrophils were significantly decreased in GMFG-deficient embryos.

Conclusion: Our results demonstrate an unexpected significant role of GMFG in regulating the generation of HSCs in the early embryo.Despite the precise mechanism underlying GMFG-mediated HSC development awaits further study, our experiments provide novel insights into a brand new signaling that may be needed to derive HSCs from ESCs or pluripotent cells.

Keywords: Hematopoietictic stem cell Zebrafish GMFG





IL-21 Treatment of in vitro Expanded Natural Killer Cell Enhances Its Cytotoxicity Effects against Neuroblastoma Tumor

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Abstract Content

Background: Neuroblastoma (NB) is the most common child's extracranial tumor that arises from developing sympathetic nervous system. First, tumors localize in the abdomen, and in infants under a year of age there is a higher incidence of tumors in the thoracic region. Immune cell therapy has emerged as a novel tool to treat high-risk neuroblastoma in addition to surgery, radio- and chemotherapies. Among these immunotherapies infusion of natural killer (NK) cells is an emerging therapy for NB tumors. Development of the clinically applicable methods to produce fully functional NK cells is a critical step to develop the potential of this therapy. Hence, we tested the IL-21 activation of NK cells cytotoxicity against neuroblastoma tumor.

Methods: Mononuclear cells (MNC) from donor's blood were separated on a FicoII paque and washed twice in PBS. Purified unstimulated NKs were obtained by CD56 enrichment of MNCs using the MACS system (Miltenyi Biotec). Purified NKs were incubated with 10 IU/mL human IL-2 with/without 10-20 IU/mL human IL-21 in RPMI 1640 supplemented with 10% FBS. The expanded and activated NKs were tested on NB tumor bearing nude mice.

Results: NK cell recovery increased to 200-fold after 14 days and 1000-fold after 21 days of culture. IL-21 didn't affect the expansion rate of NK cells significantly but icreased secretion of TNF- α and IFNY. Median percentage of CD56⁺ cells was 60% on day 7, 90.0% on day 14, and 97% on day 21. The IL-21 treated NK cells were significantly more cytotoxic than their untreated counterparts. The 90-day survival in mice models that were treated with IL-21 cytokines was 71%. In contrast, the survival rate for untreated group was zero (*P<0.05).

Conclusion IL-21 treatment of NKs could induce more cytotoxicity against neuroblastoma tumor *in vivo* without any significant effect on their proliferation. It has a dramatic effect on activation of NKs against neuroblastoma in the preclinical model and could be translated in human clinical trials for pediatric patients suffering from relapse of high-risk neuroblastoma after HSCT, in the near future.

Keywords: Immune cell therapy, Interleukin 21, Neuroblastoma, NK cell



3D culture system mediated by self assembled polypeptide biomaterials enhanced the amplification of mouse hematopoietic stem cell and progenitor cell compared with 2D culture system

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Abstract Content

Objective: To explore that the 3D induction system mediated by the self assembling peptide biomaterial will do help to provide a good platform for in vitro research of the HSC generation from PSC, we further evaluated that whether the 3D induced system is effective for the expansion of murine fetal liver or bone marrow derived hematopoietic stem cell and progenitor cell compared with 2D culture system or not.

laying the foundation for researching the mechanisms of the generation of HSC from PSC via 3D inducement system.

Methods:To expand the ckit+ cells derived from bone marrow using 3D self assembling peptide hydrogel biomaterials combined with hematopoietic cytokines and small molecular compounds. Comparing the expansion efficiency within 2D environment under the same condition. Observating the growth condition of ckit+ cells under light microscope. Flow cytometry analysis was used to compare the ratio of Lineage-Sca-1+ckit+(LSK) cells under two different conditions and evaluate the hematopoietic lineage cells in 3D and 2D culture system. CFU assay was used to compare the difference of clone formation ability under two different expansion conditions.

Results: Comparing with 2D same culture conditions, 3D self assembling peptide hydrogel combined with cytokines and small molecular compounds can better amplify the ckit+ cells and maintain hematopoietic stem cell and progenitor cell. In 3D culture system LSK cells owned the higher ratio compared with 2D under the same condition. CFU assay showed that the total number of CFU in 3D condition is higher than 2D culture system with significantly differences.

Conclusion: 3D culture systemmediated by self assembling peptide biomaterial is more conducive to the maintenance of bone marrow derived hematopoietic stem cell and progenitor cell compared with 2D culture system. Meanwhile, 3D culture system is used to the growth of hematopoietic downstream lineage cells. Comparing with 2D, 3D system can better simulate the nich of HSC to provide a theoretical basis for exploring the HSC differentiation from PSC.

Keywords: 3D self assembled peptide hydrogel, mouse hematopoietic stem cell, 2D





Scarless correction of Wiskott Aldrich Syndrome patient-specific iPSCs using CRISPR/Cas9 and *piggyBac*

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Abstract Content

Wiskott–Aldrich Syndrome, one of the most severe immunodeficiency diseases, is caused by mutations in the WAS gene. Generation of integration-free patient-specific induced pluripotent stem cells (iPSCs) provide a safe approach to cure this disorder. Gene editing using CRISPR/Cas9 technology together with the *piggyBac* transposon system enables scar-less correction of the mutant gene as well as the restoration of cell function. In this study, we corrected the mutation in an integration-free WAS patient-specific iPS (WAS-iPS) without leaving any exogenous sequences in genome DNA. The corrected WAS-iPSCs (cWAS-iPSCs) can be differentiated towards myeloid-monocytic and megakaryocytic lineages in vitro. When differentiated into monocytes, the gene corrected cells reconstituted the expression of WASp as well as the IgG-regulated phagocytosis function. The macrophages we generated from corrected cells also obtained the formation of podosomes. We also restored the function in gene corrected megakaryocytes and gained normal-sized platelets compared with the parental WAS-iPSCs. Our study provides a promising safe solution towards future clinical usage of patient-specific iPSC-based cell therapy.

Keywords: CRISPR/Cas9; piggyBac; Gene correction; WAS-iPSCs; Differentiation





Ex Vivo Expansion of CD34+CD90+CD49f+ Hematopoietic Stem & Progenitor Cells from Non-enriched Umbilical Cord Blood with Novel Azole Compounds

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Abstract Content

Introduction:

In order to expand hematopoietic stem and progenitor cells (HSPC) from human umbilical cord blood (UCB), specifically those expressing the primitive phenotype (CD34+CD90+CD49f+) from non-enriched mononucleated cells (MNC), we developed a proprietary library of 50 small molecules using structure-activity relationship studies of the parent p38 mitogen-activated protein kinase (MAPK) inhibitor SB203580. This compound was chosen since prior RNAi screening identified MAPK14 as a druggable suppressor for human HSPC expansion. Inhibition of p38 MAPK has also been shown to restore hematopoiesis in myelodysplastic syndrome.

Methods:

The parent compound SB203580 underwent structural activity relationship to generate 50 new structural analogues. The compounds were tested for their ability to expand HSPC from frozen-thawed, non-enriched UCB-MNC using a validated platform.

Results:

Screening data from expansion cultures lasting up to 11 days showed, one specific structural analog, C7 (structure shown in Fig 1), to support expansion of absolute HPC (CD45+CD34+CD38-CD45RA-) by at least 1500-fold when compared to culture initiating cells and this expansion was at least 3.7-fold higher than control cultures (Fig 1). Representative flow cytometer contour and dot plots showing the HSPC population (including CD90+CD49f+ populations) in non-cultured and C7 expanded grafts are shown in Fig 2. The cytokine cocktail necessary for C7 based expansion was stem cell factor, thrombopoietin and Fms-related tyrosine kinase 3 ligand. Comparison of C7 to other HSPC expanding molecules such as SR-1, UM171 and NAM showed that C7 gave optimal expansion when cultures were initiated with MNCs. Colony forming unit assays showed significant increase of granulocyte, erythrocyte, monocyte, megakaryocyte (GEMM) multipotent colonies from C7 treated cells compared to cytokine control. Transplantation of UCB-MNC expanded with C7 grafts (fresh or cryopreserved) via tail-vein injection to sub-lethally irradiated NOD SCID Gamma (NSG) mice resulted in 3.2- and 2.1-fold higher engraftment of human CD45+ cells in the PB by day 21 compared to non-expanded and cytokine expanded grafts respectively. The frequency of severe combined immunodeficiency (SCID) repopulating cells contributing to early PB engraftment was 2.48-fold higher in C7 expanded grafts compared to unmanipulated grafts. Analysis of NSG BM at week 2 post-transplant showed that C7 grafts resulted in higher engraftment of human CD34+ HSPC with a balanced proportion of myeloid and lymphoid cells that resulted in better survivability of the transplanted mice. Long-term (>4 months) multilineage hematopoiesis in NSG BM was observed for UCB-MNC expanded with C7 and these cells harvested from BM of primary recipients retained ability to repopulate secondary recipient mice. Expansion of purified CD34+ cells resulted in >280-fold expansion of absolute CD34+CD38- cells within 11-days which was equivalent to those reported in literature for SR-1 or NAM. Transplantation of these CD34-selected and C7 expanded grafts into NSG mice gave significantly better human hematopoiesis up to 7-months in primary recipient with multi-lineage reconstitution in PB and BM.



Conclusion:

C7 is the first proprietary small molecule that could expand UCB HSPC without the need to perform prior CD34/CD133 based stem cell enrichment. With CD34 selection this molecule was able to attain superior HSPC expansion.

Keywords: Haematopoietic Stem Cells; Cord Blood Transplantation; Ex Vivo Expansion





ENGRAFTMENT OF HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH CRYOPRESERVATION USING 5-PERCENT DIMETHYL SULFOXIDE AT -80°C WITH UNCONTROLLED-RATE FREEZING PROTOCOL

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Abstract Content

Background: Cryopreservation of hematopoietic stem cells with the rate-controlled method is considered standard method in the majority of canters with hematopoietic stem cell transplantation (HSCT) facility. In recent years, there has been a trend toward the simplification of the process.

Aim: To evaluate our experience in HSCT using simplified method in cryopreservation

Study design: Retrospective case series of HSCT in Dr. Kariadi Hospital from January 2016 – December 2017

Methods: A simplified method for cryopreservation was developed with 5-percent dimethyl sulfoxide (DMSO) as the sole cryoprotectant without rate-controlled freezing. With DMSO concentrations from 5-percent, the best recovery and viability for hematopoietic progenitor cells were observed. Hematopoietic stem cells with plasma and 5-percent DMSO were frozen -20° C for 1 hours then stored in a temperature -80° C using mechanical freezer. Engraftment was define if ANC $\geq 500/\mu$ L and platelet count $\geq 20 \times 10^{6}/\mu$ L were established in at least two consecutive examination. All data were analyzed using descriptive statistic.

Results: Thirteen adults patients with hematologic malignancies underwent transplantation with autologous and allogeneic hematopoietic stem cells. Indication for HSCT in our series as follows: acute myelocytic leukemia (n=5), non-hodgkin malignant lymphoma (n=4), multiple myeloma (n=3), and myelodysplasia syndrome (n=1). The median number of transfused mononuclear cells was 8.12 (3.14-14.22) x 10⁸/kg BW with CD34⁺ cells 3.33 (2.00-6.50) x 10⁶/kg BW. The mean times to reach an ANC of 500/µL and a platelet count of 20 x 10⁶/µL were 11.57±1.57 and 12.00±1.39 days, respectively. All patients showed rapid and sustained engraftment.

Conclusion: This simplified cryopreservation technique will be useful for institutions without rate-controlled freezing facilities. Rapid and sustained engraftment were able to be documented in all patients.

Keywords: Cryopreservation, uncontrolled-rate freezing, engraftment, hematopoietic stem cell transplantation

Keywords: Cryopreservation, uncontrolled-rate freezing, engraftment, hematopoietic stem cell transplantation







GVHD prophylaxis using Tacrolimus + Mini-MTX in umbilical cord blood transplantation

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Abstract Content

[Background]

Umbilical cord blood is a well-established alternative donor source for allogeneic hematopoietic stem cell transplantation. Calcineurin inhibitor and short-term methotrexate (MTX) is a standard GVHD prophylaxis but optimal dose of MTX for cord blood transplantation (CBT) remains to be determined.

[Methods]

We conducted a retrospective study to evaluate a combination of tacrolimus and reduced dose of MTX as a GVHD prophylaxis in CBT. We analyzed the clinical outcome of 58 patients with hematological malignancies who received standard-dose (St-MTX, 15 mg/m² of MTX on day 1 and 10 mg/m² on days 3 and 6) MTX or mini-dose short-term MTX (Mini-MTX, 5 mg/m² of MTX on days 1, 3 and 6) in CBT in our institution between 2004 and 2018.

[Results]

Thirty-two patients received St-MTX and 21 patients received Mini-MTX. Cumulative incidence of neutrophil engraftment was significantly higher in Mini-MTX group (St-MTX; 71.9 %, Mini-MTX; 85.7 %, P = 0.0269). Bloodstream infection prior to neutrophil engraftment was significantly increased in St-MTX group compared to Mini-MTX group (43.8 % vs 14.3 %, P = 0.0199). Cumulative incidence of grade II to IV and grade III to IV of acute graft-versus-host disease (GVHD) were 34.4 % and 6.2 % in St-MTX group, and 33.3 % and 9.5 % in Mini-MTX group with no statistical significance. Day 180 non-relapse mortality rate tended to be lower in Mini-MTX group compared to St-MTX group (25.0 % vs 4.8 %, P = 0.0567), whereas relapse rate was almost equivalent between these groups. Day 180 overall survival were 71.9 % in St-MYX group, and 85.7 % in Mini-MTX group (P = 0.312), and event-free survival were 62.5 % in St-MYX group, and 76.2 % in Mini-MTX group (P = 0.498).

[Conclusion]

Our study suggested that GVHD prophylaxis using reduced dose of short-term MTX is feasible and reduce transplant-related complication early after CBT.





High frequency of 0–1-antigen-mismatched donors among firstdegree relatives in Japan

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Abstract Content

Introduction

Hematopoietic stem cell transplantations (HCTs) from 1-antigen-mismatched, related donors (HLA-A, -B, and -DR loci) have shown favorable outcomes with acceptable risks of graft-versus-host disease (GVHD). These outcomes were further improved by low-dose anti-thymocyte globulin (ATG) as GVHD prophylaxis. Recently, HLA has been more frequently examined at the allele level, and transplantations from up to 2-allele-mismatched donors (HLA-A, -B, -C, and -DRB1 loci) are also expected to benefit from low-dose ATG. Although HCTs from multiple-antigen-mismatched donors show promising outcomes owing to the development of post-transplant cyclophosphamide, GVHD prophylaxis should be modified depending on the number of HLA mismatches. First-degree relatives can be good donor candidates, yet the availability of 0–1-antigen-mismatched and 0–2-allele-mismatched donors among first-degree relatives has rarely been discussed. Therefore, we calculated the frequencies of HLA-mismatched, related donors using a large dataset of HLA in Japanese families.

Methods

HLA data from 2,838 patients and their relatives were collected at HLA laboratory in Japan. The frequency of 0–1-antigen-mismatched donors in the graft-versus-host (GVH) direction at the HLA-A, -B, and -DR loci and that of 0–2-allele-mismatched donors at the HLA-A, -B, -C, and -DRB1 loci were calculated according to the numbers of potential donors and the homologous antigens of the recipient.

Results

The frequencies of 0-1-antigen-mismatched and 0-2-allele-mismatched donors among siblings were 33.9% and 32.1%, respectively, for one candidate and 49.8% and 49.4%, respectively, for two candidates. Meanwhile, these frequencies among parents were 20.2% (0-antigen-mismatch, 9%; 1-antigen-mismatch-MM, 15.3%) and 18.6% (0- allele-mismatched, 4.0%; 1- allele-mismatch, 4.2%; 2- allele-mismatches s 10.4%) for the mother or father, and 29.1% (0-antigen-mismatched, 7.4%; 1-Ag-MM, 21.7%) and 27.9% (0allele-mismatch, 4.9%; 1-allele-mismatch, 7.2%, 2-allele-mismatches, 15.8%) for both parents. These frequencies were remarkably high when the recipients possessed homozygous HLA loci. Also, HLA-C antigen-mismatched donors were found in 18.1% of 0/6 antigen-mismatched parents. The frequencies of 1/8 and multiple (\geq 2/8)-allele-mismatched donors among 0-antigen-mismatched sibling donors were 3.0% and 0.5%, respectively, whereas these frequencies were higher among parent donors (29.5 % and 14.4%, respectively). The frequency of 1-2/8-allele-mismatched donors was 40.9% (1-allele-mismatch, 21.5%, 2allele-mismatches, 19.5%) among 1-antigen-mismatched sibling donors and 58.5% (1-allele-mismatch, 25.3%, 2-allele-mismatches, 33.1%) among 1-antigen-mismatched parent donor. Among the 1-antigenmismatched parent donors, 73.8% had multiple ($\geq 2/8$)-allele-mismatches. Majority of these allele mismatched pairs possessed HLA-B allele-mismatch (82.9%) and 77.0% of these HLA-B allele mismatched pairs also possessed HLA-C allele-mismatch.

Conclusion

HLA 0–1-antigen-mismatched donors in the GVH direction at the HLA-A, -B, and -DR loci were found with a probability of over 20% for each candidate among first-degree relatives. HLA examination is strongly recommended for recipients' parents and children if they fail to find HLA-matched sibling donors. The HLA-C locus should also be examined, as HLA-C Ag/allele mismatches were frequently found in combination with mismatches at other loci, particularly at the HLA-B locus. Further, HLA alleles should be examined, because multiple-allele-mismatched donors are frequently observed among 0–1-antigen-mismatched donors.

Keywords: HLA, antigen-mismatch, allele-mismatch





Full-matched unrelated donor is considered an alternative choice rather than sibling donor for elderly patients undergoing allogeneic hematopoietic stem cell transplantation for acute leukemia and myelodysplastic syndrome

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Abstract Content

Abstract

Objectives

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are hematological diseases predominantly occurring in older patients. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the curative therapy for refractory AML or high-risk MDS, old age is often a hurdle to the procedure. Although the stem cells source from sibling donors are widely considered better than unrelated donors', it remains unclear for elderly patients because their sibling donors are also old. Aging may have negative impacts on qualities and quantities for stem cells, leading to poor outcomes for elderly patients. Therefore, we conducted a retrospective cohort study to investigate the outcomes for elderly patients with diagnosis of AML or MDS undergoing allo-HSCT, under full-matched unrelated donors, or sibling donors allo-HSCT

Materials and methods

We reviewed data of patients diagnosed with acute leukemia or MDS, who underwent allo-HSCT at age more than 50 years in Taiwan Bone Marrow Transplantation (TBMT) registry and collected the clinical characteristics including age, sex, underlying disease, disease status after transplantation, and presence of acute graft-versus-host disease (GVHD) or chronic GVHD. Full-matched unrelated donor indicated full-matched in HLA-A, HLA-B, HLA-DR, and HLA-C. The outcomes are measured by overall survival (OS), and graft-versus-host disease-free, relapse-free survival (GRFS) after allo-HSCT. The survival analyses according to sibling donors or full-matched unrelated donors are demonstrated by Kaplan-Meier and log-rank method.

Results

A total of 161 elderly patients were included, with the median age at allo-HSCT being 56 years. 101 patients received sibling donors, and approximately 80% of patients undergoing allo-HSCT for AML. Moderate to severe chronic GVHD is more common for patients receiving sibling donors than those with full-matched unrelated donors (24% vs. 11%; P=0.065). Basic information is demonstrated on table 1. For survival analyses, OS is similar for patients receiving sibling donors and full-matched unrelated donors (log-rank P=0.68), while patients receiving full-matched unrelated donors transplantation have better outcomes in GRFS than those with sibling donors (long-rank P=0.05). OS and GRFS curves are plotted in figure 1 and figure 2.

Conclusion

This cohort study suggests the stem cell source from full-matched unrelated donors is considered to be an alternatively choice for elderly patients undergoing allo-HSCT for AML and MDS. Elderly patients experiencing full-matched unrelated donor allo-HSCT would have similar OS as compared to those with sibling donors, and may enjoy better GRFS, probably benefit from less moderated to severe chronic GVHD. Further prospective study is indicated to investigate this important issue.



 Table 1 Characteristics comparison for elderly leukemia and myelodysplastic syndrome receiving

 sibling or full matched unrelated donor in allogeneic hematopoietic transplantations (n=161)

-			
Elderly patient under			
Sibling donor	Full matched unrelated donor	P-value	
(n=101,%)	(N=60,%)		
56 [IQR: 52-60]	58 [IQR: 54-61]	0.124	
49 (48)	37 (61)	0.141	
79 (78)	49 (81)	0.689	
19(18)	6 (10)	0.178	
25 (24)	7 (11)	0.065	
32 (31)	18 (30)	0.862	
	Elderly patient underg Sibling donor (n=101,%) 56 [IQR: 52-60] 49 (48) 79 (78) 19(18) 25 (24) 32 (31)	Elderly patient undergoing allo-HSCT Sibling donor Full matched unrelated donor (n=101,%) (N=60,%) 56 [IQR: 52-60] 58 [IQR: 54-61] 49 (48) 37 (61) 79 (78) 49 (81) 19(18) 6 (10) 25 (24) 7 (11) 32 (31) 18 (30)	

Keywords: acute leukemia, myelodysplastic syndrome, older patient, allogeneic hematopoietic stem cell transplantation, survival





A single center experience of Haploidentical Haematopoietic Stem Cell Transplant (HSCT) in Hong Kong

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Abstract Content

Introduction

The QMH Adult HSCT unit is the only transplant unit performing allogeneic HSCT for patients >=18 years in Hong Kong serving a population over 7.4 million. In 2017, we received 116 unrelated HSCT referrals. During the same period, we performed 37 unrelated HSCT, of which 15(41%) were mismatched (<7/8) grafts. Donor availability remains a major challenge to the success of allo-HSCT, especially in non-Caucasian population. In 2016, haploidentical transplants have overtaken cord blood transplants in both US (CIBMTR 2017 summary) and in the EBMT registry (Passweg, 2018). Our center performed our first haplo-HSCT on 27/1/15. Here we retrospectively reviewed our first 14 HLA-haploidentical transplants.

Methods:

All patients received T-cell replete unmanipulated grafts. Patient undergoing 2nd transplants or with significant comorbidities received non-myeloablaive (NMA) conditioning with PTCY-based Flu-Cy-TBI as per John Hopkins University protocol. All other patients received myeloablative conditioning (MAC) with either the ATG-based modified BuCy as per Beijing protocol, or PTCY-based Flu(150)-TBI(12Gy) for lymphoid and Flu(125)-Bu(12.8) for myeloid malignancies. Cyclosporin was the CNI used in all cases. After we lost our first case to primary graft failure, all subsequent patients were screened for donor specific antibody pre-transplant.

Results:

From December 2014 to July 2018, we have performed 14 haploidentical transplants in 13 patients (M:F = 7:6). The median age at transplant was 32 years (range 20-62). One patient had a second haplo-HSCT from his mother, due to relapse five months after his first haplo-HSCT from his father. Three patients were still early post-transplant in their pre-engraftment period.

Nine patients had acute lymphoblastic leukaemia (B-lineage n=6 including Ph+ B-ALL n=3, T-lineage n=3), two AML, one MDS-EB1 and one CML with T315I mutation. Ten patients were in advanced stage disease >CR1 or in CML-AP at time of their haplo-HSCT. Four had prior transplants. Two had received chimeric antigen receptor T-lymphocytes (CART) for salvage as bridge to their transplants.

All but the first patient received PBSC only grafts. Median infused PBSC CD34 was 5.81x10[^]6/kg. Seven donors were HLA-mismatched siblings, four fathers, two mothers, one son. Nine transplants were performed using MAC conditioning ATG-based (n=4) and PTCY based (n=5), five using NMA conditioning.

Excluding the three patients in their pre-engraftment phase, the median follow-up among surviving patients was 234 days (range 57 to 859). Median time to neutrophil recovery was 18 days (range 14-23). There was



one primary graft failure. One patient suffered stage II aGVHD skin, and one patient suffered stage III aGVHD of gut. No patients suffered extensive cGVHD. At the time of analysis, 3 patients had died. Cause of death primary graft failure (n=1), relapse (n=1), and PTLD followed by AML relapse (n=1). The 100 days probability of OS and PFS were 74% and 64% respectively.

Conclusion

Our preliminary experience with haplo-HSCT is encouraging with good tolerability and disease control even in the advanced stage heavily pre-treated patients. We need longer follow-up to verify this observation. Haplo-HSCT will hopefully allow our near 60% patients who lack standard donors to benefit from earlier and more timely allo-HSCT in future.

Keywords: Haploidentical transplant, Hong Kong





Total nucleated cell dose less than 2x107/kg in CBT predicts slower engraftment but comparable incidence of neutrophil recovery to those who received ≥2x107/kg

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Abstract Content

[Introduction]

Total nucleated cell count (TNC) of donor cord blood per patient's body weight has been reported to have a significant impact on the incidence of neutrophil recovery after CBT. Engraftment ratio after CBT has improved in recent years due to recognition of negative impact of DSA or of hemophagocytosis on engraftment. We aimed to investigate the impact of TNC dose less than 2 x 10⁷/kg in recent years

[Materials and methods]

From Jan. 2010 to Dec. 2015, 565 had received CBT. 22 CB recipients who had received grafts with less than 2 x 10^7 /kg TNC were selected from institutional data base of allo-HSCT, and were subjected to the following analysis.

[Results]

Median age was 54 (range, 18-70) years, 21 were male, and median body weight was 69.6 (range, 45.7-95) kg. AML (n=8), ALL (n=5), CML/MDS/ML (n=2 each), and ATLL/CMML/SAA (n=1 each) were included. 16 of them were in non-remission status. 14 received myeloablative conditionings, and 15 received tacrolimus + MMF as GVHD prophylaxis. Median TNC was 1.91 (range, 1.57-1.91) x 10^7 /kg, and median CD34⁺ cells were 0.8 (range, 0.39-1.41) x 10^5 /kg. 17 received CB unit with 2-antigen mismatches and 16 had sexmismatch. 20 achieved neutrophil recovery (>500/µL) at the median of 23 days (range, 12-43), and the cumulative incidence was 90.9% at day 45 post-transplant. 2 who failed engraftment died early after transplant from brain hemorrhage on day 6 and from alveolar hemorrhage on day 25, respectively. No rejection of donor cells was observed in this cohort. With the median observation time of survivors as 1181.5 (range, 190-3136) days post-transplant, cumulative incidences of acute GVHD (grade II and greater) and chronic GVHD in 3 years post-transplant were 50% and 40.9%, respectively. Cumulative incidences of relapse and NRM were 14.1% and 50.5%. The overall survival at 3 years post-transplant was 35 (95% CI 16.1-64.7) %.

[Conclusion]

This study demonstrated that CB unit of low TNC (<2 x $10^7/kg$) can provide comparable rate of engraftment to those with TNC $\ge 2 \times 10^7/kg$, although there was slight delay in the day of neutrophil recovery from transplant. Low cell dose of selected unit should not be the sole reason for not performing CBT.

Keywords: cord blood transplantation; engraftment; low total nucleated cell dose





Haplo-identical transplants using post transplant cyclophosphamide (PTCy) are associated with good outcomes if transplanted with early disease – a single centre analysis from India

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Abstract Content

Introduction: Haploidentical transplants are increasingly being used in patients who need a transplant but do not have a matched sibling or unrelated donor. The easy availability of a family donor makes it very attractive but it is associated with its own specific complications. We present the outcomes of haplo-identical transplants from a single centre in India

Patients and methods: We reviewed the outcomes of all patients who underwent Haplo-identical transplant at the Christian Medical College, Vellore, India between 2010 to 2017 using post transplant Cyclophosphamide (PTCY) as graft versus host disease (GVHD) prophylaxis. Data was collected from individual medical records and databases available in the department. The disease status of all patients was classified into early, intermediate and advanced disease based on a modification of the CIBMTR criteria for malignant disease. Early disease included patients transplanted in CR1 for malignant disease, patients with aplastic anemia (AA) with <20 transfusions, no active infection or exposure to immunosuppressive therapy while Intermediate disease consisted of transplant in CR2 for haematological malignancies, AA failure post ATG or > 20 transfusions and primary immunodeficiency syndromes (PID) who have had previous infection. Patients who were transplanted >CR2 or refractory disease, second transplants or presence of active infection were classified as Advanced disease.

Results: Between 2010 and 2017, 149 patients underwent 158 haplo-identical transplants. This included 101 males and 48 females with a median age of 18.1 years (range: 0.9 - 58). Seventy patients (46.9%) were children (< 15 years of age). Patients underwent transplants for both malignant (n = 85) and non-malignant (n = 73) indications. Disease status was classified as Early in 20, Intermediate in 84 and Advanced in 54. Conditioning included both myeloablative (n = 90) and non-myeloablative conditioning (n = 68) and graft source was predominantly peripheral blood stem cells (PBSC in 93%). Engraftment was seen in 90.9% while graft failure occurred in 8% and death prior to engraftment occurred in 2%. Acute GVHD was seen in 32% of evaluable patients. Infections were a major problem with bacteraemia seen in 41% (majority were gram negative) and viral infections in 68% (CMV and BK virus). The 1 year OS for the entire cohort is 44.1 ± 4.1% while the 2 year OS is 39.2 ± 2.1%. The 1 and 2 yr OS for early disease was 71.8 ± 1.1 and 63.8 ± 1.2% respectively compared to 50 ± 5.8% and 48 ± 5.9% for intermediate disease and 23.4 ± 5.9% and 18.2 ± 5.6% for advanced disease.

Conclusions: Haplo-identical transplants are feasible and associated with moderate outcomes in a developing country like India. Infectious complications are the major challenge with haploSCT and early transplantation remains the key to improving outcomes.

Keywords: Haplo-identical transplant, good survival, early disease





Comparison of Spectra Optia using continuous mononuclear cell protocol and COBE Specra AutoPBSC apheresis system for peripheral blood stem cell collection

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灣)

Abstract Content

Background: Continuous mononuclear cell (CMNC) is a new protocol of peripheral blood stem cell (PBSC) collection using the Spectra Optia apheresis system. The aim of this study was to compare the yields of Spectra Optia using the CMNC protocol and COBE Spectra AutoPBSC apheresis system for PBSC collections.

Methods: In each subject, PBSCs were harvested by leukapheresis daily for 2-3 consecutive days. Each procedure processed 10 liters of whole blood. Each subject used Spectra Optia and COBE Spectra apheresis system alternatively. In each subject, we randomly selected the yields of Spectra Optia and the yields of COBE Spectra.

Results: Data of 90 collection procedures from 45 subjects (M:F = 26:19; age: 46.8 ± 16.3 years, range: 15-68 years; body weight: 69.6 ± 14.1 kg, range: 50.4 - 108.5 kg) were analyzed. There are 35 autologous patients (lymphoma: 18, multiple myeloma: 11, germ cell tumor: 4, follicular dendritic cell sarcoma: 1, Ewing's sarcoma: 1) and 10 allogeneic donors. Pre-apheresis median white blood cell (WBC) counts were 16,300/microL (range: 3,000-47,000 /microL) for patients, and 42,500/microL (range: 20,000-53,000/microL) for allogeneic donors. Yields of PBSC including volume, WBC, mononuclear cell (MNC), CD34+ cell, red blood cell (RBC) and platelet were shown in Table 1.

		Volume	WBC	MNC	MNC	CD34+ cell	RBC	Platelet
	n							
		(mL)	(×10 ⁸ /kg)	(×10 ⁸ /kg)	(%)	(×10 ⁶ /kg)	(mL)	(×10 ¹¹)
COBE	45	71.5±12.9	2.40±0.83	2.37±0.95	94.6±7.9	2.01±1.96	2.1±1.4	0.87±0.69
Optia	45	93.4±44.7	4.05±2.33	3.47±2.08	84.3±16.2	2.82±3.71	4.2±2.1	1.03±0.64
P-valu	Je	<0.001	<0.001	<0.001	<0.001	0.074	<0.001	0.03

Table 1. Comparison of yields of PBSC collections between COBE Spectra and Spectra Optia

Conclusion: The products of Spectra Optia using the CMNC protocol had significantly higher MNC count and platelet count when compared to the products of COBE Spectra AutoPBSC apheresis system, but granulocyte contamination was significantly higher in the products of the Spectra Optia.





HLA antigen and haplotype distribution in Malaysian candidates for hematopoietic stem cell transplantation

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Abstract Content

Background: Histocompatibility matching of human leukocyte antigens (HLA) between recipient and their family members is essential to identify suitable donors for allogeneic hematopoietic stem cell transplant (AHSCT). Data on HLA antigen and haplotype frequencies may allow better prediction of the probability of finding HLA-matched donors, consequently enhance the donor search strategy. This study aims to determine the distribution of HLA antigens and haplotypes in patients who had undergone HLA typing for AHSCT in University of Malaya Medical Centre and to review the outcome of the transplant. To our knowledge this is the first haplotype frequency report in Malaysia.

Methodology: This retrospective study involves the analysis of HLA typing results of patients and their potential donors who had undergone HLA matching in University of Malaya Medical Centre (UMMC) from 2003 to 2017. The patients and donors' HLA typing results were collected through their laboratory reports. The Centre routinely tests for HLA antigen/allele group by intermediate resolution solid phase assay. Only the siblings of the patients were tested in view of the patient require full HLA matched donor for transplantation. HLA typing for HLA-A, -B, -DR, and -DQ from each patient and potential donor were collected to derive the haplotype present in the patient's family. The frequency of recurring haplotype and antigen present was then directly counted and recorded. Recurring haplotype and antigen present within a family were counted as 1 unit to the overall haplotype and antigen frequency.

Results: A total of 143 patients and their family members (mean no. of siblings = 2.7, SD \pm 1.4) were recruited for this study. Majority of the patients were Chinese (62.9%), followed by Malay (29.4%), and Indian (4.9%). While, 81 (56.6%) found HLA-matched donors, however only 42 (29.4%) patients proceeded with AHSCT. Majority of the Malays found a match within their family (69%), followed by Indians (57%), and Chinese (52%). 53%, 52%, and 25% of Chinese, Malays, and Indians respectively from the matched group proceeded with transplant. No significant association was found between number of siblings screened and number of HLA-matched siblings (p = 0.71). Of the 42 patients who proceeded for AHSCT, 44 haplotypes were successfully derived from 11 patients and their families. Of the 44 haplotypes determined, 6.8% were haplotype HLA-A*33-B*58-DRB1*17-DQB1*02, while HLA-A*33-B*58-DRB1*13-DQB1*06, HLA-A*24-B*75-DRB1*12-DQB1*07, HLA-A*02-B*60-DRB1*09-DQB1*09, HLA-A*02-B*46-DRB1*16-DQB1*05, HLA-A*02-B*13-DRB1*15-DQB1*06 were each 4.5% respectively. No disease relapse occurred within the haplotype determined group, however one death was reported post-transplant. The most frequent antigens observed from the patients and their families of the transplanted group was HLA-A*11 (18.2%), HLA-B*58 (15.9%), HLA-DRB1*12 (13.6%), and HLA-DQB1*06 (18.2%).

Conclusion: Malaysia is comprised of a multi-ethnic population in which the haplotype distribution may vary among ethnic groups. Though the results suggested the six most common haplotypes, a larger scale study in healthy population shall be performed to validate the findings.

Keywords: Haplotype Frequency; Allogeneic Hematopoietic Stem Cell Transplant; Human Leukocyte Antigen,





Expansion of umblical cord blood CD34+ hematopoietic stem cells with inhibition of TGF-β1 receptor II by using SiRNA in presence of bone marrow mesenchymal stem cells

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Abstract Content

Introduction: One of main source of HSC is cord blood stem cell (CBSC). One major drawback in using this source in adults is the low hematopoietic stem cell (HSC) dose available. Thus, Ex vivo expansion of HSCs is a solution to overcome this limitation. Mesenchymal stem cells (MSCs) as feeder layer would support expansion of HSCs in culture media and increase self renewality of HSC. It is suggested TGFb signaling play an important role in inhibiting of self renewality of cells. In this study it is evaluated effect of inhibition of TGFb signaling on self renewal of HSC and expansion of HSCs.

Materials and method: BM-derived mesenchymal stem cells were isolated from BM-mononuclear cells and cultivated. CB-HSCs were isolated using miniMACS magnetic separation system from cord blood. Isolated CD34+ transfected by Si RNA against TGFbR2 and suppression of expression of gene confirmed by REAL TIME PCR. Transfected CD34 cells co-cultured with MSC and expansion of CB-HSC detected by using flow cytometry for expression of CD34, total nucleated cells (TNC) and colonigenic assay.

Results: The average of CD34 cells positive and TNC at day 8 compare to day 0 in culture condition including cells transfected with siRNA against TGFBR2 co-cultured with MSC using growth factors were 71.8 \pm 6.9 and 93.16 \pm 10.2. While, In culture condition including non transfected cells with co-cultured MSC using growth factors were 40.9 \pm 7.3 and 63.5 \pm 8.1. These differences in cell numbers were significant (p<0.05).

Conclusion: It is concluded that HSC CD34+ population increase dramatically with inhibiting of TGFbR2 using SiRNA in presence of MSC. Furthermore, colonigenic assay confirmed expansion of CB-HSC in culture.

Keywords: Cord blood stem cells; mesenchymal cells; SiRNA; TGFbR; REAL TIME PCR




Topic: Alternative stem cell sources / Histocompatibility Abstract No: 8974

The Frequency of Human Leukocyte Antigen (HLA) DP Alleles and Haplotypes of HLA- DRB1, -DQB1 and DP in National Taiwan University hospital

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Abstract Content

Background

HLA-DP, a group of antigens in human leukocyte antigen (HLA) system, has been reported to associate with kidney transplantation failure. Clinical studies show that the organ transplant recipients own donor specific HLA-DP antibodies develop recurrent acute antibody-mediated rejection (AMR) and graft failure. Other studies also indicate that desensitization after kidney transplantation be unable to overcome the AMR because of the existence of preformed HLA-DP Donor specific antibodies (DSA). It seems important to detect any mismatched HLA-DP antigenic determinants before transplantation and to monitor HLA-DP antibody level carefully. For assigning HLA-DP typing report, there is no allele frequency of HLA-DP in Taiwanese population. It was useful for operator to select the most possible allele pairs. Thus, we needed the common and well document (CWD) of HLA-DP for assigning the report of HLA-DP.

Study design and methods

We collected 54 individuals for analyzing HLA-DP typing by reverse Sequence-Specific oligonucleotides (r-SSO). Analyzing the allele frequency of HLA-DP,-DRB1, DQ and the linkage disequilibrium with HLA-DRB1,-DQB1, and –DPB1 by expectation-maximization (EM) algorithm.

Result

The common HLA-DPB1 allele are DPB1*05 (0.528), DPB1*02 (0.194), and DPB1*04 (0.102). For HLA-DPA1 allele, DPA1*02 is dominant. To investigate haplotype, there is no significant association between -DRB1, -DQB1 and -DPB1. The most haplotype is DRB1*12-DQB1*03-DPB1*05 (13.9%).

Conclusion

The allele frequency of HLA-DP will set up CWD for operator to report the result of HLA-DP. Comparing with the donor's HLA-DP typing and the data of recipient's HLA-DP antibodies could help us to find HLA-DP DSA.

Keywords: Sequence-Specific oligonucleotides, linkage disequilibrium, haplotype, expectationmaximization





Transplant outcomes of haploidentical activities, GIAC-like versus PTCy-based, for hematological malignancies in Taiwan: Results from Taiwan Blood and Marrow Transplantation Registry (TBMTR)

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Abstract Content

Background: There are two most noteworthy strategies of haploidentical stem cell transplantation (haplo-SCT), the Baltimore post-transplantation cyclophosphamide (PTCy) and the Beijing G-CSF primed bone marrow plus peripheral blood stem cells (GIAC-like, G-BM/PBSC). We aimed to compare these two approaches for hematological malignancies based on the Taiwan Blood and Marrow Transplantation Registry (TBMTR).

Materials & Methods: From July 2012 to December 2017, 148 patients underwent haplo-SCT, either by PTCy (n = 61) or G-BM/PBSC (n = 87), were registered. All the PTCy-based grafts were PBSC, while all the G-BM/PBSC received both BM and PBSC. Totally, 66% of PTCy-based group received anti-thymoglobulin (ATG) for graft-versus-host-disease (GvHD) prophylaxis, but the entire G-BM/PBSC-based group received ATG.

Results: The 28-day neutrophil recovery rate and 100-day platelet recovery were significantly higher in the G-BM/PBSC than in the PTCy group (99% *vs* 96%, *P*<0.001, and 94% *vs* 84%, *P*<0.001, respectively). Patients in the G-BM/PBSC group had a significantly higher 2-year survival rate (53% vs 35%, *P*=0.002) and a lower 1-year non-relapse mortality rate (17% vs 42%, *P*=0.020). There were no significant differences in terms of grade III/IV acute GvHD (16% for the G-BM/PBSC and 13% for the PTCy, *P*=0.560) or extensive chronic GvHD (42% vs 21%, *P*=0.208). Among the G-BM/PBSC group, the 2-year survival was significantly higher for those in first or second remission (CR1/CR2, n=45) compared to those with advanced diseases (n=42) (69% vs 38%, *P*=0.010). However, among the PTCy group, the 2-year survival rates were similar among those in CR1/CR2 (n=30) and not (n=31) (43% vs 23%, *P*=0.171). The cumulative relapse rates were similar among the G-BM/PBSC and PTCy groups (*P*=0.269).

Conclusions: Haplo-SCT, with different protocols in Taiwan, was a feasible treatment modality for hematologic malignancies. Designation of prospective clinical trials may be beneficial to determine a more safe and effective method.

Keywords: Haploidentical, Bone marrow stem cells, Peripheral blood stem cells, Post-transplant cyclophosphamide





The effect of elapsed time and temperature on the viability and apoptosis of CD34+ cells in the thawed and DMSO-repleted cord bloods

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Abstract Content

Introduction: Assessment of the viability of hematopoietic stem cells (HSCs) after thawing of cryopreserved peripheral blood stem cells or cord bloods (CBs) is very important to predict engraftment during transplantation process. We investigated the impact of elapsed time, storage temperature, and dimethyl suloxide (DMSO) on the viability of HSCs as well as apoptotic changes in the thawed CBs.

Methods: Thirteen units of cryopreserved CBs were thawed and each half of samples were stored at room temperature (RT) and 4°C, respectively, without removal or dilution of DMSO. Flow cytometry was performed using a FACSCantoll (Becton-Dickinson) to enumerate TNC, total/viable CD34+ cell counts, and early/late apoptotic cell counts. Anti-CD45, Anti-CD34 antibody, and annexin V(AnV), 7-amino actinomycin D(AAD) staining were performed to detect viable CD34+ cells (CD34+45+AnV-AAD-), early (CD34+CD45+AnV+AAD-) and late (CD34+CD45+AnV+AAD+) apoptosis. Samples were tested at 6 different time points (immediately post-thaw, and 1, 2, 6, 24, 48 hours post-thaw) during storage at RT and 4°C.

Results: In CBs stored at 4°C after thawing, we could not observe any significant changes of TNC, total/viable CD34⁺ cell counts, and early/late apoptotic cell counts upto 48 hours. However, these cells showed significant changes according to elapsed time points in storage at RT. Total and viable CD34⁺ cell counts have not been changed at least until 6 hours at RT in the thawed and DMSO-repleted CBs. Viable CD34⁺ cell counts decreased significantly from 24 hours elapsed, and total CD34⁺ cell counts from 48 hours. Early and late apoptosis showed increasing tendency according to elapsed time, however, late apoptosis increased significantly from 24 hours elapsed. There were significant differences of viable CD34⁺ cell counts and early apoptosis from 48 hours between RT and 4°C.

Conclusion: There were no significant changes of the viability and apoptosis of DMSO-repleted CBs stored at 4°C until 48 hours after thawing. And, in RT, there were no significant changes of total/viable CD34+ cell counts as well as the proportion of apoptotic cells at least until 6 hours after thawing, even in DMSO-repleted CBs.

Keywords: Cord blood; Viability; Apoptosis; DMSO





A novel recombinant human thrombopoietin therapy for promoting platelet engraftment in haematological malignancies after single umbilical cord blood transplantation: a prospective randomized controlled trial

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Abstract Content

Background: Umbilical cord blood transplantation (UCBT) has emerged as a widely accepted treatment for a wide variety of hematologic malignancies. However, delayed platelet engraftment (DPE) and platelet engraftment failure still remain the common problems following UCBT. So far, no standard therapy has been recommended. A few studies have demonstrated that recombinant human thrombopoietin (rHuTPO) could play an effective role in advancing platelet recovery after allo-HSCT. Nevertheless, it remains unknown whether rHuTPO plays the same role while it is applied in UCBT. We designed this prospective randomized controlled trial with the purpose of determining whether rHuTPO improves platelet engraftment in patients undergoing single UCBT(sUCBT) and further evaluating the function of rHuTPO in sUCBT.

Methods: We enrolled 120 patients with haematological malignancies between October 2016 and March 2018 undergoing sUCBT in Department of Hematology, the First Affiliated Hospital of University of Science and Technology of China. This trial was approved by the Medical Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China and registered on www.chictr.org.cn(ChiCTR-IPR-16009357). 60 patients were randomly assigned into the experimental group, in which they received rHuTPO on Day 14 after sUCBT with a dose of 300 U/kg once daily for a period of 14 days; the remaining 60 patients formed the no-treatment control group. Among 120 patients, 19 received total body irradiation (TBI) based conditioning and others received modified myeloablative conditioning without antithymocyte globulin (ATG) as myeloablative conditioning. All patients were given cyclosporin (CsA) and mycophenolate mofetil (MMF) preventing graft-versus-host disease (GVHD). Supportive care and other treatments were provided following our center's protocols.

Results: With a median follow-up of 336 days (ranging between 96-618) for the surviving patients the cumulative incidence of PLT engraftment in the rHuTPO group (89.7%, 95% confidence interval [CI], 77-95.5) was significantly higher than that in the control group (78.9%, 95%CI, 65.3-87.6) (p=0.0294);themedian time of PLT engraftment was 35 and 40days (ranging between 18-144 and 19-170 respectively, P=0.155). The median time of PLT recovery in the rHuTPO group was 43days(ranging between 25-171days), which was significantly shorter than that in the control group(53days, ranging between 28-195, P=0.034). The rHuTPO group also showed an advantage over the control group in infused PLT units (6 vs 8, p=0.0294). The cumulative incidence of ANC engraftment was 98.3% (95% CI, 75.2-99.9) and 94.9% (95% CI, 83.8-98.5) (p=0.111) respectively in two groups. Multivariate analysis confirmed the significance of differences in platelet engraftment between two groups. The cumulative incidences of grade II-IV and III-IV acute graft-versus-host disease (GVHD), relapse, non-relapse mortality (NRM) and the probabilities of overall survival(OS) and leukemia free survival (LFS) did not differ between the two groups. No severe adverse effects were observed in all patients.

Conclusions: Our results demonstrate that rHuTPO could noticeably improve platelet engraftment and promote platelet recovery in patients with haematological malignancies receiving sUCBT; in the meantime, it could also reduce the requirement for platelet transfusion. This study indicated that rHuTPO could be a good option for promoting platelet engraftment and recovery in haematological malignancies after sUCBT.



Keywords: harmatological malignancy; cord blood; transplantation; platelet engraftment

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Topic: Graft processing Abstract No: 8927

A pilot prospective single-arm clinical study on Decitabine plus CAG or IA followed with HLA-mismatched nonmyeloablative transplantation (micro transplantation) on de novo elderly Acute Myeloid Leukemia and Int-2/high risk Myelodysplastic Syndrome patients

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Abstract Content

Objective: To observe the efficacy and safety of Decitabine plus *CAG* or *IA* followed with HLA-mismatched nonmyeloablative transplantation (micro transplantation) on *de novo* elderly acute myeloid leukemia and Int-2/high risk myelodysplastic syndrome patients.

Methods: Till submission of this article, 10 patients were enrolled in this prospective clinical study. Patients were admitted from January 2017 to June 2018 to our centre. 6 of whom were elderly AML (\geq 60 years) and 4 were Int-2/high risk MDS according to IPSS-R scoring system. Induction chemotherapy were decitabine (15 mg/m2) for 5 days followed with CAG (cytarabine 10 mg/m² q12h; aclarubicin 10 mg/day and G-CSF at 300 µg/day x 6 days for AML and 4 days for MDS), then followed with a transfusion of HLA-mismatched (\leq 7/10 matched HLA loci) related donor peripheral stem cells 24 hours after chemotherapy. Consolidation therapy was another 3 courses of chemotherapies which were decitabine (15 mg/m2) for 5 days (6 days) for MDS, followed by micro transplantation 24 hours after each course.

Results: The average age of the patients was 63.5 years (55-71 years). The average number of transfusion mononuclear cells (MNC) at per course was 3.26 (1.87-5.25) x 10^8 /kg, the average CD34⁺ cells was 1.12 (0.34-3.16) x 10^6 /kg, and the average of CD3⁺ T cells was 3.93 (1.87-7.17) x 10^7 /kg. Among them, 5 cases (50%) obtained CR (CR+CRi), 3 cases obtained PR (30%). The ORR was 83.3% for elderly AML patients, 75% for MDS patients and 80% for all patients. The median recovery time (from the end of chemo to neutrophil $\ge 0.5 \times 10^9$) were 9 days for neutrophil and 8.5 days for platelets (from the end of chemo to platelets $\ge 20 \times 10^9$). 1 patient developed severe aGVHD and died, 1 patient died of heart failure, no other serious adverse events were observed in rest patients. 7 of 10 cases developed peripheral T cell increase after stem cell transfusion with an average peak at day7. The increased T cells were verified as host origin by short tandem repeat (STR) detection performed on 1 patient. 8 of 10 cases occurred cytokine related fever (CRF) after stem cell transfusion. The fever was usually happened within 24 hours after stem cell transfusion, with an average duration of 5 days and a mean peak temperature at 39.7 °C. With CRF there was an increase of cytokines with different patterns in different patients but majorly on IL-6, IL-2, IFN-r and TNF-a. Patients with CRF had a CR+CRi rate at 62.5%.

Conclusion: Our preliminary results of this study indicate that Decitabine plus *CAG* or *IA* followed with micro transplantation have an ORR at 80% in *de novo* elderly Acute Myeloid Leukemia and Int-2/high risk Myelodysplastic Syndrome patients with controllable recover time of neutrophils and platelets. The presence of cytokine related fever may associate with the increase of hosts' T cells, which may relate to the improvement of therapeutic response. Larger cohorts and more researches need to be done to make the mechanism of micro transplantation clearer.

Keywords: Micro transplantation, Elderly acute myeloid leukemia, Myelodysplastic syndrome



Topic: Graft processing Abstract No: 8961

Plerixafor for mobilization of hematopoietic stem cells for autologous transplantation in Japanese patients with non-Hodgkin lymphoma and multiple myeloma

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Abstract Content

[Introduction] Plerixafor is a selective and reversible inhibitor against the direct binding of stromal cellderived factor-1 α to its receptor CXC chemokine receptor 4, and has been used for stem cell mobilization in combination with G-CSF. Plerixafor was approved in December 2016 in Japan, and we retrospectively assessed the efficacy and safety of plerixafor in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) undergoing hematopoietic cell transplantation (HCT).

[Methods] Nineteen consecutive patients receiving plerixafor as part of their upfront stem cell mobilization and one patient as the second collection at our institute were retrospectively reviewed. Median age of the patients was 61 years old (range, 42-72) and their diagnoses included NHL (n = 11), MM (n = 8), and POEMS syndrome (n = 1). The minimum target CD34+ cell count in patients with NHL and MM was set at 2.0×10^6 cell/kg and 4.0×10^6 cell/kg, respectively. All the patients received G-CSF (filgrastim, 400 µg/m²/day) for 4 days prior to the first dose of plerixafor. Plerixafor was started on the evening of Day 4 and for up to 2 days, patients received plerixafor (0.24 mg/kg/day) + G-CSF. First apheresis started on the morning of Day 5. If the number of collected cells did not reach to the target dose, the second apheresis was performed on Day 6.

[Results] The number of CD34+ cells/µl in the peripheral blood increased significantly from median 11.5 (range, 0-51.0) to median 62.0 (range, 12.0-232.0) (P < 0.001). In poor mobilizer (n = 7, including the one with previous history of mobilization) on Day 4 by G-CSF (CD34+ cells/µl < 10), the number of CD34+ cells exceeded 10 cells/µl in all patients after giving plerixafor. However, the mobilizing effect of plerixafor remained unchanged between the first and the second infusion. In patients with NHL (n = 11), nine achieved a collection of ≥2 × 10⁶ CD34+ cells/kg by the first apheresis and one achieved the cell dose after the second apheresis. One did not receive the second apheresis. In patients with MM (n = 8), five achieved ≥4 × 10⁶ CD34+ cells/kg by the first apheresis and two achieved the cell dose after the second apheresis. Sixteen patients underwent transplantation, and restored normal hematopoiesis including two patients whose collected cell dose did not reach the target dose. There were no severe adverse events associated with the infusion of plerixafor.

[Conclusion] We confirmed that plerixafor was safe, and effective for the mobilization of hematopoietic stem cells for autologous transplantation in Japanese patients with NHL and MM.

Keywords: plerixafor; autologous; mobilization;





The Efficacy of Palifermin on Oral Mucositis and acute GVHD after Hematopoietic Stem Cell Transplantation in Hematologic Malignancy Patients: A Systematic Review and Meta-analysis study

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Abstract Content

Oral mucositis (OM) is one of the most common side effects after hematopoietic stem cell transplantation (HSCT) and palifermin is used for prophylactic use to prevent OM. We conducted a meta-analysis study that evaluates the efficacy of palifermin on OM after HSCT in hematologic malignancy patients. Databases of PubMed/Medline, Web of Science and Cochrane Library for English-language publications were searched for finding the relevant studies. The RevMan 5.3 software with random-effects models (odds ratio (ORs) and 95% confidence intervals (CIs)) was used for to estimate of the efficacy of palifermin in palifermin group compared with control group. Begg's and Egger's tests were used for assessment of bias between the studies. Ten studies were included in the meta-analysis study. The results of the meta-analyses showed that there were significant differences in OM (grade 1-4) [odds ratio (OR) = 0.17; 95%CI = 0.10,0.29; p < 0.00001], OM (grade 2-4) [OR= 0.11; 95%CI= 0.05,0.24; p < 0.00001], OM (grade 3-4) [OR= 0.22; 95%CI= 0.15,0.33; p <0.00001], after auto-HSCT for OM (grade 1-4) [OR= 0.13; 95%CI= 0.04, 0.35; p <0.0001], OM (grade 2-4) [OR= 0.03; 95%CI= 0.00, 0.21; p =0.0006] or OM (grade 3-4) [OR= 0.25; 95%CI= 0.13, 0.48; p <0.0001], after allo-HSCT for OM (grade 1-4) [OR= 0.23; 95%CI= 0.11, 0.51; p =0.0002], OM (grade 2-4) [OR= 0.14; 95%CI= 0.03, 0.74; p =0.012] or OM (grade 3-4) [OR= 0.19; 95%CI= 0.08, 0.46; p =0.0002] and fever [OR=0.51; 95%CI=0.29, 0.87; p = 0.01], but there were no significant differences in acute graft versus host disease (aGVHD) grades, infection and blood stream infection between two groups. The meta-analysis showed that palifermin was associated with reductions in the incidence and severity of OM and also was effective and safe on OM after allo- or auto-HSCT, but did not seem to effect on the incidence and severity of aGVHD.

Keywords: Hematologic Malignancy, Oral Mucositis, Palifermin, Stem Cell Transplantation





A mesenchymal stromal cell (MSC)-derived combination of CXCL5 and anti-CCL24 is synergistic and superior to MSC and cyclosporine for the treatment of graft-versus-host disease

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Abstract Content

The immunosuppressive properties of mesenchymal stromal cells (MSCs) have been clinically proven to be effective in treating graft-versus-host disease (GVHD). However, MSC therapy is limited by the need for laborious and expensive manufacturing processes that are fraught with batch-to-batch variability. Substitution of MSC therapy with key MSC-mediated immunomodulatory factors could be an option for GVHD treatment. Using a simulated in vitro model of the immunosuppressive effects of MSC on allogeneic graft reactions, a synergistic two-factor combination (2FC) of CXCL5 and anti-CCL24 was identified from a panel of over 100 immunomodulatory factors as being superior to MSC in the modulation of mixed lymphocyte reactions. This 2FC was superior to cyclosporine in ameliorating both moderate and severe GVHD, while being equivalent to MSC in moderate GVHD and superior to MSC in severe GVHD. Its immunosuppressive efficacy could be further improved by extended treatment. Mechanistic studies revealed that, in vitro, the 2FC could only reduce the proliferation of TH1 cells and TH17 cells; while in vivo, CXCL5 acts in concert with anti-CCL24 antibody to reduce not only transplanted TH1 cells. TH17 cells but also cytotoxic T lymphocytes and NK cells, increase mouse immunosuppressive neutrophils without affecting human hematopoietic stem cell reconstitution. Concurrently, it reduced circulating human pro-inflammatory cytokines IFN-y, IL-6, IL-17A, IL-8, MIP-1ß and MCP-1. Both in vitro and in vivo data suggest that CXCL5 and anti-CCL24 antibody act in concert to ameliorate GVHD via suppression of T_H1 and T_H17 responses. We propose that this novel 2FC could substitute for MSC therapy in GVHD treatment.

Keywords: Graft-versus-host disease (GVHD); mesenchymal stromal cell (MSC); MSC-derived factors; anti-Eotaxin-2 (anti-CCL24); ENA-78 (CXCL5)





Graft-versus-host disease free, relapse-free survival after allogeneic stem cell transplantation for myelodysplastic syndrome

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Abstract Content

Graft-versus-host disease-free, relapse-free survival (GRFS) is a composite endpoint that measures survival free of relapse or significant morbidity following allogeneic hematopoietic stem cell transplantation (HSCT). Consecutive 324 adult patients who received HSCT with fluarabine and busulfan based conditioning for myelodysplastic syndrome (MDS) or secondary acute myeloid leukemia evolved from MDS were retrospectively analyzed. 1-year and 3-year GRFS rates were 47.8% and 34.5%, respectively. Three fixed factors (circulating blast >3%, high cytogenetic risk, and high comorbidity index) and two factors (which is) modifiable by clinicians [myeloablative conditioning and low-dose (<7.5mg/kg) of antithymocyte globulin (ATG)] were independent factors for poor GRFS. Based on these five factors, three groups (3-year GRFS: 64.9% in low-risk, 33.6% in intermediate-risk, and 6.6% in high-risk, p<0.001) were identified. Fixed factors-adjusted GRFS in patients receiving reduced intensity conditioning (RIC) plus high-dose ATG (≥7.5 mg/kg) was superior (p <0.001) to those receiving MAC and/or low-dose ATG. Favorable influences of RIC plus ATG ≥7.5 mg/kg was evident in the low-risk group defined by fixed factors (3-year GRFS: 38.9% vs. 4.4%, p<0.001), but not evident in the high-risk group (3-year GRFS: 0.0% vs. 5.3%, p=0.678). Conclusively, this study suggests that risk-adapted selection of conditioning intensity and ATG could improve qualified HSCT outcomes.

Keywords: Hematopoietic stem cell transplantation; myelodysplastic syndrome; GVHD-free, relapse-free survival; reduced intensity conditioning; antithymocyte globuline





Occurrence and Severity of DLI associated Chronic GVHD Influence the Clinical Outcomes in Relapsed Acute Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract Content

The aim of this study was to investigate the occurrence and severity of chemotherapy plus donor lymphocyte infusion (Chemo-DLI) associated chronic graft-versus-host disease (cGVHD) in a consecutive cohort of patients with acute leukemia who experienced relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT; n = 104). The 5-year cumulative incidence of complete remission (CR) after Chemo-DLI was 81.0% (95% CI, 73.3-88.7%) and 84.6% (95% CI, 74.5-94.7%) in the moderate and severe cGVHD groups, respectively, which was significantly higher than that of the mild cGVHD 40.9% (95% CI, 29.3-52.5%) and non-cGVHD groups 29.2% (95% CI 23.1-35.3%) (Figure 1). The cumulative incidence of non-relapse mortality was comparable between patients with and without cGVHD . The 5-year probabilities of progression-free survival after Chemo-DLI were 42.9% (95% CI, 26.2-70.2%) and 34.6% (95% CI, 15.3-78.2%) in moderate and severe cGVHD groups, respectively, which were both significantly higher than those of mild cGVHD 9.1% (95% CI, 2.4-34.1%) and non-cGVHD groups 8.3% (95% CI 3.3-21.3%) (Figure 2). The 5-year probabilities of overall survival after Chemo-DLI were 56.7% (95% CI, 38.9-82.7%) and 43.1% (95% CI, 22.1-84.0%), in moderate and severe cGVHD groups, respectively, which were both significantly higher than those of the mild cGVHD 9.1% (95% CI 1.8-47.1%) and non-cGVHD groups 14.9% (95% CI, 7.3-30.2%) (Figure 3). Our observations highlight the close relation between cGVHD and immune-mediated graft-versus-leukemia (GVL) effect in patients with relapse receiving Chemo-DLI; however, mild cGVHD may not be associated with a sufficiently strong GVL effect to induce remission and improve survival.

Keywords: chronic graft-versus-host disease; donor lymphocyte infusion; hematopoietic stem cell transplatnation; National Institutes of Health consensus criteria; acute leukemia





STEROID-REFRACTORY ACUTE GASTROINTESTINAL GRAFT VERSUS HOST DISEASE (SRGVHD) SUCCESSFULLY TREATED WITH RUXOLITINIB: A CASE REPORT

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Abstract Content

Introduction

Acute Graft versus host disease (aGVHD) is a major cause of morbidity and mortality following allogeneic hematopoietic stem cell transplant (HSCT). Current standard treatment is corticosteroids. Steroid-refractory aGVHD is associated with poor prognosis. Numerous therapeutic agents have been studied but none have demonstrated causing long-term benefit contributing to the high rate of morbidity and mortality and most of them are not available in the Philippines. Ruxolitinib, an oral Janus kinase (JAK) 1/2 inhibitor approved for myelofibrosis, has recently been used in steroid-refractory aGVHD.

Case Report

We report a case of a 30-year-old male, Filipino with multiple recurrences of classical Hodgkin lymphoma, who developed steroid-refractory acute gastrointestinal GVHD (aGVHD) following allogeneic peripheral blood stem cell transplantation. He received a reduced intensity conditioning regimen consisting of fludarabine and melphalan followed by allogeneic peripheral blood stem cell transplantation from a 5/6 HLA matched donor. Acute gastrointestinal GVHD stage I grade II developed on day 55 which he responded initially with oral prednisone at 1mg/kg/day. Following a withdrawal of immunosuppression for progressive disease, on day 183 he developed a maculopapular skin rash involving > 50% body surface area, oral mucositis, crampy abdominal pain followed by copious watery diarrhea amounting up to 1500 ml/day necessitating re-admission, acute gastrointestinal GVHD (aGVHD) persisted despite resumption of steroids and Anti-Thymocyte Globulin (ATG) administration. On day 208, ruxolitinib 5 mg/tab, orally, 2 times a day was then started which resulted in resolution of diarrhea and improvement of overall clinical condition. On day 219 patient clinical condition gradually improved.

Conclusion

The treatment of refractory GHVD continues to be challenging with no established standard of treatment. Ruxolitinib, an oral JAK 1/2 inhibitor has the potential to treat steroid-refractory aGVHD. This case demonstrates the effectiveness of ruxolitinib in refractory GVHD.

Keywords: Allogeneic hematopoietic stem cell transplantation; JAK; Steroid-refractory graft versus host disease; Ruxolitinib





Acute Graft-Vs-Host Disease(A-GVHD): Pathobiology and Management

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Abstract Content

Acute graft-vs-host disease (GVHD) is a major obstacle to safe allogeneic hematopoietic stem cell transplantation (HSCT), leading to a significant morbidity and mortality. GVHD occurs when transplanted donor T lymphocytes react to foreign host cells. It causes a wide variety of host tissue injuries. This review focuses on the pathobiological basis, clinical aspects, and current management strategies of acute GVHD. Afferent phase of acute GVHD starts with myeloablative conditioning, i.e., before the infusion of the graft. Total-body irradiation (TBI) or high-dose chemotherapy regimens cause extensive damage and activation in host tissues, which release inflammatory cytokines and enhance recipient major histocompatibility complex (MHC) antigens. Recognition of the foreign host antigens by donor T cells and activation, stimulation, and proliferation of T cells is crucial in the afferent phase. Effector phase of acute GVHD results in direct and indirect damage to host cells. The skin, gastrointestinal tract, and liver are major target organs of acute GVHD. Combination drug prophylaxis in GVHD is essential in all patients undergoing allogeneic HSCT. Steroids have remained the standard for the treatment of acute GVHD. Several clinical trials have evaluated monoclonal antibodies or receptor antagonist therapy for steroid-resistant acute GVHD, with different successes in a variety of settings. There are some newer promising agents like mycophenolate mofetil, glutamic acid-lysine-alanine-tyrosine (GLAT), rapamycin, and trimetrexate currently entering in the clinical studies, and other agents are in development. Future experimental and clinical studies on GVHD will shed further light on the better understanding of the disease pathobiology and generate the tools to treat malignant disorders with allogeneic HSCT with specific graft-vs-tumor effects devoid of GVHD.

Keywords: Acute GVHD, Management, GVHD Pathobiology





nTreg and iTreg immunosuppressed functions are potently suppressed by the Janus kinase 1/2 (JAK1/2) inhibitor Ruxolitinib in vitro

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Abstract Content

Introduction

Graft versus host disease (GVHD) is a major complication of allogeneic hematopoietic cell transplantation (allo-HCT), for which administration of FoxP3+ Treg cells has been proposed as a therapy. Ruxolitinib, an inhibitor of Janus kinases 1 and 2 (JAK1/2), had been reported the ability to prevent GVHD. JAK/STAT-signaling is known to be involved in the regulation of various immune cells including natural (nTreg) and induced Treg (iTreg) cells, which significantly orchestrate inflammatory responses. The aim of our study is to investigate the mechanism of the immunosuppression of nTreg and iTreg by Ruxolitinib.

Methods

We provide an in depth analysis of nTreg and iTreg functions upon Ruxolitinib exposure. Highly purified nTreg and CD4+ T cells, isolated from healthy human peripheral blood mononuclear cell (PBMC), were stimulated for 3.5 days with phytohaemagglutinin (PHA) and IL-2 in the presence of increasing concentrations of Ruxolitinib (0.01μ M – 100μ M) or the respective vehicle control (DMSO). In addition, CD4+ T cell were exposed to IL-2 and TGF β in order to induce Treg. Then, nTreg cell and iTreg cells were isolated. The phenotype and surface molecules were analyzed by FACS. The immunosuppressed function were detected by CFSE dilution analysis by mixed leukocyte culture (MLC) test and cytokine production was quantified by ELISA.

Results

Under the nTreg expansion system in vitro, nTreg proliferation is significantly and dose-dependently suppressed by Ruxolitinib (p<0.05). However, Ruxolitinib (100nM) could promote CD4+ T cell polarize into iTreg and expand the stability (p<0.05). Of note, under higher concentration of Ruxolitinib, both nTreg and iTreg immunosuppressive functions were dramatically improved (p<0.01). To clarify the underlying mechanisms, we evaluated the expression of immunosuppressed molecules and cell factors in MLC which were associated with Treg cells. The expression of ICOS was critically enhanced (p<0.05) according to the value of median fluorescence intensity (MFI) and the intensity of CTLA4 were also enhanced to some extent. The production of pro-inflammatory cytokines such as IL-6, IL-10 and TNF- α in MLC were inhibited by dose-dependently Ruxolitinib treated Treg from ELISA analysis(p<0.05).

Conclusion

We assume that Ruxolitinib could enhanced the induction efficiency of iTreg while no impact on nTreg expansion. Also, high-concentration Ruxolitinib potently affects nTreg and iTreg immunosuppressed function in vitro by upregulating surface immunosuppressed molecules such as ICOS and CTLA4. At the same time, the expression of inflammatory factors could be suppressed in a way. These data provide a rational explanation for how Ruxolitinib alleviate GVHD. However, some patients showed an increase proportion of Treg indicating the complex environment in vivo and need to be further researched.

Keywords: Ruxolitinib;natural and induced regular T cells;Graft versus host disease



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Topic: Graft-versus-Host disease / Graft-versus-Leukemia effects Abstract No: 8891

IMPORTANCE OF PERIPHERAL BLOOD ABSOLUTE LYMPHOCYTE COUNTS (ALC) IN PREDICTING TRANSPLANT OUTCOMES IN PREPARATIVE REGIMENS USING ANTI-THYMOCYTE GLOBULIN OR ALEMTUZUMAB: AN INTERNATIONAL 2 CENTRE EXPERIENCE.

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Abstract Content

Background: Antithymocyte globulin (ATG) and anti-CD52 antibody (alemtuzumab) are used as prophylaxis for graft-versus-host disease (GVHD) in unrelated donor allografts (URD) for leukaemia. Dosing regimens are empiric or weight-based. Recently, it is shown that recipient peripheral blood absolute lymphocyte count (ALC) on day of ATG administration interacts with the dose of ATG administered to predict transplantation outcomes (Kennedy et al). We hypothesized that a similar phenomenon may be occurring when using alemtuzumab, and compared the outcomes of ATG vs alemtuzumab based regimens.

Methods: We retrospectively compared 364 patients, 124 patients receiving ATG (anti-thymocyte globulin) for GVHD prophylaxis, and undergoing unrelated first allogeneic transplant for myeloid and lymphoid malignancies (group 1) to 240 patients receiving alemtuzumab (group 2), in similar time period.

Results: In the alemtuzumab group, 80/240 patients received 60mg of alemtuzumab and 160/240 patients received 100mg of alemtuzumab. In the ATG group, 67/124 patients received 5mg/kg, 33/124 patients received 7.5 mg/kg and 24/124 patients received 10mg/kg of ATG respectively. In the ATG group, 76 (61%) patients were older than 52 years compared to 171 (71%) patients in the alemtuzumab group. As compared to ATG group, alemtuzumab group had significantly more number of patients receiving 9/10 mismatched donor grafts (6/124 (4%) vs 56/240 (22%), p=<0.001), patients with intermediate disease risk index, (70/124 (57%) vs 188/240 (78%), p<0.001), higher exposure to myeloablative regimen, (28/124 (22.6%) vs 98/240 (40%), p<0.001), and more patients with myeloid disorder (85/124 (68%) vs 203/240 (84%), p<0.001). The median follow up was 26 months (range, 1-98 months) in the ATG group and 33 months (range, 0.6-150 months) in the alemtuzumab group, respectively. The 2-year overall survival (OS), progression free survival (PFS), relapses and 1 year NRM (non-relapse mortality) for alemtuzumab group was 48%, 46% 32% and 20%, respectively and was comparable to ATG group, being 42%, 40% and 42%, 18% respectively, except for early relapses before 2 years (42% vs 32%, p=0.04) being better for alemtuzumab group. The incidence of severe (grade 3 and 4) acute and chronic GVHD were 12% and 11% vs 16% and 25% for alemtuzumab and ATG respectively, and was comparable (p=0.3, p=0.27). All outcomes were comparable between 60mg and 100mg doses of alemtuzumab. In a multivariate analysis of the patients who received alemtuzumab, we found recipient ALC on second day of alemtuzumab administration (ALC day 2) as strongest predictor of OS, DFS, and relapse (OS: p=0.05, HR 1.81, 95%CI 0.9-3.3; DFS: p=0.002, HR 2.41, 95%CI 1.3-4.2; relapse: p=0.003, HR 2.78, 95%CI 1.4-5.2). For ALC of 0.08 x 109/lit or more on day 2 of alemtuzumab the outcome (DFS) was particularly inferior.

Conclusions: Our study demonstrates that, like ATG, the interaction between alemtuzumab dose and recipient's peripheral blood ALC may have the ability to predict OS, DFS and relapses.Pre-transplant recipient peripheral blood ALC on second day of alemtuzumab administration (day 2) is strongest predictor of outcomes, with higher ALC associated with inferior DFS. Our approach has the potential to introduce individualized alemtuzumab dosing based on recipient ALC to improve outcomes without compromising immune reconstitution.

Keywords: Alemtuzumab, absolute lymphocyte counts, anti-thymocyte globulin, unrelated donor transplant, targeted dosing





Fecal microbiota transplantation for acute refractory gastrointestinal graft-versus-host disease

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Abstract Content

Introduction: The first-line therapy for acute graft-versus-host disease (aGvHD) is glucocorticoids, but approximately half of the patients don't respond to this treatment. So the prognosis of patients with steroid refractory aGVHD, including gastrointestinal (GI) aGvHD, was found to be poor. Recently, the alterations of intestinal microbiota, a dense and diverse microbioal community which is in symbiosis with the host in GI tract and exerting a considerable influence on the physiological, metabolic, nutritional, and immunological state of the host, have been proved to be correlated with aGVHD. After allogeneic hematopoietic stem cell transplantation (allo-HSCT), loss of intestinal microbial diversity was found in patients with aGvHD. Fecal microbiota transplantation (FMT) is a therapy that refers to the infusion of a fecal suspension from a healthy donor into the GI tract of a patient to restore a healthy microbiota and cure disease. FMT is highly effective in *Clostridium difficile* infection (CDI). In view of the poor prognosis of refractory GI aGVHD and the limited therapeutic options, we attempted to treat refractory GI aGVHD with FMT.

Methods: 13 patients with refractory GI aGVHD following allo-HSCT at our center from January 2017 to April 2018 were enrolled. The detailed patient data are compiled in Table 1. The mean time of the onset of GI aGvHD (days after allo-HSCT) was 28 days (ranging from 21 to 74 days). They suffered from grade III-IV GI aGvHD, while 6 also had skin GvHD and 2 had liver involved. Patients were treated with standard first-line treatment with corticosteroids (methylprednisolone, 2mg/kg body weight) and at least one second-line therapy, such as Basiliximab and Etanercept, but had no response. CDI didn't observed in all patients. Then, FMT was performed. Frozen fecal microbiota was obtained from Chinese stool bank, then suspended in warmed normal saline. It was administered to the patient via a nasoduodenal tube. FMT patients were assessed by symptoms, such as abdominal pain, stool volume, and bloody purulent stool. Clinical remission was defined as the disappearance of diarrhea or decrease of stool volume ≥500ml in 7 days, with relieve of intestinal spasms and/or bleeding. If the volume of diarrhea decreased <500ml, then the spasticity and/or bleeding improvement were included in the improved group.

Results: 7 patients were given FMT once, and 6 patients were given twice. Expect for one patient, the other 12 patients showed responses to FMT. 5 patients achieved clinical remission. 6 patients had improvement after the first FMT. Among these 6 patients, one died of cerebral hemorrhage caused by thrombocytopenia, one gave up treatment and died due to economic reasons, and one developed severe infection at 1 week after FMT and died of multiple organ failure. The recurrence of GI GvHD was found in one patient at 11 days after second FMT, which caused the death of the patient. Although severe infection appeared in one patient, no other severe adverse events were observed during and after FMT procedure.

Conclusion: These results suggested that the treatment for refractory GI aGVHD with FMT was efficient and safe.

Keywords: fecal microbiota transplantation, allogeneic hematopoietic stem cell transplantation, graftversus-host disease





Ruxolitinib Combined With Etanercept for Patients With Corticosteroid-refractory Acute Graft versus Host Disease After Allogeneic Stem Cell Transplantation: A Multi-center Prospective Study

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Abstract Content

Background and Aim: Acute graft versus host disease (aGVHD) remains a major problem after allogeneic hematopoietic stem cell transplantation (allo-SCT). About 50% of patients show resistance to the first-line steroids. To date, no consensus has been reached regarding the optimal salvage treatment for SR-aGVHD. We performed a prospective, multi-center clinical trial to assess the efficacy and safety of the combination of ruxolitinib and etanercept as a novel approach to treat grades II–IV SR-aGVHD.

Methods: Thirty-one malignant hematologic disease patients with grades II–IV SR-aGVHDfrom three centers in East China were enrolled from January 2017 to January 2018. All of them received ruxolitinib and etanercept as salvage-therapy for SR-aGVHD. Ruxolitinib was initiated at a dose of 5-10 mg BID for 2 months, and then tapered gradually for another one month. Etanercept was administrated at 25mg BIW for 2-8 weeks.

Results: At day 30 after starting the combination treatment, overall response was 90.3% with 74.2% being complete response (CR). The incidences of CR per organ were 93.5%, 84.2% and 82.6% for skin, liver, and gut involvement, respectively. The median time from combination therapy to the optimal response was 12 days.

The patients who received ruxolitinib within 14 days after aGVHD onset have a higher CR rate that those with delayed ruxolitinib therapy (94.7% vs. 50.0%, p=0.007). And the patients without gut infections have a higher CR rate than infected cohort (90.0% vs. 54.5%,p=0.037). Only time from aGVHD to ruxolitinib (RR=3.17, 95%CI 2.40~5.33, p=0.009) were independent predictors for incomplete response. III-IV Cytopenia and CMV-reactivation were observed during ruxolitinib treatment in 29.0% and 41.9% of patients. A significant decline in the level of IL-6, IFN-y and TNF- α was observed during 2-week treatment. The number of peripheral effector Tregs and Treg/Th17 ratio were significantly increased in responding patients.

Compared with the historical cohort of basiliximab and etanercept for SR-aGVHD in our center (n=31), no significant difference was found on the baseline, such as age, gender, underlying disease, disease status, conditioning intensity, as well as SR-aGVHD characteristics. Although the ORR in patients treated with ruxolitinib and etanercept is identical with the historical cohort (90.3% vs. 90.3%), ruxolitinib group achieved rapider remissions in liver aGVHD and gut aGVHD than the historical cohort (median time to remission for liver aGVHD: 21days vs. 28 days, p=0.0049; median time to remission for gut aGVHD: 11 days vs. 17 days, p=0.0026).

Among 31 patients in the study cohort, 9 cases (29.0%) were complicated with severe infection >= 2 grade, including military tuberculosis (n=1), CMV-interstitial pneumonia(n=1), sepsis(n=2), invasive fungal infection (IFI,n=1), human herpesvirus-6 acute limbic encephalitis (n=1) and bacteria pneumonia (n=3). The 1-year overall survival (OS) and 1-year non-relapse mortality (NRM) were 73.9% and 22.9%, respectively, and the 1-year relapse rate was 8.3% after ruxolitinib.



Conclusion: Combined treatment with ruxolitinib and etanercept resulted in a rapid CR to visceral aGVHD and meanwhile reserve graft anti-leukemia (GVL) effect. The various infection complications associated with ruxolitinib merit more attention.

Keywords: Ruxolitinib ; Etanercept ; Corticosteroid-refractory Acute Graft versus Host Disease ;





Checkpoint blockade with pembrolizumab induce graft-versushost disease for patients with refractory acute leukemia heavily treated after allogeneic transplantation

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Abstract Content

Introduction:

Refractory acute leukemia post allogeneic hematopoietic stem cell transplantation (allo-HSCT) carries a particularly grave prognosis. Immune checkpoint blockade with anti-PD1 antibody could theoretically induce graft-versus-host disease (GVHD) and possibly the graft-versus-leukemia (GVL) effect. Recently, anti-PD1 Nivolumab had shown activity against Hodgkin lymphoma relapse after allo-HSCT, while checkpoint blockade with Ipilimumab had shown to induce marked immune reaction for patients relapse after allo-HSCT. In this study, we aim to evaluate the treatment response and side effects of the anti-PD-1 antibody, pembrolizumab, in heavily treated patients with relapsed and refractory acute leukemia post allo-HSCT.

Materials&Methods:

Between Sep 2015 and Jun 2018, sixteen adult patients received pembrolizumab as salvage therapy for refractory acute leukemia (11 AML, 4 ALL, 1 MPAL) post allo-HSCT at National Taiwan University Hospital. The baseline patient characteristics, treatment responses and side effects were retrospectively reviewed. Progression-free survival (PFS) was evaluated with the Kaplan-Meier survival analysis. The pilot use of Pembrolizumab in this population had been approved by the hospital Research Ethics Committee.

Results:

The median duration between allo-HSCT and the administration of the first dose of pembrolizumab in this study was 315 days (range 79-836). Before pembrolizumab administration, they had failed multiple lines of treatment after allo-HSCT (median 4, range 1-8), including repeated donor lymphocyte infusion, second allo-HSCT and chemotherapy, and only six of them had grade I acute GVHD. Pembrolizumab was given at the dose ranging from 1 to 1.6 mg/kg (14 patients received one dose, and 2 patients two doses). Immediate acute GVHD-like reaction occurred in all patients after pembrolizumab administration, including spiking fever (N=16, median 5 days, range 3-15 days), elevated hepatic enzymes (N=10), and skin rashes (N=9, 5 patients had >75% body surface area involved). No treatment related mortality was encountered. The overall response rate (ORR) was 43.8% (7/16), including 5 complete remissions (CR) (31.2%) and 2 partial remissions (PR). After a median follow-up of 15.4 months (range 0.3-23.8 months), 5 patients remain alive (2 disease-free), while 11 had died of leukemia progression. The estimated 6-month and 12-month PFS and was 41% and 20%, respectively.

Conclusion:

In this report, we observed that immediate and remarkable immune response, reminiscing aGVHD/cGVHD could occur after checkpoint blockade therapy. It should therefore to be used with caution, especially for those with ongoing or severe GVHD. Some responsive patients could be seen even in these heavily pre-treated refractory patients, particularly in those with severe and special immune response.

Keywords: immune checkpoint blockade, pembrolizumab, hematopoietic stem cell transplantation, refractory acute leukemia, graft-versus-host disease



The incidence and risk factors of hepatic veno-occlusive disease after hematopoietic stem cell transplantation in Taiwan

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Abstract Content

Hepatic veno-occlusive disease (VOD) is an uncommon, but potentially fatal complication of hematopoietic stem cell transplantation (HSCT). We conducted this study to investigate the incidence and risk factors of hepatic VOD for patients receiving HSCT in Taiwan. We retrospectively analyzed the data from a nationwide registry for patients receiving HSCT which was collected by Taiwan Society of Blood and Marrow Transplantation. The data collection period was from 2009 to 2014. A total 2,345 patients were reviewed and 39 patients among them were diagnosed as having hepatic VOD. The cumulative incidence of hepatic VOD in the whole cohort of 2,345 patients was 1.66%. In multivariate analysis, disease diagnosis of myelodysplastic syndrome, chronic HCV infection, condition regimens of bulsulfan intravenously administered, and antithymocyte immunoglobulin were independent factors to predict higher risk of hepatic VOD. The overall mortality rate for patients with hepatic VOD was 79%. Patients with hepatic VOD had significant worse survival outcomes when compared with those without hepatic VOD (P=0.00063). In conclusion, although the incidence is low, hepatic VOD remains a serious complication after HSCT in Taiwan. The findings of this study could be the basis for developing prophylactic or early treatment strategies for hepatic VOD.

Table 1. Incidence of hepatic VOD

Patient characteristics	No. with hepatic VDO/No. evaluated (incidence %)	P value
Whole cohort	39/2345 (1.66%)	
Adult patients (age≧18 years old)	33/2130 (1.55%)	0.1749
Pediatric patients (age<18years old)	6/215 (2.79%)	
Autologous HSCT	1/1018 (0.10%)	<0.0001
Allogeneic HSCT	38/1326 (2.87%)	
HLA-matched unrelated donor	13/289 (4.50%)	<0.0001
HLA-mismatched unrelated donor	10/387 (2.58%)	
HLA-matched sibling	13/552 (2.36%)	
HLA partial mismatched related donor	2/66 (3.03%)	
Haplotype donor	0/25 (0.00%)	
BM graft	0/84 (0.00%)	0.4917
PBSC graft	38/2223 (1.71%)	
Umbilical cord blood	1/26 (3.85%)	

Keywords: hematopoietic stem cell transplantation; incidence; risk factors; veno-occlusive disease.





Evaluation of the association of CMV immunoglobulins (cytomegalovirus) with transplantation time in patients with bone marrow transplantation in Kermanshah

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Abstract Content

Evaluation of the association of CMV immunoglobulins (cytomegalovirus) with transplantation time in patients with bone marrow transplantation in Kermanshah

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Introduction: Cytomegalovirus (CMV) infection is one of the most important factors in the incidence and mortality of bone marrow transplantation. The incidence of CMV infection is seen in a period of time (less than 100 days) after transplantation and can involve several organs, including the lung, intestine, gastrointestinal tract, eyes, central nervous system, etc. Common tests for the detection of CMV infection in these patients include the anti-CMV test and the CMV DNA polymerase (PCR) assay. The purpose of this study was to measure the relationship between CMV presence and transplantation time.

Method: IgM-Anti CMV and IgG-Anti CMV tests were performed for transplant patients and transplant recipients, as well as CMV-PCR for all patients. Patients with chemotherapy leukemia who referred to Imam Reza Hospital who needed bone marrow transplantation were examined.

Statistical analysis was performed using SPSS software (version 21) and P-value less than 0.005 was considered as significant level.

Results: Sixty-six patients underwent transplantation of bone marrow stem cells, 48 patients (77.4%) had autologous transplantation and 14 patients (22.6%) had allogeneic transplantation. The mean transplantation time was 9.4 ± 1.89 days and 2 patients (22.2%) died. One patient (61.1%) was IgM-Anti CMV positive and 35 patients (56.4%) were IgG-Anti CMV positive. The prevalence of IgM-Anti CMV and IgG-Anti CMV in transplant recipients (allogeneic) was 0% and 71.4%, respectively. The incidence of CMV-PCR was 4.8%. There was no significant relationship between the presence of CMV with the timing of transplantation (P> 0.005). The association between IgM-Anti CMV and IgG-Anti CMV in patients and patients was significant (p <0.001).



Conclusion: Although the results of this study showed that there is no significant relationship between prolongation of transplantation and CMV infection, But its early diagnosis is important in preventing progression of the disease Because most CMV infections are initially asymptomatic and in case of neglect, most cases of activated infection of the virus (due to the weakening of the immune system of these patients) can not be controlled.

Keywords: bone marrow transplantation, cytomegalovirus, transplantation time

Pseudomonas aeruginosa refractory to treatment

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Abstract Content

Pseudomonas aeruginosa refractory to treatment

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Pseudomonas aeruginosa is a Gram-negative strict aerobic Bacillus that causes around 10% of nosocomial infections. This bacillus can become resistant to multiple antibiotics, and it has been described mainly in inmuno compromised patients. The prevalence of multidrug resistant Pseudomonas has been increasing over the last few years. Currently we have presented a MM case with septic shock due to Pseudomonas aeruginosa refractory to all line of drugs.

A 61 year-old man, diagnosed with the known case of Multiple Myeloma, was admitted to the hospital on January 31st, 2018. After the preparatory procedures, he underwent Autologous Stem Cell Transplant on February 13th. Thereafter, on February 21th, the patient ran a fever and signs of weakness and lethargy emerged in him. Then, a blood culture test was run on February 21st, which was positive. Moreover, there were signs that the refractory Pseudomonas aeruginosa infection was developing in him, which was treated through administration of various antibiotics. At the same time, the patient's skin was spotted with infected lesions in the form of acne, based on culture test was run. According to the results of the said test on the 26th of February, a case of refractory Pseudomonas aeruginosa infection was reported. Further, a culture test was prepared from Shaldon catheter, and the result was negative. The blood culture was conducted using disc diffusion and E-test methods, which were all resistant. Furthermore, the patient underwent two emergency dialysis due to kidney problems. U new agents to treat this type of infection. Doripenem is the new B-lactam from the carbapenem family, which has demonstrated in vitro the best activity against multidrug resistant Pseudomonas aeruginosa in different studies.

This agent has been indicated in the treatment of several infections, such as complicated intra- abdominal infections, complicated urinary tract infections and nosocomial pneumonia. The principal difference between doripenem and the other carbapenems, is the capacity of preventing the generation of resistant strains of Pseudomonas aeruginosa, so it is especially useful for severe infections caused by multidrug resistant Pseudomonas aeruginosa.

Promoting rationale use of antibiotics to treat infections caused by Pseudomonas aeruginosa may be critical to make the emergence of multidrug resistant strains difficult.

nfortunately, none of the treatments were effective and the patient passed away on March 2nd, 2018.

Keywords: Pseudomonas aeruginosa – BMT transplants - Multiple Myeloma



Retrospective analysis of human herpes virus-6 (HHV-6) myelitis cases after allogeneic hematopoietic stem cell transplantation

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Abstract Content

[Introduction] Human herpes virus-6 (HHV-6) could reactivate under the immunosuppression after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and has a potential to cause serious central nervous system (CNS) complications. Encephalitis causing seizure and impaired consciousness is recognized as a typical clinical feature. In addition, sporadic cases of myelitis have been reported. In this study, we retrospectively analyzed the cases of HHV-6 myelitis to elucidate its characteristics.

[Methods] By using the database and medical records, cases of HHV-6 myelitis developing after allo-HSCT at Keio University between 2003 and 2018 were identified. HHV-6 myelitis was defined as the clinical symptoms consistent with myelitis in combination with the positive HHV-6 DNA in the cerebrospinal fluid (CSF).

[Results] Nineteen patients (male, 11; female, 8) fulfilled the definition of HHV-6 myelitis and enrolled into the analysis. Median age at transplant was 50 years old (range, 17-61). All of the underlying diseases were hematological malignancies. Donor and stem cell sources were cord blood (N=11) and bone marrow from unrelated donors (N=8). Conditioning was myeloablative in 12 patients and reduced-intensity in 7. Cyclosporine or tacrolimus in combination with short-term methotrexate was used for graft-versus-host disease (GVHD) prophylaxis. Median onset of myelitis was day 19 post-transplant (range, 13-31). Median copy number of HHV-6 DNA at the onset was 3000 copies/ml (range, 200-10000). Initial symptoms were pruritus without skin manifestations in 10 cases, pain in 5, numbness in 2, malaise of the legs in 1, involuntary movement in 1, and dyschezia in 1. In three cases, HHV-6 encephalitis subsequently developed. All patients were treated with antiviral agents such as ganciclovir and foscarnet. Seventeen cases were fully recovered, while the remaining two cases had neurological sequelae.

[Conclusion] Pruritis and/or pain without identifiable causes should be recognized as the initial symptoms of HHV-6 myelitis after allo-HSCT. With an early intervention with the effective antiviral agent guided by detecting HHV-6 in the CSF, the prognosis of HHV-6 myelitis was considered favorable.

Keywords: HHV-6, myelitis





Non-infectious neurological complications presenting with myelopathy and neuropathy after umbilical cord blood transplantation

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Abstract Content

Introduction: An infectious encephalo-meningitis is one of the most common neurological disorders following allogeneic hematopoietic cell transplantation. Especially for patients transplanted umbilical cord blood, human herpes virus 6-associated limbic encephalitis still remains as an unsolved issue. On the other hand, we have little information about non-infectious neurological complications (NINCs) after umbilical cord blood transplantation (CBT).

Methods: To investigate NINCs after CBT, we retrospectively studied the patients who underwent CBT in our hospital as the first transplantation between July 2012 and March 2018. We excluded the patients whose performance status scale was 3 or 4, and who had neurological symptoms before transplantation.

Results: A total of 459 patients were reviewed. Eight patients developed NINCs which needed therapeutic interventions (2 myelopathies and 6 peripheral neuropathies [PN]). The cumulative incidence of NINCs was 1.74% at 2 years after transplantation (95% confidence interval, 0.54 - 3.93). The median age at transplantation was 53 years (range, 37 - 62), and 5 were males. The underlying diseases were as follows: AML-NOS (n = 5); AML with MRC (n = 1); therapy-related MDS or AML (n = 2). All patients except one were not in remission before transplantation. The conditioning regimen was FLU/BU/MEL with or without HDAraC for all patients. GVHD prophylaxis regimens were as follows: Tac alone (n = 2); Tac/MMF (n = 5); Tac/MTX (n = 1). The median onset day of NINCs was 90 days after transplantation for all patients (range, 25 - 255); 40 days for myelopathy, and 100 days for PN. No patients could walk by themselves at diagnosis. In line with several previous reports, axonal degeneration was confirmed by nerve biopsy in 2 patients with PN, although its precise mechanisms were unknown. Within 2 weeks before the emergence of neurological symptoms, 2 patients experienced hemorrhagic cystitis caused by BK and JC virus. Grade 2 or 3 of acute GVHD preceded NINCs in all patients. After the diagnosis of NINCs, all patients were treated with high dose intravenous immunoglobulin (IVIG) (400 mg/kg for 5 days). The median interval from diagnosis to treatment was 28 days (range, 5 - 71). IVIG was administered for the median of 2 courses (range, 2 - 5). In two patients, rituximab or steroid pulse therapy was added on IVIG, respectively. After these treatments, 6 out of 8 patients became walk alone (1/2 of myelopathy and 5/6 of PN). The remaining one died of severe liver acute GVHD and another one is hospitalized until now without recovery. Finally, 7 out of 8 patients are alive.

Conclusion: NINCs developed within 1 year after CBT with low incidence. IVIG had a therapeutic potential for them, and their prognosis was not dismal.



The influence of cumulative steroid dose on the evaluation of kidney function and sarcopenia index up to 90 days after allogeneic hematopoietic stem cell transplantation

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Abstract Content

[Introduction] Systemic steroids are widely used for the treatment of complications such as graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). Steroid myopathy is one of various complications caused by administration of steroid at high doses, and the weakness of muscles is latently expressed in about 15 days from the start of steroid therapy, and interferes with activities of daily living (ADL). Among kidney function markers filtered by glomeruli, serum creatinine level is affected by muscle mass but serum cystatin C level is not affected. Both serum markers are used to estimate glomerular filtration rate (eGFR). Therefore, a sarcopenia index (SI) defined by (serum creatinine level / serum cystatin C level) × 100 is proposed as a new measure for estimating skeletal muscle mass.

[Methods] This study is a prospective cohort study to investigate the influence of systemic steroid administration on eGFR and SI in patients who received allogeneic HSCT at our institution from April 2017 to March 2018. Serum creatinine level and serum cystatin C level were measured before the conditioning regimen, 30 days and 90 days after HSCT and the eGFR using these 2 serum markers was calculated: eGFRcre by serum creatinine level and eGFRcys by serum cystatin C level.

[Results] This study included 42 cases with a median age of 49.5 years (range, 19-68 years), and 27 patients were male. At 30 and 90 days after HSCT, eGFRcys was significantly lower than eGFRcre (median: pre-transplantation 96.7 vs. 96.5 mL/min/1.73 m², P = 0.618; 30 days after transplantation 101.6 vs. 76.8, P < 0.001; 90 days 77.3 vs. 71.4, P = 0.006). SI of post-transplantation increased significantly compared with that of pre-transplantation (median: pre-transplantation 118.3; 30 days after transplantation 174.4, P < 0.001; 90 days 138.2, P = 0.001 vs. pretransplantation 118.3; 30 days post-transplantation significantly increased in the group with high cumulative dose of steroids (median: PSL 20 mg/kg or less vs. more than 20 mg/kg, 126.9 vs 165.5; P = 0.028), ECOG-PS and incidence of acute GVHD were not correlated with SI at 90 days (ECOG-PS>1, 134.3 vs. 163.9, P = 0.242; aGVHD Grade II- IV, 127.0 vs. 164.0, P = 0.080; Grade III-IV, 135.3 vs. 148.7; P = 0.374).

[Conclusion] In patients who received high-dose systemic steroid therapy after allogeneic HSCT, SI increased probably because of a reduction in skeletal muscle mass. In such cases, serum creatinine levels might be inappropriate to estimate the kidney function, and serum cystatin C level should be also used to estimate the kidney function.

Keywords: Steroid myopathy;Kidney fuction;eGFR;Cystatin C;Sarcopenia index





Risk factors for thrombotic microangiopathy and its impact on the outcome in patients after allogeneic hematopoietic stem cell transplantation

Abstract Content

[Introduction]

Transplant-associated thrombotic microangiopathy (TA-TMA) is one of the critical complications after allogeneic hematopoietic stem cell transplantation (HSCT), with a reported incidence of 0.5%–75%, which is possibly attributed to the wide variety of diagnostic criteria and challenges in the precise diagnosis. Moreover, no large cohort-based study has determined risk factors for TA-TMA and its impact on the overall survival (OS) based on the uniform diagnostic criteria. An upsurge in higher-risk HSCT for aged patients or from HLA-mismatched donors warrants comprehensive analysis using a recently enrolled large cohort of patients.

[Methods]

In this retrospective cohort study conducted in the Kyoto Stem Cell Transplantation Group, including Kyoto University and its affiliated hospitals, we enrolled adult patients (age ≥16 years) with hematological diseases who underwent allogenic HSCT after 2000. We analyzed a correlation with each pre- or post-transplant factor and the incidence of TA-TMA using the chi-square tests and adjusted confounding factors with multivariate analyses using the logistic regression model. Furthermore, we evaluated the OS in patients with or without TA-TMA using the Kaplan–Meier method after the landmark of day 60 post-HSCT and compared with the Cox proportional hazard model.

[Results]

We enrolled 2,448 patients [median age at HSCT, 47 (range: 16-74) years] in this study. Overall, 1,244 patients were transplanted for acute myeloid leukemia or myelodysplastic syndrome, followed by acute lymphoblastic leukemia (382 patients) and non-Hodgkin lymphoma (NHL; 355 patients). The disease stage at HSCT was advanced (non-remission status) in 1,162 patients (52.4%). The HCT-CI score was higher (≧ 3) in 215 patients (8.8%), and 364 patients (15.5%) were transplanted at poorer performance status (PS 2-4). Regarding donor sources, 476 patients (19.4%) received related bone marrow transplantation (BMT), whereas 427 (17.4%) received related peripheral blood stem cell transplantation (PBSCT), 876 (35.8%) unrelated-BMT, and 669 (27.3%) unrelated cord blood transplantation. The HLA was mismatched in 1,469 (60.0%) patients. After HSCT, 153 patients (6.3%) developed TA-TMA. Regarding risk factors of TA-TMA, poorer PS [odds ratio (OR), 1.55; 95% confidence intervals (CI), 1.02-2.34; P = 0.04], higher HCT-CI (OR, 1.72; 95% CI, 1.06-2.79; P = 0.03), and HLA-mismatch (OR, 1.74; 95% CI, 1.13-2.68; P = 0.01) were significant risk factors for the development of TA-TMA in multivariate analyses. HLA-mismatched HSCT exhibited highest OR for TA-TMA in the PBSCT cohort. (OR, 2.37; 95% CI, 1.08-5.19; P = 0.03). The development of TA-TMA correlated with the remarkably inferior OS (at 3-year with vs. without TA-TMA, 56.3% vs. 20.2%; hazard ratio, 3.19; 95% Cl, 2.56–3.97; P < 0.01). Besides these pre-transplant factors, some post-transplant complications, including cytomegalovirus reactivation, hemorrhagic cystitis, fungal infection, and acute GVHD, correlated the higher incidence of TA-TMA significantly.

[Conclusion]



Using the most updated and largest cohort, this study clarifies the incidence of TA-TMA and risk factors, among which HSCT from HLA-mismatched donors especially in PBSCT was the most prominent. Enough attention should be paid on the development of TA-TMA in case of HLA-mismatched HSCT such as transplantations from haploidentical donors in the future.





The incidence of CMV reactivation and CMV diseases in the haplo-identical hematopoietic stem cell transplantation – a single-center experience

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Abstract Content

Cytomegalovirus (CMV) disease is a major complication after the allogeneic hematopoietic stem cell transplantation (allo-HSCT). Recently, the number of the patients undergoing haplo-identical HSCT increases rapidly because it becomes more difficult to search the fully matched donors. In our study, we tried to compare the incidences of CMV reactivation and CMV disease in the patients receiving allo-HSCT, especially those undergoing haplo-identical HSCT. We retrospectively collected the clinical information of the 537 patients undergoing allo-HSCT at National Taiwan University Hospital (NTUH) between 2013 and 2017. We excluded the patients younger than 20 years at the time of allo-HSCT (n=71), those without comprehensive CMV survey before allo-HSCT (n=5), and those without CMV viral loads after allo-HSCT (n=1). Among the 460 included patients, 110 (23.9%) of them underwent allo-HSCT from haplo-identical donors (haplo-HSCT group), 178 (38.7%) from fully matched sibling donors (MSD group), and 172 (37.4%) from matched unrelated donors (MUD group). The patients in the haplo-HSCT group were younger than others (median age, 42.3 years in haplo-HSCT, 47.5 years in MSD group, and 51.2 years in MUD group, P = 0.000096). The diagnosis and the status of CMV infection were no difference between each group. In the haplo-HSCT group, the proportions of the patients receiving fludarabine, anti-thymocyte globulin (ATG), and post-transplantation cyclophosphamide (PTCy) were higher than others. After allo-HSCT, 94 (85.5%) patients in the haplo-HSCT groups, 104 (64.0%) in the MSD group, and 146 (84.9%) in the MUD group had detectable CMV virus in the serum (P < 0.0001). Eighty-six patients (78.2%) in the haplo-HSCT group, 122 (70.9%) in the MUD group, and 75 (42.1%) in the MSD group had a peak CMV viral load more than 1000 copies/mL. However, only 22 (20%) patients in the haplo-HSCT group, 20 (11.6%) in the MUD group, and 12 (6.7%) in the MSD group experienced CMV diseases (P=0.0197). There was a positive correlation between CMV reactivation and CMV diseases. Fifty-two (18.4%) patients with CMV viral load more than 1000 copies/mL, two (2.8%) with CMV viral load between 150 and 1000 copies/mL developed CMV diseases, but none of the patients without CMV viremia experienced CMV diseases (P < 0.0001). The cumulative incidences of CMV reactivation (Figure. A; defined as CMV viral load more than 1000 copies/mL) and CMV disease (Figure. B) were significantly higher in the haplo-HSCT group than those in other groups. In conclusion, the patients undergoing haplo-identical HSCT had higher incidences of CMV reactivation and CMV diseases compared with other types of allo-HSCT.

Keywords: CMV infection; haplo-identical hematopoietic stem cell transplantation



Management of Evans syndrome following cord blood stem cell transplantation in severe aplastic anemia with rituximab

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Abstract Content

Aim; Evans syndrome is an autoimmune disease, its overall pathology resembles a combination of autoimmune hemolytic anemia and immune thrombocytopenic purpura. The immune dysregulation or incomplete immune reconstitution may be the pathogenetic mechanism leading to the development of this complication. We present a case report of Evans syndrome that occurred after double-unit cord blood transplantation (CBT) in 17-year-old male patient with severe aplastic anemia (SAA).

Case; A 17-year-old male patient who diagnosis with SAA had double-unit CBT. The conditioning regimen consisted of fludarabine, melphalan, and 4 Gy of total body irradiation. Engraftment was achieved with one unit from an O+ female matched for 5/6 HLA antigens; containing 1.2×10^7 /kg nucleated cells with 0.4×10^5 /kg CD34+ cells and another unit from a B+ female matched for 5/6 HLA antigens; containing 1.6×10^7 /kg nucleated cells with 0.5×10^5 /kg CD34+ cells. Complete donor-type chimerism was confirmed on day 35 (98.8% of mean donor cells, donor 1; 89% and donor 2; 9.8%). The Bone marrow biopsy after double-unit CBT revealed normocellular marrow (70% cellularity) on day 30. Six months later, he complained epistaxis and petechia, his peripheral blood counts showed 12.51×10^9 /L WBC, 5.8 g/dL hemoglobin, 27% reticulocytes and a PLT count of 41×10^9 /L. Complete donor-type chimerism was observed (96.1% of mean donor cells, donor 1&2). Laboratory test showed positive direct/indirect antiglobulin test, increased LDH, and indirect hyperbilirubinemia. He received 1 mg/kg/day prednisolone then 375 mg/m2 rituximab weekly $\times 4$ doses. After 3 months, with steroid tapering to 20mg/day of prednisolone, his peripheral blood counts showed 4.47×10^9 /L WBC, 11.4g/dL hemoglobin, 5% reticulocytes and a PLT count of 123×10^9 /L.

Conclusion; We describe a case of Evans syndrome successfully treated with rituximab following doubleunit CBT in severe aplastic anemia who was resistant to steroids.

Keywords: Evans syndrome; transplantation; cord blood; rituximab



Validation of treatment outcomes according to revised EBMT severity criteria for SOS/VOD: A multicenter retrospective study in Korea

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Abstract Content

Sinusoidal obstruction syndrome or veno-occlusive disease (SOS/VOD) is one of the lethal complications after hematopoietic cell transplantation (HCT). Conventional diagnostic and severity criteria were determined retrospectively but inappropriate for therapeutic intervention. Data of 203 patients with SOS/VOD were collected from 6 transplantation centers in Korea between Jan 2011 and Dec 2015, and analyzed for validation of revised EBMT severity criteria. All 203 patients satisfied the modified Seattle criteria, and 125 and 123 patients satisfied the EBMT criteria and the Baltimore criteria, respectively. By traditional severity criteria, mild grade was not observed while 63.1% was moderate and 36.9% was severe SOS/VOD. However, according to the revised EBMT severity criteria, majority of the patients (63.1%) categorized to very severe group followed by 18.2% of severe, 12.8% of moderate, and 5.9% of mild group. The 100-day overall survival (OS) of mild group was 83.3%, moderate group was 84.3%, severe group was 94.6%, and very severe group was 58.6% (Fig 1). The 100-day OS of very severe SOS/VOD was significantly lower than the others (58.6% vs. 89.3%, p<0.0001). The 100-day transplantation-related mortality (TRM) was 25.2% in the entire patients, 8.3% in mild, 8.0% in moderate, 2.7% in severe, and 36.7% in very severe SOS/VOD (p<0.0001). Very severe grade newly subdivided by revised EBMT severity criteria accounted for the majority of SOS/VOD associated 100-day OS and TRM, and intervention should be applied for moderate to severe SOS/VOD at the latest before deterioration.

Keywords: veno-occlusive disease; sinusoidal obstructive syndrome; EBMT; Validation





Hyperbaric Oxygen Therapy for Hemorrhagic Cystitis after the Allogeneic Stem Cell Transplantation-A Case Report

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Abstract Content

Hemorrhagic cystitis (HC) is a significant clinical problem that occurs after allogeneic transplantation and is often refractory. The patient was a 40-year-old man who had HC after two months of transplantation of allogeneic stem cells. Several treatments were used to improve the patient, but no improvement. At the doctor's proposal, 5 sessions of Ozone therapy were performed for the patient, After the completion of the sessions, the clinical symptoms associated with HC disappeared completely. This study shows that HC treatment with ozone therapy is an effective and tolerable method and does not have any clinical complications.





Efficacy and Safety of Defibrotide by Veno-occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS) Diagnostic Criteria in an Expanded-Access (T-IND) Study

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Abstract Content

Introduction: Hepatic VOD/SOS is a potentially life-threatening complication of conditioning for hematopoietic stem cell transplant (HSCT). VOD/SOS with multi-organ dysfunction (MOD; renal and/or pulmonary) may be associated with >80% mortality. Traditionally, VOD/SOS has been clinically diagnosed with Baltimore criteria (bilirubin ≥ 2 mg/dL [34 µmol/L] plus ≥ 2 of hepatomegaly, ascites, and weight gain $\geq 5\%$), modified Seattle criteria (≥ 2 of bilirubin >2 mg/dL, hepatomegaly or right upper quadrant pain, and weight gain >2% [sometimes >5%]), or by biopsy. VOD/SOS is dynamic and may be progressive, and traditional criteria require overt clinical manifestation (eg, Baltimore criteria requires hyperbilirubinemia), which may occur relatively late or not at all, even in the course of severe disease. Defibrotide is approved to treat severe hepatic VOD/SOS post-HSCT in patients aged >1 month in the European Union, and hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the United States and Canada. This analysis compares Day +100 survival in subgroups of post-HSCT patients who were diagnosed with VOD/SOS by Baltimore criteria, modified Seattle criteria, or biopsy, and were treated with defibrotide in the T-IND program (2007–2016).

Methods: The original T-IND protocol (to 2012) required VOD/SOS post-HSCT per Baltimore criteria or biopsy, and MOD; it was amended to include patients without MOD and patients with VOD/SOS per modified Seattle criteria. Diagnosis criterion was selected on the case report form by the investigator. Patients received defibrotide 25 mg/kg/d (6.25 mg/kg q6h) recommended for ≥21 days.

Results: Of 1000 patients in the T-IND with VOD/SOS post-HSCT, 635 (63.5%) were reported as diagnosed by Baltimore criteria, 331 (33.1%) by modified Seattle criteria, and 34 (3.4%) by biopsy. MOD was present in 512 (51.2%) patients (378 [59.5%] in the Baltimore group, 112 [33.8%] modified Seattle group, and 22 [64.7%] biopsy group). Kaplan-Meier estimated Day +100 survival among all defibrotide-treated patients with VOD/SOS post-HSCT was 58.9% (95% CI, 55.7%–61.9%) with 51.6% (95% CI, 47.6%–55.5%) for the Baltimore group, 72.3% (95% CI, 67.0%–76.8%) for the modified Seattle group, and 67.6% (95% CI, 49.2%–80.6%) for the biopsy group. In the subgroups with and without MOD, patterns of Day +100 survival similar to those in the overall population were shown among patients diagnosed by Baltimore vs modified Seattle criteria (**Figure**). Treatment-emergent and treatment-related adverse events (AEs) occurred in 66.4% and 18.8% of all patients, 71.6% and 17.9% of Baltimore patients, 61.2% and 20.5% of modified Seattle patients, and 50.0% and 8.3% of biopsy-proven patients. Hemorrhage occurred in 25.4% of all patients, 28.4% of Baltimore criteria patients, 22.4% of modified Seattle patients, and 16.7% of biopsy-proven patients.

Conclusions: Patients diagnosed by the more stringent Baltimore criteria, which require hyperbilirubinemia, had lower survival rates vs patients diagnosed using modified Seattle criteria or biopsy. Treatment-emergent AEs were consistent with previous reports of defibrotide treatment. The lower overall survival in the Baltimore group suggests that requiring hyperbilirubinemia for VOD/SOS diagnosis may result in patients with more severe disease, leading to worse outcomes. These results corroborate data published by Yakushijin et al (*Bone Marrow Transplant*, 2016).

Support: Jazz Pharmaceuticals.

Keywords: veno-occlusive disease; sinusoidal obstruction syndrome; defibrotide; baltimore criteria; modified seattle criteria



Pooled Analysis of Studies of Defibrotide for the Treatment of Veno-occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS) after Hematopoietic Stem Cell Transplantation (HSCT) or Chemotherapy Without HSCT

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Abstract Content

Introduction: Hepatic VOD/SOS is a potentially life-threatening complication of conditioning for HSCT or of nontransplant-associated chemotherapy. With multi-organ dysfunction (MOD; typically defined as renal and/or pulmonary dysfunction), VOD/SOS may be associated with a 20%–30% Day +100 survival. Defibrotide at 25 mg/kg/day (6.25 mg/kg q6h) is approved to treat severe hepatic VOD/SOS post-HSCT in patients aged older than 1 month in the European Union and to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in Canada and the United States. A pooled analysis was conducted to evaluate Day +100 survival data from defibrotide studies in patients with VOD/SOS with or without MOD.

Methods: Published literature was systematically searched for English-language papers with the term "defibrotide" in the title or abstract published up to July 10, 2017. Case reports with <10 patients were excluded. After screening the initial results for exclusion criteria, the remaining full-text articles were reviewed for eligibility. When necessary, additional data tables for these studies were requested. A random effects model was used to pool efficacy data; interstudy heterogeneity was assessed with Cochran's Q-test. The percentage of total variation across studies was evaluated by the l^{ρ} measure. Reported adverse events (AEs) were reviewed and summarized.

Results: Of 606 citations identified, there were 25 relevant records; 8 of these were excluded because they were *post hoc*, reviews, duplicates, case reports, or a prevention trial. Ten of the remaining 17 records included data for 2073 patients treated with ~25 mg/kg/day. Six of the 10 studies identified patients with MOD (n=1127), with 3 also identifying patients without MOD (n=913). Of all 10 studies, MOD status was not available for 33 patients. The other 7/17 studies included off-label/unreported dosages. Estimated Day +100 survival for patients receiving defibrotide ~25 mg/kg/day across all studies was 56% (95% confidence interval [CI], 49%–62%; **Figure**). Pooled subgroup results showed estimated Day +100 survival rates of 42% (95% CI, 34%–49%) in the MOD subgroup and 69% (95% CI, 61%–77%) in the no MOD subgroup.

Safety results were not pooled due to differences in reporting methodology; however, results of individual studies were generally consistent with the safety profile found in the phase 3 historically controlled trial in VOD/SOS patients with MOD, in which all but 1 of the 102 defibrotide-treated patients and all 32 controls experienced ≥1 AE. Hypotension was the most frequent AE (39% for defibrotide, 50% for controls), and common hemorrhagic AEs (ie, pulmonary alveolar and gastrointestinal hemorrhage) occurred in 64% of defibrotide-treated patients and 75% of controls. Related AEs in the defibrotide arm included hemorrhagic events and hypotension.

Conclusions: In this pooled analysis of studies of defibrotide for the treatment of VOD/SOS (~25 mg/kg/day), estimated Day +100 survival was 56% in the 2073 patients with or without MOD. As expected, estimated survival in the subgroup without MOD was greater at Day +100 (69%) than in the subgroup with MOD (42%). Safety results in the individual studies were generally consistent with the known safety profile of defibrotide.

Support: Jazz Pharmaceuticals.



Keywords: veno-occlusive disease; sinusoidal obstruction syndrome; defibrotide; hematopoietic stem cell transplantation

ALL FOR





The impact of voriconazole antifungal prophylaxis after allogeneic hematopoietic stem cell transplantation compared with fluconazole

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Abstract Content

Background:

Invasive fungal infection (IFI) after hematopoietic stem cell transplantation (HSCT) is a serious complication, and antifungal prophylaxis is recommended for patients undergoing HSCT. In Japan, voriconazole was recently approved for antifungal prophylaxis after HSCT. However, the efficacy of voriconazole for fungal infection has not been evaluated in a real-world setting. Therefore, this study retrospectively evaluated the efficacy of voriconazole compared with that of fluconazole for antifungal prophylaxis after HSCT.

Methods:

We retrospectively analyzed patients who received HSCT in our institution between January 2005 and March 2018. Patients received preventive administration of voriconazole (200 mg, po bid) or fluconazole (200 mg, po qd) from day 0 after HSCT. All patients were placed in laminar airflow rooms until neutrophil reached 1000/µl. Chest computed tomography (CT) scan was performed and serum β D-glucan and galactomannan were measured for patients with persistent fever. IFI was defined using the criteria proposed by the European Organization for Research and Treatment of Cancer and National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG) in 2002; patients categorized as "proven" IFI, "probable" IFI, and "possible" IFI were defined as positive IFI cases. The frequency of CT abnormality, serum β D-glucan and galactomannan elevation, IFI till day 100, and overall survival were compared between voriconazole and fluconazole prophylaxis groups.

Results:

Forty patients (20 voriconazole, 20 fluconazole) were enrolled consecutively. The characteristics of patients in the voriconazole and fluconazole groups were comparable (table 1). There were no significant betweengroup differences in incidence of CT abnormality or serum β D-glucan and galactomannan elevation (table 2). The number of patients in the voriconazole and fluconazole groups who were categorized as proven IFI were 0 and 2, respectively; probable IFI, 1 and 2, respectively; and possible IFI, 3 and 5, respectively (Fisher's exact test, p=0.331, table 2). Of the two patients categorized as proven IFI in the fluconazole group, one patient was diagnosed with invasive aspergillosis by a transbronchial lung biopsy, and the other patient was diagnosed with *Candida parapsilosis* sepsis by a blood culture. Overall survival at day 100 for the voriconazole and fluconazole groups were 79.7% and 75.0%, respectively (Log-rank test, p=0.878).

Conclusions:

Although there was no statistically significant difference in the incidence of IFI between the two groups, the incidence of proven IFI in the fluconazole group was higher than that in the voriconazole group. Additionally, one case of invasive aspergillosis was observed in the fluconazole group. Antifungal prophylaxis with voriconazole may provide added protection against aspergillosis for patients in a laminar airflow room. However, further randomized large-scale studies are necessary to determine the efficacy of voriconazole for antifungal prophylaxis.

Keywords: antifungal prophylaxis, fungal infection, voriconazole




Evaluation of the bacterial and fungal infection status in hematopoietic stem cell transplantation patients in HCMC Blood Transfusion and Hematology Hospital.

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Abstract Content

INTRODUCTION:

Bacterial and fungal infection are the major threat to hematopoietic stem cell transplantation (HSCT) patients and is one of the main causes that contribute to the increased complication and mortality. The aim of this study is to investigate the characteristics of the bacterial and fungal infection and isolated pathogens in hematopoietic stem cell transplantation at our institution.

METHODS:

This study is retrospective descriptions of 113 hematopoietic transplantation recipients from 1/2015 to 3/2018 at HCMC Blood Transfusion and Hematology Hospital, both autologous and allogeneic HSCT. We collected and analyzed the data about conditioning regimens, number of infection episodes, the date when infection occurred, isolated pathogens and antibiotic/antifungal susceptibility ... within first 100 days after transplant.

RESULTS:

The median age at the time of transplantation was 44 (range, 4-66). There were 64 autologous (56.6%) and 49 allogeneic (43.4%) patients. The most common indication for HSCT was hematologic malignancies such as multiple myeloma (31.9%), acute myeloid leukemia (24.8%), non-Hodgkin Lymphoma (17.7%).

There were 20 patients receiving nonmyeloablative HSCT. 108/113 patients (95.5%) were infection following HSCT with 166 infection episodes.

Most infections occurred during the neutropenic period. About one-third of patients had two or more infection episodes. There were 17 patients with positive blood culture, including 3 fungal and 14 bacterial bloodstream infections. 26 infection episodes (15.6%) had isolated pathogen. Gram-negative bloodstream infection was more frequent than Gram-positive (50.4% vs 34.5%). On the other hand, the rate of fungal bloodstream infection was 15.3%. We considered that 50% of Gram-negative bacteria were resistant to Carbapenem and Amikacin. Gram-positive pathogens were still sensitive to both Vancomycin and Teicoplanin. The rate of Amphotericin B susceptibility in fungal infection was 75%. Transplant-related mortality (TRM) at day 100 after transplantation was 4%.

CONCLUSION

The incidence of bloodstream infection was still high, especially during neutropenia. These results will help guide initial antibiotic treatment and develop strategies to prevent bacterial and fungal infection in the future.

Keywords: infection; hematopoietic stem cell transplantation;





Impact of donor-recipient ABO mismatch on outcomes in Allogeneic Haematopoietic stem cell transplant - Indian multicenter data.

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Abstract Content

Abstract

Background: Conflicting results have been reported on the impact of ABO mismatch on various transplant outcomes such as neutrophil and platelet engraftment, acute and chronic graft versus host disease (GVHD), non-relapse mortality and overall survival. Pure red cell aplasia (PRCA) is a known complication which is described after major ABO mismatched transplants. Here we report the first largest ABO mismatch outcome data from multiple transplant centres in India.

Methods: We analysed data of 1104 patients who had undergone allogeneic haematopoeitic stem cell transplant (HSCT), between 2012 to 2016, at 8 different centres across the country. In this study we evaluated the demographic and clinical characteristics of patients, the effect of ABO mismatch and graft source on HSCT outcomes, such as engraftment, graft versus host disease (GVHD), non-relapse mortality (NRM), and overall survival (OS). The incidence of PRCA was not addressed in this analysis.

Results: Out of 1104 patients, 740 (67%) were males, the median age was 23 (range 10- 38yrs) years and 39.6% belonged to the paediatric age group (<18 years). PBSC was the major source of graft (85.5%), and matched sibling donor was predominant (60%). Among the recipients, 55% were ABO compatible, 21% had ABO minor mismatch, 16% had ABO major mismatch and 8% had bi-directional mismatch. Thirty percent of the patients developed acute GVHD (grades I-IV) and 24% developed chronic GVHD. The average time to neutrophil engraftment was 14 days and platelet engraftment was 15 days, which were similar in all patients irrespective of ABO match/mismatch status (p=0.480 and p=0.847 respectively). The 1year, 3 year and 5 year, overall survival rates for the ABO compatible group were 73.6%, 65.5% and 63.5% respectively, compared to 72.6%, 60.5% and 60% for the ABO mismatched group, which was not statistically significant (p- 0.746, 0.298 and 0.262)(Fig 1). The 1year overall survival in the ABO mismatched groups were, 73.0% in minor mismatch, 72.2% in major mismatch and 72.3% in bidirectional mismatch. The overall survival was similar in ABO compatible and mismatch patients irrespective of ABO mismatch grades (Figure 2; p=0.369) with a tendency towards better survival in the bidirectional mismatch group.

Conclusion: Regardless of stem cell source and donor type, ABO mismatch does not influence the outcomes of allogeneic stem cell transplant with regard to engraftment, GVHD and survival rates.

Keywords: ABO MISMATCHED HSCT; GVHD; SURVIVAL



A Prospective Observational Study of Incidence of Early Cytomegalovirus Reactivation and Factors Affecting It Following Allogeneic Stem Cell Transplantation

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Abstract Content

Introduction - Cytomegalovirus (CMV) remains one of the most important complications after allogeneic hematopoietic stem cell transplantation (HSCT) associated with high morbidity and mortality. Multiple co-infecting pathogens including bacterial, opportunistic fungal pathogens, pneumocystis and viral infections can confound the clinical presentation. The number of patients undergoing allogenic HSCT has increased steadily in developing countries, but data is scarce on CMV reactivation following HSCT in India.

Methods -We aimed to evaluate the incidence of early CMV (≤100 days) reactivation following allogeneic HSCT, and study the factors associated with reactivation and time to reactivation. Ninety-seven consecutive patients undergoing allogeneic HSCT for malignant and non-malignant haematological diseases were analysed prospectively for cytomegalovirus reactivation till day +100 post-transplant from March 2017 to April 2018 at Mazumdar Shaw Medical Center, Narayana Health City, Bangalore. Qualitative CMV polymerase chain reaction (CMV PCR) positivity or quantitative CMV PCR >60 copies were considered as criteria for CMV reactivation. Pre-emptive therapy was administered in patients with quantitative CMV PCR ≥1000 copies, or ≥500 copies in high risk transplants such as Cord blood transplants, T-cell depleted transplants and therapies. Information regarding donor and recipient CMV serology status, conditioning regimens, source of stem cells, HLA match, T-Cell depletion, immunosuppressants used and acute graft versus host disease were collected and recorded.

Results -Baseline characteristics of study population are shown in Table.1. Fifty-three patients (54.6%) developed CMV reactivation (Figure.1) and 37 patients (38.1%) required pre-emptive therapy (Figure.2). One patient (1.0%) developed gastrointestinal CMV disease.

Median day of reactivation of cytomegalovirus in this series was 29 days (Range 8-98 days) and median number of CMV copies was 4339 copies/ml (Range 66 to 275,000 copies/ml). Eighteen of 37 treated patients (48.7%) had undetectable CMV copies after 1 week of treatment. Majority of donors and recipients were positive for CMV IgG which constituted eighty-six (88.7%) patients. Multivariate analysis of factors affecting CMV reactivation (on pre-emptive therapy) revealed CMV infection was significantly increased in patients who were receiving steroids ≥10mg prednisone or equivalent (Odds ratio [OR], 5.18; 95% confidence interval [CI] 1.37 to 19.56; P=0.015). While other factors such as mycophenolate (OR 3.41; 95% CI 0.92-12.57; P=0.065) and grade 2-4 acute graft versus host disease (aGVHD) (OR 2.38; 95% CI 0.51 to 10.96; P=0.263) were associated with increased odds to reactivation but were not significant statistically (Figure.3).Median time to reactivation was significantly shortened in anti-thymocyte globulin (ATG) arm(24 days, IQR 12.0-23.0),(P=0.014) compared to non-ATG arm (37 days, IQR 15.0-27.0 days). Among other factors only matched unrelated donor transplantation group showed earlier reactivation (24 days, IQR 20.5-25 days) compared to matched sibling transplantation group (32.5 days, IQR 17.0 to 25.5) but was not statistically significant (P=0.690) (Figure.4).

Conclusion -This study shows that incidence of CMV reactivation burden is significant in post transplantation period ranging from 38.1% to 54.6% depending on criteria for CMV reactivation though CMV disease has drastically reduced in era of pre-emptive therapy. Among factors affecting CMV reactivation, steroids were associated with significantly increased risk of CMV reactivation while ATG was associated with earlier CMV reactivations.

Keywords: CMV REACTIVATION; HSCT



Establishment of novel monitoring assay, digital PCR, for HHV-6 reactivation after allogeneic stem cell transplantation

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Abstract Content

[Introduction] Human herpesvirus 6 (HHV-6) causes life-threating central nervous system disorders such as encephalitis after allogeneic hematopoietic stem cell transplantation (HSCT). Quantitative monitoring of HHV-6 DNA is commonly performed by real-time PCR, but more accurate and sensitive detection methods of HHV-6 DNA are required. In this study, the results of digital PCR methods for detecting HHV-6 DNA in the plasma were shown in comparison with the conventional real-time PCR methods. In addition, we evaluated the risk factors of HHV-6 reactivation detected by this novel method.

[Methods] Thirty-four patients who underwent allogeneic HSCT for hematological diseases at Keio University Hospital (Tokyo, Japan) were consecutively enrolled. Blood samples were collected before conditioning, the day of transplantation, and weekly for the first month after transplantation. After DNA extraction from the plasma, U90 IE-1 transactivator region of HHV-6B was measured by the QuantStudio[™] 3D Digital PCR System. Dynamic range of the assay was determined by the measurement of HHV-6 DNA plasmid. To determine the diagnostic sensitivity, 13 healthy donor plasma samples were also evaluated. The number of HHV-6 DNA copies per reaction was calculated to copies per mL of plasma.

[Results] The copy numbers measured by digital PCR showed high degree of linearity and correlation with the standards ($R^2 = 0.997$). Based on the maximum HHV-6 DNA copy number in healthy donors, more than 7 copies/mL plasma was defined as positive for HHV-6 DNA. Of the 136 samples, the digital PCR had significantly higher detection rate than the real-time PCR (31% vs. 13%, P < 0.01). On individual patient basis, positive resulys were obtained in 23 patients (68%) with digital PCR, while 17 (50%) with real-time PCR. In real-time PCR-positive patients (N = 17), digital PCR became positive earlier in 5 patients. The correlation coefficient of both methods was 0.833 (P < 0.01). In multivariable analysis, peripheral blood stem cell transplantation compared with other sources (odds ratio (OR) = 0.05, 95% confidence interval (CI): 0.00 - 0.65; P = 0.02), and use of anti-thymocyte globulin in the conditioning (OR = 0.05, 95% CI: 0.00 - 0.83; P = 0.04) were significantly associated with the decreased incidence of HHV-6 reactivation.

[Conclusion] The results of our study suggest that digital PCR could be a sensitive and accurate detection method for detecting HHV-6 reactivation after allogeneic HSCT. In future studies, a further optimization is needed for clinical application of this methods.

Keywords: human herpesvirus 6; allogeneic hematopoietic stem cell transplantation; digital polymerase chain reaction; quantitative polymerase chain reaction; HHV-6 reactivation



Successfully treat of severe hemorrhagic cystitis by intravesicle hyaluronic acid in a case of haploidentical stem cell transplant-a case report

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Abstract Content

Introduction

Hemorrhagic cystitis(HC) is one of common complications following Hematopoietic stem cell transplantation (HSCT). Its incidence has been reported from 7-68% with a median time to onset of 30days after transplantation. The risk factors include viral infection,cyclophosphamide and busulfan usage,pelvic irradiation,older age at transplantation, allogeneic HSCT and Graft-versus-host disease(GVHD). The most common treatments for HC were: hyper-hydration, bladder catheter drainage with/without irrigation, platelet transfusion, hyperbaric oxygen therapy. However, there is no better therapeutic strategy of hemorrhagic cystitis after haploidentical transplantation. Here we presented a case of hemorrhagic cystitis after haploidentical transplantation with successful therapy by hyaluronic acide (HA).

Case presentation

A53- year-old male with history of acute myeloid leukemia in 2nd remission status received haploidentical HSCT with a standard conditioning regimen with FB4-PTCy(Cyclophosphamide (29mg/kg), Fludarabine (120mg/kg) and Busulphan(12.8mg/kg) and thymoglobulin (5mg/kg) and post-transplantation cyclophosphamide (PTCy)), Cyclosporine A and MMF(Cellcept)for GVHD prophylaxis were prescribed but he experienced a Grade IV hemorrhagic cystitis with grade 2 of aGVHD.

The gross hematuria and painful voiding pain began on 21 days after transplant with grade 2 of skin GVHD. There was a limit effect after hydration and irrigation by a saline solution via Foley catheter and transfusion therapy with medications. However, gross hematuria with much large clot formation were still noted, requiring irrigated, PRBC and platelet transfusion on a regular basis, and Tranexamic acid treatment. Cystoscopy and biopsy were performed, which revealed chronic cystitis and hemorrhage, compatible with hemorrhagic cystitis. Due to persisted gross hematuria without improvement by previous treatments for more than 100 days, Intravesical HA at a dose of 40mg in a 50ml Solution through Foley catheter irrigated (claimed for 1h and the drained) was start on the Day 127, Day 132, Day 139. Afterward, he became symptom-free and urine turned back to a normal appearance after second dose HA.

Discussion

Zheng FM. et. al found that the cumulative incidence of HC in haploidentical transplantation(HID) around 45.6%. Severe HC often required prolonged and expensive hospitalization and occasionally resulted in death without optimal therapies. Several reviews revealed the promising experience of Hyaluronic acid(HA) treatment in interstitial cystitis. Our case revealed that intravesical HA therapy could help in severe hemorrhagic cystitis after stem cell transplant with promising effects.

Keywords: hemorrhagic cystitis, haploidentical stem cell transplant



An Experience of Donor Lymphocyte Infusion after Reducedintensity Conditioning Allogeneic Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease

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Abstract Content

Back ground: Chronic granulomatous disease (CGD) is an inherited disorder in one of the five subunits of the neutrophilic NADPHoxidase, resulting in the failure of phagocytes to mount the respiratory burst essential for efficient killing of microorganisms. Affected patients experience life threatening bacterial and fungal infections. Allogeneic hematopoietic stem-cell transplantation (HSCT) is a well known curative treatment for chronic granulomatous disease patients. Reduced-intensity regimens (RIC) have been used to diminish transplant-related mortality, but carry the risk of mixed donor-recipient chimerism that may progress to graft loss. The likelihood of graft rejection in the mentioned approach could be reduced by infusions of donor lymphocytes after transplantation. We describe here the experience of our center with a reduced toxicity regimen for patients with CGD and donor lymphocyte infusion (DLI) in those who appeared to have mixed chimerism.

Patients and method: A retrospective analysis was performed in 10 patients with chronic granulomatous disease who underwent a reduced intensity conditioning regimen consisting of melphalan, fludarabine, and antithymocyte globulin. Graftversus-host-disease prophylaxis consisted of cyclosporine A and methotrexate for all patients. Donor lymphocyte infusion was used in three representative patients who developed mixed donor chimerism.

Results: From May 2012 to October 2016, ten patients with CGD were submitted to HSCT in our center. The median age at diagnosis was 10.9 months (range, 2 months-9 years). Three month after HSCT, low donor chimerism (less than 40%) was encountered in 4 patients among which DLI was employed for 3 patients. In the first patient after one episode of DLI, chimerism was reached from 40% to 95%. In two other patients even after three episodes of DLI, donor chimerism sustained in a level about 30% with which patients remained symptom free until the present time (figure 1).

Conclusion: After at least 2 years of follow-up, 8 of the 10 patients are alive and well. HSCT from a matched related donor with a reduced intensity conditioning regimen from an HLA-identical sibling could benefit CGD patients and DLI could be a good hand for those who are leaning towards graft failure.

Keywords: CGD , RIC , HSCT





Repurposing nilotinib for cytomegalovirus infection prophylaxis after allogeneic hematopoietic stem cell transplantation: a singlearm, phase 2 trial

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Abstract Content

Objectives: Platelet-derived growth factor receptor-alpha (PDGFRa) is a critical receptor for CMV entry into cells, leading to subsequent infection. This trial tested whether PDGFRa inhibition by nilotinib could prevent CMV infection in patients after allo-HSCT.

Methods: Nilotinib (200 mg/day) was given continuously after engraftment, and plasma CMV DNA levels were monitored weekly. The primary endpoint was successful prophylaxis of cytomegalovirus infection, defined as plasma CMV DNA copies less than 10,000 copies/ml, no anti-CMV treatment initiated, and no clinical CMV disease, by day 100.

Results: All the thirty-seven enrolled recipients and their donors were CMV seropositive. Thirty patients received matched-siblings transplants, 15 received non-myeloablative conditioning regimens, and 15 received anti-thymocyte globulin as a part of graft-versus-host disease prophylaxis. The median interval from transplantation to nilotinib treatment was 23 days, and the median duration of administration was 76 days. None of the 31 evaluable patients had nilotinib-associated grade 3/4 adverse events or nilotinib discontinuation. Twenty-five out of 31 evaluable patients (80.6%) fulfilled the pre-defined criteria for successful CMV prophylaxis, and none of them had clinical CMV disease. Only one out of the six failed patients developed CMV colitis.

Conclusion: Nilotinib is well tolerated in allo-HSCT recipients, and its preliminary efficacy results suggest that blocking CMV entry to prevent CMV infection may warrant further exploration. (ClinicalTrials.gov identifier: NCT01252017)

Keywords: cytomegalovirus; stem cell transplantation; PDGFRa; nilotinib



Liver transplantation for the treatment of hepatic veno-occlusive disease after allogeneic hematopoietic stem cell transplantation

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Abstract Content

Introduction

Liver transplantation (LT) can be considered as a veno-occlusive disease (VOD) treatment, but it is not a clinically easy procedure. We summarized the case of liver transplantation in adult VOD patients after allogeneic stem cell transplantation.

Method and Results

A 34-year-old man was diagnosed with Philadelphia chromosome negative B-cell acute lymphoblastic leukemia. The patient treated with VPDL induction regimen, resulting in complete remission. Following 4 cycles of consolidation chemotherapies, he underwent allogeneic HSCT (allo-HSCT) from an 8/8 matched unrelated donor. The myeloablative conditioning regimen consisted of busulfan and fludarabine, and prophylaxis against VOD was performed with UDCA and PGE1.

On the day 20 of allo-HSCT, he appealed for right upper quadrant (RUQ) pain, anuria, and weight gain (>5% of baseline at transplant). A blood test revealed a WBC of 25,800 /µL, PLT of 72,000 /µL, creatinine of 6.25 mg/dL, AST of 358 IU/L, ALT 256 IU/L, and a total bilirubin (TB) of 1.3 mg/dL. There were no symptoms that could be suspected of acute GVHD. In Doppler ultrasound, hepatic veins showed a relatively triphasic waveform but the flow of portal vein was decreased, and a lot of ascites was founded (Fig.1). Hepatic VOD was most suspected and subcutaneous injection of LMWH 1mg/kg twice a day was started. Conventional hemodialysis (cHD) was also started. On the day 23 of allo-HSCT (after 4 days of heparin treatment), weight gain (>10% of baseline at transplant) persisted, and the TB elevated to 2.2 mg/dL. According to the EBMT criteria, severe VOD was diagnosed and the treatment of defibrotide was started. A total of 97 days of defibrotide-treatment was maintained, however, symptoms due to VOD persisted. A transjugular liver biopsy was performed sinusoidal dilatation with congestion and hemorrhage and obstruction of a central vein by fibrin and fibrosis were observed (Fig.2).

We concluded the defibrotide-treatment failed, and prepared the LT. First, bone marrow (BM) study and short tandem repeats analysis (STRA) were performed to confirm that his leukemia was well controlled. The BM study showed hypocellular marrow without residual leukemic blasts. STRA showed complete engraftment of donor cells. Second, the ABO typing of the patient was examined to determine the ABO type of the LT donor. He underwent major ABO-incompatible allo-HSCT (recipient; A+, donor; AB+). The ABO typing showed that cell [A:4+, B:3+] and serum [Anti-A:-, Anti-B:1+]. We conclude that it is most appropriate to receive a liver transplant from an AB donor. After 30 days of discontinuation of the defibrotide, the patient received a cadaveric LT from a donor of type AB. After LT, symptoms due to VOD, and liver function test abnormalities were all normalized, but the cHD was maintained. The patient has been currently undergoing outpatient follow-up without recurrence of leukemia one year after liver transplantation.

Conclusion

Liver transplantation can be considered as the treatment of hepatic VOD after allo-HSCT in adults. More studies are needed to determine the criteria for medical treatment failure and the selection of liver transplant donor.

Keywords: Hepatic veno-occlusive disease; Liver transplantation





Validation of recently proposed risk and prognostic factors for thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia

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Abstract Content

Background

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a significant complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and may affect 20% of recipients on average. A few groups have proposed risk or prognostic factors for TA-TMA, including a recent prospective study in a cohort with children and young adults (Jodele *et al.* Blood 2014), yet there has been no reproducing or validating data for a consensus. Furthermore, with rapid advances in transplantation technology, such as a variety of donors, conditioning regimens, and graft-versus-host disease (GVHD) prophylaxis, currently used diagnostic criteria for TA-TMA need to be re-evaluated using recent large cohorts.

Patients and methods

We retrospectively analyzed 613 consecutive patients with acute myeloid leukemia (AML) who received allogeneic hematopoietic stem cell transplantation (allo-HSCT) from matched siblings (n=260), matched unrelated donors (n=167), or haploidentical family donors (n=186) from 2012 to 2017. In this study, TA-TMA was diagnosed primarily with previously published diagnostic criteria proposed by our group (Cho *et al.* Transplantation 2010). Then, we investigated risk and prognostic factors in this recent large cohort. In addition, particularly, predictive factors for TA-TMA suggested by Jodele *et al.* were validated in adult AML patients.

Results

The cumulative incidences of MAHA positivity above 2/HPF and TA-TMA were 20.4% (n=116) and 12.6% (n=71). MAHA positivity and TA-TMA were each strongly related to poor overall survival, of 17.5% and 13.0%, respectively. Univariate and multivariate analyses revealed that haploidentical allo-HSCT, grade III-IV acute GVHD, LDH >1.5 x upper normal limit (UNL), and proteinuria \geq 30mg/dL were each significantly associated with an increased risk of TA-TMA (*p*<0.001). In addition, proteinuria, elevation of LDH, and grade III-IV acute GVHD occurred a median of 31.6 days, 45.0 days, and 73.4 days prior to TA-TMA diagnosis, respectively. In 71 patients with TA-TMA, grade III-IV acute GVHD (hazard ratio (HR) 1.947, *p*=0.01918) was the only factor significantly related with inferior survival (<20% at one year).

Conclusion

This study validates the feasibility of diagnostic criteria for TA-TMA proposed by our group in a recent large cohort with AML, and points out the role of haploidentical familial transplantation as a risk factor for TA-TMA in AML. Of note, proteinuria and elevation of LDH prior to the appearance of MAHA proposed by Jodele *et*



al. with a younger population were also validated in this adult population with AML, suggesting the importance of their careful monitoring as predictive factors for TA-TMA.

Keywords: TA-TMA;AML;HSCT;Haploidentical'Proteinuria





Effect of Immunoglobulin G2 subclass level on late-onset bacterial infection after allogeneic hematopoietic stem cell transplantation

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Abstract Content

[Introduction] Immunoglobulin (Ig) G2 subclass deficiency is known to be associated with recurrent bacterial respiratory infections caused by capsulated bacteria. Its impact after allogeneic stem cell transplantation (HSCT) has not been fully assessed, mostly evaluated in pediatric patients.

[Methods] We retrospectively evaluated the IgG2 subclass and infectious episodes in 74 adult patients who survived longer than 2 years after HSCT. Patients with severe hypogammaglobulinemia (serum IgG less than 400mg/dl) and / or receiving Ig replacement were excluded. Data were collected from the institutional database and the medical records and retrospectively and cross – sectionally analyzed. This retrospective analysis was approved by the Institutional Review Board of Keio Medical University.

[Results] IgG2 level was significantly correlated with total IgG level (rank correlation coefficient was 0.586, P < 0.0001), but 6 patients (8.1 %) with suboptimal IgG2 level showed normal serum IgG level. In multivariate analysis, ongoing corticosteroid therapy (odds ratio: 265.0, 95%CI: 10.8 – 6530.0, P < 0.001), history of rituximab therapy (odds ratio: 300.0, 95%CI: 16.6 – 5400.0, P < 0.0001), cord blood as stem cell source (odds ratio: 17.1, 95%CI: 2.3 – 126.0, P < 0.01) and the short duration after HSCT (odds ratio: 17.7, 95%CI: 1.7 – 184.0, P < 0.05) had significantly associated with suboptimal serum IgG2 level. Furthermore, it revealed that the IgG2 / IgG ratio significantly declined in patients after rituximab therapy (odds ratio: 9.13, 95%CI: 1.82 – 45.9, P < 0.01) and cord blood stem cell transplantation (odds ratio: 4.84, 95%CI: 1.15 – 20.4, P < 0.05) in multivariate analysis. Nine of 74 patients were suffered from severe bacterial pneumonia. Not only serum IgG2 levels but also IgG2 / IgG ratio were significantly lower in patients with infectious episode than those without (143 mg/dl vs. 287 mg/dl; P < 0.01, 0.19 vs. 0.26; P < 0.05).

[Conclusion] Especially for the patients after cord blood transplants and rituximab treatments, attention will be required to late recovery of serum IgG2 level. Suboptimal serum IgG2 level could contribute to the susceptibility to bacterial infection even several years after allogeneic HSCT.

Keywords: Immunoglobulin G2 deficiency; Capsulated bacteria; Streptococcus pneumoniae; pneumonia; allogeneic hematopoietic stem cell transplantation



Favorable long-term outcome of nephrotic syndrome in patients after allogeneic hematopoietic stem cell transplantation.

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Abstract Content

Background :

Chronic graft-versus-host disease (cGVHD) is one of the most common late complications after allo-HSCT, which affects the kidneys can lead to nephrotic syndrome (NS). The etiology and pathogenesis of this disease are still unclear. In this study I, we investigate the clinical manifestations, pathological features, prognosis of NS, and to analyze the possible risk factors for NS after allo-HSCT.

Methods:

This study analyzed 1130 patients who had survived for more than 100 days after allo-HSCT in our center from June 2007 to March 2008. Ten patients developed NS. Forty patients after Transplantation in the same period were selected as control group. Nested case-control study was used to study the clinical manifestations, pathological features, curative effect. The risk factors were further analyzed, including sex, age, serum cholesterol level, serum triglyceride level, immunosuppressive status in NS patients, as well as HLA matching, donor-recipient blood group, cytomegalovirus (CMV) infection, acute graft versus host disease(aGVHD), and aGVHD in organs other than kidneys. Statistical analysis using SPss22.0 statistical software univariate and multivariate Logistic regression analysis.

Results:

Ten patients (0.885%) had post-transplant NS with median onset 15.95 (5.39-48.39) months. Three had aGVHD and 5 had cGVHD in other organs. Nine cases of NS underwent renal biopsy, including 8 cases of membranous nephropathy (MGN) and 1 case of minimal change (MCD). One patients were not punctured because of low platelets counts. With the treatment of immunosuppressive agents (calmodulin inhibitors and/or glucocorticoids), complete remission (CR) was achieved in 8 cases, partial remission (PR) in 1 case who died of pulmonary infection. Chronic renal failure in 1 case due to ineffective treatment (NR). In the 8 patients with CR, 1 died of advanced esophageal cancer, 7 survived with CR, 6 survived without leukemia, and 1 survived with remission after relapse. The urine protein was continuously negative in 7 patients, the serum protein and lipid levels were normal. Univariate analysis showed that the incidence of NS was not significantly correlated with gender, age, HLA matching, donor-recipient relationship, aGVHD, cGvHD, serum triglyceride and cholesterol levels before transplantation, triglyceride levels half a year after transplantation and cholesterol levels 1 year after transplantation. There was a statistical trend in cholesterol level in half a year after transplantation (P = 0.07) and triglyceride level in one year after transplantation (P = 0.076). Multivariate analysis showed that there was significant difference in CMV infection (P = 0.011) and triglyceride level (P = 0.045) one year after transplantation. The 5-year OS in the observation group and the control group were 88.9% and 75.7% respectively (P = 0.815). The 5-year RFS in the observation group and the control group were 77.8% and 76.6% respectively (P = 0.891).

Conclusion:

NS after Allo-HSCT is a rare complication. The major pathological type is MGN, followed by McD. NS may be a clinical manifestation of chronic GVHD. Calmodulin inhibitors combined with glucocorticoids are effective and most patients can achieve long-term disease-free survival. CMV infection after transplantation and high serum triglyceride level one year after transplantation are risk factors for NS after allo-HSCT.

Keywords: nephrotic syndrome; chronic graft-versus-host disease; allogeneic hematopoietic stem cell transplantation.





Invasive Fungal Infections after Hematopoietic Stem Cell Transplantation in Taiwan – Data from Taiwan Blood and Marrow Transplantation Registry (TBMTR)

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Abstract Content

Introduction:

Invasive fungal infection (IFI) is an important threat after hematopoietic stem cell transplantation (HSCT). In this abstract, we describe the current status of IFI after HSCT in Taiwan from the data in Taiwan Blood and Marrow Transplantation Registry (TBMTR).

Methods:

We analysis the data collected from 17 HSCT centers participating in the TBMTR program from 2009 to 2016. The diagnosis of IFIs was defined by the revised 2008 EORTC/MSG criteria, and only infections before relapse are accounted. Mold and candida infections are analyzed separately, and only the first infection episode was accounted.

Results:

There are 2874 HSCT events in this analysis, including 1285 autologous HSCTs (auto-HSCTs) and 1589 allogeneic HSCTs (allo-HSCTs). Totally 172 IFI events were noted, with 151 proven/probable IFIs and 21 possible IFIs. The 2-year cumulative incidence of all-category IFIs is $11.1\pm1.1\%$ for allo-HSCT, and $6.0\pm0.9\%$ for auto-HSCT. The most prevalent site of IFIs is lower respiratory tract (52%), followed by blood stream (20%). Aspergillus infections take 66.7% of proven/probable infections, *Candida spp.* infections take 26.8%, and mucormycosis 2.4%. Their survival after IFIs was poor: the median survival time after all-category IFIs was 15.3 months for allo-HSCT recipients; IFIs are also an independent prognostic factors for survival in multi-variate analysis. In univariate analysis, age above 45 y/o, grade 2-4 GVHD, reduced-intensity condition, CMV infection/disease and previous IFIs are the risk factors for IFIs, but only grade 2-4 GVHD and previous IFIs are predicting factors for IFIs in multivariate analysis.

Conclusion:

In TBMTR data, the incidence of IFIs in Taiwan is among the highest ones in the world, probably due to the environmental factors and other treatment-related factors. The prognosis of IFIs after HSCT is poor, no matter in auto-HSCT or allo-HSCT recipients. And currently CMV infection/disease is found as a predicting factor for IFIs after HSCT.

Keywords: Hematopoietic stem cell transplantation, Invasive fungal infections, Taiwan Blood and Marrow Transplantation Registry



Adoptive donor immunity protects resolved HBV reactivation after allo-HSCT in the world's largest single center study

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Abstract Content

Reactivation of hepatitis B virus (HBV) by seroconversion (HBV-RS) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been intermittently reported in patients with resolved HBV infection (rHBV, defined as negative HBV surface antigen and positive anti-HBV core-antigen antibody), and may cause fatal hepatitis. But the incidence, risk factors, and outcome were seldom defined. We enrolled 950 patients in this largest single center cohort study. The 3-year and 5-year cumulative incidence of HBV-RS after allo-HSCT was 8.7% and 10.5%, respectively, with a median 16 months after allo-HSCT. Nineteen percent of rHBV developed HBV flares, but none experienced hepatic decompensation or hepatic failure, neither did it impact non-relapse mortality or overall survival after allo-HSCT in this study. Multivariate analysis revealed that transplantation from a donor lacking anti-HB surface-antigen antibody (anti-HBs) immunity protection, and extensive chronic graft-versus-host disease (cGVHD) were independent risk factors for HBV-RS. Patients with the two risks had the highest 5-year incidence of HBV-RS, which may alter future donor selection algorithm, and combining the extensive cGVHD provides a good prediction model for HBV-RS after allo-HSCT.

Keywords: Reverse seroconversion; resolved hepatitis B infection; allogeneic stem cell transplantation, risk factors



Identifying important factors that influence the quality of life in survivors after allogeneic bone marrow transplantation in childhood

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Abstract Content

Introduction

Quality of life (QOL) is one of the most important issues faced by survivors who have undergone allogeneic bone marrow transplantation (BMT) in childhood. Identifying factors that have adverse impacts on QOL after transplantation is the first step to improve QOL after allogeneic BMT.

Methods

We conducted a nationwide cross-sectional study including 2-year treatment-free survivors who underwent allogeneic BMT at 20 years old or younger between 1995 and 2009. The survivors completed the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Multidimensional Fatigue Scale (aged 15 years or younger) or the 36-Item Short Form (SF-36) (older than 15 years) questionnaires. Multivariate logistic regression analysis was performed to identify factors significantly influencing QOL, based on the results of bivariate analyses (*P*-value <.20) and previous studies. The objective variables were six summary scores: PedsQL (below the mean score or not) Physical Summary, Psychosocial Summary, and Total Fatigue Scores; and SF-36 (below -1 standard deviation score from the mean score or not) Physical, Mental, and Role/Social Component Summaries.

Results

Data of 102 survivors from the PedsQL and 179 survivors from the SF-36 were available. The mean age when the surveys were completed were 12.47 ± 2.10 and 21.42 ± 4.22 years, respectively. Diagnoses were acute lymphoblastic leukemia (33.3% and 32.4%, respectively), hematopoietic injury (28.4% and 23.5%, respectively), and acute myeloid leukemia (12.7% and 17.3%, respectively), followed by various hematological diseases.

PedsQL: Survivors with chronic graft-versus-host disease (cGVHD) showed lower Psychosocial Summary Scores (adjusted odds ratio (AOR) = 3.13, 95% confidence interval (CI): 1.03-9.49). A greater number of years after BMT correlated with higher Psychosocial Summary Scores (AOR = 0.80, 95% CI: 0.64-0.99) and Total Fatigue Scores (AOR = 0.81, 95% CI: 0.65-1.00).

SF-36: Survivors with cGVHD showed lower Physical Component Summaries (AOR = 3.99, 95% CI: 1.16-13.80) and Role/Social Component Summaries (AOR = 7.94, 95% CI: 1.99-31.7). Older age when the survey was completed correlated with lower Physical Component Summaries (AOR = 1.17, 95% CI: 1.01-1.36) and Role/Social Component Summaries (AOR = 1.16, 95% CI: 1.00-1.34). There were no significant relationships between the Mental Component Summary and explanatory variables.

Conclusion



Older age, shorter period after BMT, and cGVHD showed significant adverse impacts on various aspects of QOL in survivors. Pediatric patients with cGVHD who underwent BMT at an older age seem to be followed up carefully, especially in the earlier period after BMT. Organization of total supporting systems for survivors with cGVHD may be very important. In addition, more effective prophylaxis of cGVHD should be developed.

Keywords: QOL; Pediatric patients; cGVHD



Blinatumomab use in pediatric and adolescent patients with relapsed/refractory B-precursor acute lymphoblastic leukemia from an open-label, multicenter, expanded access study

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Abstract Content

Introduction: Blinatumomab, a bispecific T-cell engager antibody construct, has shown antileukemia activity and tolerability in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL). We further evaluated safety and efficacy of blinatumomab in pediatric and adolescent patients with relapsed/refractory B-precursor ALL enrolled in an expanded access study (NCT02187354).

Methods: Eligible patients (aged >28 days to <18 years) had \geq 5% blasts and relapsed/refractory Bprecursor ALL (refractory to prior treatments, 2nd or later relapse, or relapse after allogeneic hematopoietic stem cell transplantation [alloHSCT]). Blinatumomab was dosed by continuous intravenous infusion (4 weeks on/2 weeks off) for up to 5 cycles (\geq 5 to <25% blasts: 15 µg/m²/day; \geq 25% blasts: 5 µg/m²/day on days 1–7 in cycle 1, then 15 µg/m²/day). The primary endpoint was incidence of treatment-emergent (TE) and treatment-related (TR) adverse events (AEs). Key efficacy endpoints were complete response and minimal residual disease (MRD) response (defined as <10 4 leukemic blasts by PCR or flow cytometry) within the first 2 cycles, relapse-free survival, overall survival, and incidence of alloHSCT.

Results: Among the first 40 treated patients (median age, 9 [range, 1–17] years), 24 (60%) had experienced \geq 2 relapses, 20 (50%) had relapsed after alloHSCT, and 5 (13%) were primary refractory; 18 (45%) had \geq 50% blasts and 21 (53%) had prior alloHSCT. Safety and key efficacy outcomes are shown in the table. Twenty-five patients (63%) achieved a complete response within the first two cycles, 19 of whom had an MRD response. Eight patients relapsed and 20 died after treatment. Regardless of causality, the most frequent TEAEs were pyrexia (78%), cytokine release syndrome (CRS; 23%), vomiting (23%), and anemia (20%). All nine CRS events were grade 1 or 2 and one tumor lysis syndrome was grade 3. Ten (25%) patients interrupted treatment and 2 (5%) discontinued due to TRAEs; 13 (33%) patients had grade \geq 3 TRAEs, including two of three neurologic events (depressed level of consciousness and headache; both grade 3). Two patients experienced fatal AEs, both of which were considered unrelated to blinatumomab.

Conclusions: Blinatumomab showed antileukemia activity in pediatric and adolescent patients with highrisk relapsed/refractory B-precursor ALL including t(17;19) and AEs were consistent with those previously reported for relapsed/refractory ALL.

	All Patients N=40
All TEAEs, n (%)	39 (98)
Grade 3	15 (38)
Grade 4	12 (30)





^aWithin the first 2 cycles

Keywords: acute lymphoblastic leukemia; Blinatumomab; pediatric; adolescent



In the second second

Topic: Pediatric transplants Abstract No: 8737

Hematopoietic stem cell transplantation for pediatric acute promyelocytic leukemia in Japan: A nationwide retrospective study

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Abstract Content

BACKGROUND: Combining upfront all-trans retinoic acid (ATRA) therapy and chemotherapy has led to marked progress in the treatment of pediatric acute promyelocytic leukemia (APL), and the number of hematopoietic stem cell transplantation (HSCT) procedures performed for pediatric APL has decreased in the ATRA era. Autologous HSCT (auto-HSCT) was considered to be effective for pediatric APL patients who were in their 1st complete remission (1CR) before the ATRA era, and HSCT is still widely used as a salvage therapy for relapsed patients. However, there have not been any reports about the results of HSCT in pediatric APL, and is no general consensus about the optimal transplant type (auto-HSCT), especially for relapsed patients. Therefore, we performed a retrospective analysis of nationwide registration data to assess the HSCT outcomes of pediatric APL patients.

PATIENTS & METHODS: We retrospectively reviewed the clinical data of 95 APL patients (48 males and 47 females; age: 0-19 years old) who underwent their first HSCT between 1989 and 2014 and were registered in the Japan Society for HSCT Registry. Their median age at HSCT was 13 (range: 0-19) years. Of the 95 patients, 40 (42%), 41 (43%), and 3 (3%) underwent HSCT procedures after achieving their 1CR, 2CR, and 3CR, respectively, and 11 (12%) underwent HSCT while in a non-CR state. Thirty-three (19 in 1CR/14 in >2CR) patients received auto-HSCT, whereas 62 (21 in 1CR/41 in >2CR) received allo-HSCT. The historic and ATRA periods were defined as 1989-1995 and 1996-2014, respectively. Various subgroup analyses were performed.

RESULTS: The non-CR group exhibited significantly worse 5-year overall survival (5yOS) and disease-free survival (5yDFS) (5yOS: 46%, 95% confidence interval [CI]: 17%-71%; 5yDFS: 46%, CI: 17%-71%) than the 1CR (5yOS: 80%, CI: 64%-89%; 5yDFS: 78%, CI: 61%-88%) and 2CR+3CR groups (5yOS: 81%, CI: 66%-90%; 5yDFS: 76%, CI: 61%-87%) (*P*=0.013 and *P*<0.01 for 5yOS and 5yDFS, respectively). Although 5yOS did not differ significantly between the auto-HSCT and allo-HSCT groups (73%, CI: 46%-88%, vs. 86%, CI: 62%-95%; P=0.47), the 5-year cumulative incidence of relapse (5yRI) was significantly higher after auto-HSCT (32%, CI: 12%-53%) than after allo-HSCT (5%, CI: 0.3%-20%) (P=0.03) in the CR1 group. Only 9 patients underwent HSCT during CR1 after 1996 (the ATRA era). Of the patients treated in CR2, no significant differences in 5yOS or 5yRI were detected between the auto-HSCT and allo-HSCT groups (5yOS: 85%, CI: 60%-90%, vs. 80%, CI: 51%-96%, P=0.72; 5yRI: 9%, CI: 0.4%-33%, vs. 11%, CI: 3%-25%). Among the patients that underwent allo-HSCT in CR2, those with matched sibling donors displayed a significantly higher 5yRI (30%, CI: 6%-59%) than those with other types of donors (0%, P=0.02).

CONCLUSIONS: Advances in treatment have reduced the frequency of HSCT in CR1 among pediatric APL patients. Relapsed and refractory pediatric APL can be cured with HSCT if CR is achieved, and there was no significant difference in 5yDFS or 5yOS between auto-HSCT and allo-HSCT performed in CR2. These findings demonstrate that auto-HSCT and allo-HSCT are both effective therapies for treating children with relapsed or refractory APL.

Keywords: APL, children, auto-HSCT, allo-HSCT, ATRA era



Disease free survival in paediatric malignant disorders with cost effective care after haploidentical stem cell transplantation with post-transplant cyclophosphamide: a single centre experience from south India

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Abstract Content

Background

We present data over 5 years in children who underwent haplo SCT with PTCy for malignant disorders and the efficacy and feasibility of this modality in achieving disease free survival.

Patients and methods

We performed a retrospective analysis of case records of children up to the age of 18 years who were diagnosed to have malignancies and had undergone haplo SCT with PTCy from January 2014 to April 2018 at the paediatric blood and marrow transplant unit.

Results

A total of 24 children underwent haplo SCT of which 11 (45%) were diagnosed to have acute lymphoblastic leukaemia (ALL), 10 (41%) with acute myeloid leukaemia (AML) and one child each with mixed phenotype acute leukaemia (MPAL), chronic myeloid leukaemia with ALL blast crisis and relapsed Hodgkins lymphoma after autograft. Disease status at the time of HSCT was CR1 in 8 (33%), CR2 in 15 (62%) and active disease in one child with AML M7. Source of stem cells were predominantly peripheral blood in 22 (91%) children and bone marrow in 2 (9%). Donors were siblings in 5 (20%), mother in 2 (8%) and father in 17 (70%) children after screening for anti-HLA antibodies. Conditioning included Fludarabine /Melphalan in 7 children with AML, Fludarabine/Treosulphan/ TBI 2Gy in 6 children with ALL, Fludarabine/ TBI 12 Gy in 9 children with ALL, Flu/Cy/TBI 2Gy in the child with Hodgkins lymphoma and Thiotepa/Flu/Bu in one child with therapy related AML. Median CD34 infused was 5.6 x 10*6/kilogram recipient body weight. Engraftment by D+17-21 was achieved in 21/24 (90%) children with primary graft failure in 2 (8%) and one child dying before engraftment from sepsis. Among those who engrafted, acute GvHD was noted in 13/21 (61%) and CMV reactivation in 15/21 (71%) transplants. Grade I/II GvHD was noted in 9/13 (69%) responsive to steroids and grade III/IV was seen in 4 (30%), none being a direct cause of death. Among children with CMV reactivation 93% were responsive to valganciclovir and one child died due to refractory CMV disease. Donor lymphocyte infusions were given pre-emptively in 11 (45%) children. Relapse was noted in 2/21 (9%) children who engrafted with disease free survival of 91% in our cohort. However, overall survival was 16/24 (66%) in our cohort with varied causes of death. One child died of disseminated microsporidiasis 4 months post HSCT, another of pneumonia 9 months post HSCT and one of sepsis 6 months post HSCT. Two children died of primary graft failure, one each due to CMV disease, relapse and gram-negative sepsis. Among the 8 children who died, 6 (75%) were in CR2 while 2 (25%) were in CR1.

Conclusion

Excellent relapse free survival can be achieved with haplo SCT and PTCy in children with malignant disorders particularly in those in CR1. CMV reactivation can be high which requires monitoring. Conditioning needs to modified based on patient characteristics and tolerability with myeloablative conditioning being well tolerated. PTCy priced at USD 25 is an excellent cost-effective modality of T cell depletion with tolerable rates of GvHD.

Keywords: haploSCT ; children ; malignancy ; PTCy ; survival



Superior survival rates using peripheral blood stem cells in transplanting children with acquired aplastic anaemia in developing countries: experience over 15 years from a paediatric transplant unit in India

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Abstract Content

Background

With the increasing incidence of drug resistant infections particularly in developing countries and risk of sudden onset life-threatening bleeds in acquired aplastic anaemia, early and sustained engraftment is imperative. Peripheral blood stem cells (PBSC) provide the earliest engraftment albeit with a risk of graft versus host disease (GvHD). We present our experience where capping CD34 cell dose to 5x10⁶/kg recipient body weight in PBSC grafts can result in excellent disease free, event free and overall survival.

Patients and methods

This retrospective, uncontrolled study was conducted at the Paediatric blood and marrow transplantation unit at Apollo Cancer Institutes, Chennai, India. All children less than 18 years of age who were diagnosed to have SAA and VSAA and underwent HSCT from 2002 to February 2018 were included in the study. Data was collected on their source of stem cells, the CD34 cell dose infused, pre- and post-transplant clinical course and outcome in terms of engraftment, incidence of GvHD, DFS, EFS and OS.

Results

A total of 29 children diagnosed to have SAA and VSAA underwent HSCT including 13 girls and 16 boys, median age being 10 years. 12 had received more than 15 PRBC and platelet transfusions prior to HSCT, 11 children had more than 1 admission for febrile neutropenia. Source of stem cells included matched sibling donor in 20/29 (68%), haplomatched donor in 9/29 (31%). PBSC was used in 26/29 (90%) and bone marrow in 3 (10%). Average CD34 cells infused were 5.68 x 10⁶/kg recipient body weight. Engraftment by D+14 was note in 24 (82%) children with sustained complete chimerism in 23/24 (95%) transplants. Of the 24 that engrafted, 6 (25%) have chronic GvHD requiring low dose steroids. Two children died of sepsis prior to engraftment, two of primary graft failure, two of late sepsis and one of HHV6 encephalitis, with 87% of these having received more than 25 transfusions prior to HSC. Mortality in this cohort is 27% with an EFS 75% and OS 73%.

Conclusion

PBSC grafts in children with acquired aplastic anaemia ensure early engraftment rates of 82%. A 25% risk of chronic GvHD can be minimised by capping CD34 stem cell dose to 5 times. With increasing drug resistant organisms, PBSC as a source of stem cells would provide improved survival rates in this high risk but curable condition, particularly in developing countries.

Keywords: aplastic anaemia; pbsc; children ; survival





Haematopoietic stem cell transplantation for children with inherited bone marrow failure syndromes: a single centre experience over 15 years from India

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Abstract Content

Background

We present data over 15 years in children who underwent haematopoeitic stem cell transplantation (HSCT) for inherited bone marrow failure syndromes (IBMFS).

Patients and methods

We retrospectively analysed case records of children diagnosed to have IBMFS and who underwent haematopoietic stem cell transplantation from 2002 to April 2018 at the paediatric blood and marrow transplantation unit.

Results

A total of 68 children with IBMFS have been transplanted at our centre with Fanconi anaemia (FA) 51, congenital amegakaryocytic thrombocytopenia (CAMT) 5, pure red cell aplasia (PRCA) 9, Schwachmann Diamond syndrome (SDS) 3 transplants in 1 child.

Among children with FA, donor source was MFD in 28 (54%), MUD 2 (4%), UCB 7 (13%), haplo SCT in 14 (27%). Source of stem cells was PBSC in 39 (76%), UCB 7 (13%), bone marrow in 5 (10%). Engraftment by D+16-21 was achieved in 72% with 6 (11%) children dying before engraftment. Rate of acute GvHD was 13 (25%) and chronic GvHD 6 (11%). Overall mortality rate is 25 (49%) with survival rate of 51%. Causes of death are varied with GvHD in 9, primary graft failure in 2, sepsis in 8, AML in 2, AML 8 years post HSCT in 1, PTLD 3 years post HSCT in 1, intracerebral haemorrhage in 1 and peliosis hepatis in 1 child.

We performed subset analysis among FA patients where rejection rates were found to be 17% in MFD, 14% with UCB and 14% with haplo SCT. GvHD was seen in 14% of those with MFD of which 3 / 4 (75%) died due to GvHD. Both the children with MUD HSCT died due to severe GvHD. Among those who received UCB, GvHD was seen in 2 and both died due to GvHD. Among the haplo SCTs, GvHD rates are high at 42%, of which 2/6 died due to GvHD and 70% of these were responsive to steroids. In our cohort among FA patients, survival rates are 54% with MFD, 29% with UCB, 0% with MUD and 65% with haplo SCTs.

Among the 5 children with CAMT, 4 received haplo SCTs of which two died before engraftment and one child received MFD and died due to GvHD. Among those with PRCA, 5 received MFD, 2 MUD, one each with UCB and haplo SCT. Engraftment was achieved in 90%, one child died prior to engraftment. GvHD was seen in 3/9 (33%) of which one child died due to GvHD and the others are steroid dependant. Overall survival rate is 68%. One child with SDS underwent transplants thrice, which never engrafted and died due to primary graft failure.

Conclusion

IBMFS need trained paediatric transplant physicians with paediatric intensivists to provide optimal care and outcome with engraftment rates of 72% and overall survival of 51% among FA children. Haplo SCTs provide a feasible alternative in case of unavailability of matched family donor with survival rates of 65% in this cohort and tolerable GvHD. Children with PRCA may need prolonged steroids post HSCT with survival rates of 68%.



Calls Ind

Keywords: children, IBMFS, outcome





Haploidentical Hematopoietic Stem Cell Transplantation in Pediatric Patients – A single institution report in Taiwan

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Abstract Content

Introduction:

Hematopoietic stem cell transplantation (HSCT) has been a widely-used treatment modality for managing various diseases including malignancies, metabolic diseases, and primary immunodeficiencies. However, a human leukocyte antigen (HLA)-matched donor may not be available in some patients. Haploidentical HSCT provides an opportunity for patients without available HLA-matched donors since haploidentical donor is available in nearly all patients. Although haploidentical HSCT was reported to be associated with more severe graft-versus-host disease(GVHD) and higher graft failure rate, the outcomes were improved significantly in recent years. In this review, we would like to share our experiences in pediatric haploidentical HSCT.

Methods:

We searched our HSCT database in our hospital to identify patients receiving stem cells from a haploidentical donor. The clinical data of patients were obtained retrospectively by reviewing medical records. The date of the latest follow-up was July 12, 2018.

Results:

There were 18 patients receiving haploidentical HSCT since 2005. The mean age was 12.0 years old (0.8-24.4 years old). Among these 18 patients, 5 patients received bone marrow transplantation, 3 patients received peripheral blood stem cell transplantation, and 10 patients received bone marrow plus peripheral blood stem cell transplantation. The mean CD34⁺ cell dosage was 5.21*10⁶ cells/kg (1.51-9.55*10⁶ cells/kg). All except 2 patients with primary immunodeficiency received myeloablative condition regimens. There was only one patient suffered from graft failure. In the remaining 17 engrafted patients, the median neutrophil engraftment day was D+15 (D+10-D+19) and the median platelet engraftment day was D+28 (D+13-D+103). No late graft failure was found. Acute graft-versus-host disease(aGVHD) happened in 14 of 17 patients (82.4%). Three patients (17.6%) had grade III aGVHD and no grade IV aGVHD was noted. Thirteen patients received steroid for aGVHD treatment and 11 patients were steroid-responsive. The remaining 2 patients had steroid-dependent aGVHD but were controllable after incorporating other immunosuppressive agents. No steroid-refractory aGVHD was identified. There were 4 patients (23.5%) developed chronic graft-versus-host disease (cGVHD). Mortality happened in 16 patients. Among them, 11 patients died of original disease relapse, 4 patients died of infection, and only 1 patient died of respiratory failure due to pulmonary cGVHD with bronchiolitis obliterans.

Conclusion:

Haploidentical HSCT is associated with acceptable engraftment rate in pediatric patients, especially with myeloablative condition regimen and adequate stem cell dosage. Although the incidence of aGVHD is high, most of them were controllable by steroid or other immunosuppressive agents. High mortality rate mainly resulted from original disease relapse since only one patient died of cGVHD. Therefore, haploidentical HSCT is a safe and effective option for pediatric patients who require HSCT but without HLA-matched donors. Due to small sample sizes in this review, further large-scale studies should be conducted.

Keywords: Haploidentical Transplantation, Hematopoietic Stem Cell Transplantation, Taiwan, Pediatrics



Successful allogeneic hematopoietic stem cell transplantation in a patient with mixed phenotype acute leukemia and disseminated fusariosis: The second case report and review of the literature

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Abstract Content

Purpose: Disseminated fusariosis in acute leukemia patients has been associated with dismal outcome. The effective therapy especially for whom a HSCT is planned has not been established. To the best of our knowledge, Only one case report has been published in this respect (Kordelas, 2016). This case represents a successful experience of treating disseminated fusariosis and subsequent HSCT.

Case: A 17-year-old boy with initial white cell count 180,400/mm³ was diagnosed with mixed phenotype acute leukemia(T/myeloid). After induction therapy consisting of cytarabine and idarubicin, he became neutropenic. On the 18th hospital day small, tender nodules with central necrosis developed on his right foot. Fevers developed despite empirical antibiotics and prophylactic itraconazole. Liposomal amphotericin B was added. Over several days, multiple ecthyma gangrenosa developed and spread to arms and legs. A CT scan of the lower limbs revealed multiple subcutaneous and intramuscular abscesses with surrounding cellulitis. A skin biopsy showed obliterative vasculitis by multiple fungal thrombi. He also developed a cough and dyspnea, and a chest CT revealed multiple inflammatory nodules on both lungs. Intravenous voriconazole was added. In addition, oral terbinafine was added when Fusarium solani was identified on culture. After 2 weeks of combination treatment, he began to improve with neutrophil recovery. The cumulative dose of amphotericin was 10.2 g. The minimal inhibitory concentration by microbroth dilution testing revealed: voriconazole, 8 µg/mL; itraconazole, 8 µg/mL; posaconazole, 16 µg/mL; amphotericin B, 4 µg/mL. Still on oral voriconazole, he underwent 4 cycles of consolidation chemotherapy without recurrence of fungal infection. After myeloablative conditioning he received a full matched unrelated PBSCT while on voriconazole. His post-transplant course was complicated by delayed neutrophil recovery of neutrophil count ≥ 500/µL on D+25 and human herpesvirus-6 encephalitis identified on D+25. Foscarnet treatment resulted in improvement of encephalitis but he suffered from acute kidney injury. Currently, he remains in remission with full donor chimerism 14 months after transplant. He is free of fungal reactivation but has mild chronic graft-versus-host disease.

Conclusion: Aggressive treatment with combination antifungal therapy consisting of voriconazole, liposomal amphotericin, and terbinafine resulted in control of disseminated fusariosis in an immunocompromised patient who later underwent a successful allogeneic HSCT. A review of the literature will be presented with the report.

Keywords: Fusariosis, Allogenic hematopoietic stem cell transplantation, HSCT, Mixed phenotype acute leukemia



Two different therapy-related acute myeloid leukemias following treatment of immature teratoma in a pediatric patient with XYY syndrome: A case with successful unrelated hematopoietic stem cell transplantation

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Abstract Content

Introduction: Therapy related acute myeloid leukemia (t-AML) is a rare, but well-recognized complication seen in pediatric cancer survivors. The major contributing factors are exposure to alkylating agents, epipodophyllotoxins and radiation. In addition, genetic predisposition to cancer may be implicated. We report the first case who developed two different types of t-AML in a pediatric patient with XYY syndrome. The patient developed acute promyelocytic leukemia (APL) after therapy of immature teratoma as the first t-AML, and another AML with t(4;11)(p14;q23) as the second t-AML.

Case report: A full-term newborn was diagnosed to have a huge, immature teratoma on the left neck (10 cm-sized, Grade III). A conventional cytogenetics of peripheral blood revealed a 47, XYY. He was treated with mass extirpation and three cycles of chemotherapy. The cumulative dose of cisplatin and etoposide was 9.9 mg/kg, and 49.5 mg/kg, respectively. No TP53 mutation was found. Twenty-eight months after the completion of chemotherapy, his blood counts became abnormal: white blood cells 6,300/mm³, hemoglobin 8.4 g/dL, and platelet counts 18,000/mm³. The diagnosis of acute promyelocytic leukemia as the first t-AML was made by morphology, FISH and PCR for PML-RARA. He achieved a morphological complete remission (CR) after induction therapy of all-trans-retinoic acid (ATRA) and idarubicin. Consequently, he received two cycles of consolidation with ATRA and mitoxantrone or idarubicin, and maintenance therapy with ATRA, methotrexate and 6-mercaptopurine. The cumulative dose of anthracycline so far was 375 mg/m². Six months after the completion of APL therapy, another AML with t(4;11)(p14;q23) developed as the second t-AML. No PML/RARA gene rearrangement was detected. He achieved a CR after two courses of induction chemotherapy. Following two more courses of consolidation chemotherapy, an allogeneic SCT from 7/8 allele-matched unrelated donor was performed. Engraftment was uneventful with complete donor chimerism. He remains in continuous CR with donor chimerism 29 months after SCT without significant complications. The cumulative doses of anthracyclines and etoposide were 735 mg/m² and 1500 mg/m², respectively.

Conclusion: This case illustrates the extremely rare case of developing two different types of t-AML in a patient with XYY. A HSCT seems effective to cure, even in this very complicated case. Further studies are warranted to evaluate whether the XYY syndrome may predispose the development of t-AML.

Keywords: Therapy-related acute myeloid leukemia, t-AML, XYY syndrome



Toxicity and efficacy of thiotepa, busulfan, fludarabine conditioning before allogeneic stem cell transplantation in children with haematological malignancies

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Abstract Content

Introduction:

A myeloablative conditioning regimen combining thiotepa, intravenous busulfan and fludarabine (TBF) has emerged as an alternative to the standard protocols for patients undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT). However, no published studies have investigated this regimen in a dedicated paediatric cohort. This study describes the toxicity and efficacy of TBF conditioning prior to allo-HSCT in children with haematological malignancies.

Methods:

In this retrospective, single-centre study, we collected data from the electronic medical records of children (< 18 years) diagnosed with a haematological malignancy who received a graft from a HLA-matched sibling, unrelated or haplo-identical donor following TBF conditioning between January 2013 and February 2018. Our primary endpoint was the transplant-related mortality (TRM) at day +100.

Results:

There were 38 children (median age, 6.5 years; IQR, 1.9 - 9.6 years) included in the study. 60% of patients (n = 23) were diagnosed with acute lymphoblastic leukaemia or acute myeloid leukaemia; within this group, approximately two-thirds (n = 15) underwent allo-HSCT for relapsed disease. The remaining children were transplanted for myelodysplastic syndromes (n = 9) or juvenile monomyelocytic leukaemia (n = 6). Nearly all (37/38) patients achieved neutrophil engraftment at a median of 16 days (IQR, 11 - 24 days). The cumulative incidence of grade III - IV acute graft-versus-host disease (GVHD) at day +100 was 23% (95% CI, 12 - 43%) and the cumulative incidence of chronic GVHD at 1 year was 16.9% (95% CI 7.9 - 33.8%). Conditioning-associated toxicity was low, resulting in a cumulative incidence of TRM at day +100 of 2.7% (95% CI 0.39 - 17.7%). 4 children (10.5%) developed hepatic veno-occlusive disease. With a median follow-up time of 13 months (IQR, 3.5 - 41.9 months) the Kaplan-Meier estimate of overall survival at 1 year was 88% (95% CI, 71 - 95%). At 1 year, the cumulative incidence of relapse was 9.1% (95% CI, 3 - 26%).

Conclusions:

TBF conditioning was found to be associated with high rates of engraftment, minimal regimen-related toxicity and effective disease control in many children transplanted for high-risk haematological malignancies.

Keywords: Haematopoietic stem cell transplantation; conditioning; thiotepa; fludarabine; toxicity





TREOSULFAN BASED CONDITIONING REGIMEN – REDUCED TOXICITY WITH EXCELLENT OUTCOMES IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCY

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Abstract Content

Introduction

Primary immune deficiency (PID) has varied presentation and mortality rate is high without hematopoietic stem cell transplantation (HSCT). Tailored conditioning regimens to minimise immediate and late toxicity is now the standard of care. Reduced conditioning may result in mixed chimerism and graft rejection. We present our data of a treosulphan based conditioning regimen in children with PID at a tertiary referral centre.

Patients and Methods

We conducted a retrospective study in the department of Blood and Marrow Transplantation unit in Apollo Cancer Institutes from 2002 to 2018. All children diagnosed to have PID who received Treosulphan based conditioning were included in the study. Age at diagnosis, conditioning regimen, the source of stem cells, regimen related toxicity, graft versus host disease(GvHD), donor chimerism post transplantation and survival data was collected and analysed.

Results

A total of 68 children were diagnosed to have PID (male 44, female-24) and 55 had received a treosulphan based conditioning regimen. The diagnoses included HLH in 18 (32%), SCID in 21 (38%), LAD in 3 (5%), CVID in 2 (4%), WAS in 2 (4%), Hyper IgE in 1 (2%), Hyper IgM in 1 (2%) MSMD in 2 (4%), IL10 Ra deficiency in 2 (4%) and CGD in 3 (5%) children. The median age at presentation was one year. Allogenic related PBSC was used in 14 (25%), bone marrow in 15(27%), unrelated in 2(4%), cord blood in 9(17%) and haplo-identical bone marrow in 15(27%).

Regimen related toxicity seen predominantly were rash in 14 children (25%), conjunctivitis in 3(5%), mild mucositis in 9(16%), severe grade 4 mucositis in 3(5%). There was no major respiratory, neurological toxicity or sinusoidal obstruction syndrome. After initial complete chimerism, over 90% of the children demonstrated mixed chimerism after 60 days and this necessitated early withdrawal of immunosuppression. Acute graft versus host disease (GvHD) was seen in 8(17%) and chronic GVHD 4(7%), graft rejection in 3(5%). The mortality rate was 40% with the cause being sepsis in 7(32%), ARDS in 4(18%), disseminated CMV 3(14%), disseminated aspergillosis in 1(4%), encephalopathy in 2 (10%), refractory immune cytopenia in 1(4%), progressive HLH in 3(14%) and chronic liver GVHD in 1(4%).

Conclusion

Treosulphan based conditioning regimen is ideally suited for children with PID as they present with significant co-morbidity. However, the donor chimerism needs to be followed up carefully with withdrawal of immunosuppression when chimerism drops to less than 95% to prevent graft rejection. This data is particularly relevant in India where busulphan pharmacokinetics is not available and individualised therapy is the key to a successful outcome.

Keywords: reduced intensity conditioning, treosulfan, mixed chimerism, regimen related toxicity



What will be the fate of children and adolescents with idiopathic non-severe aplastic anemia?

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Abstract Content

Introduction: Data are scarce on the fate of idiopathic non-severe aplastic anemia (iNSAA) in children and adolescents. This study aimed to identify the clinical course and risk factors associated with disease progression in young patients with iNSAA.

Methods: We reviewed the medical records of patients with iNSAA who were younger than 20 years when their diagnosis was made. We defined iNSAA as two- or three-lineage cytopenia with hypocellular bone marrow that did not fulfill the SAA criteria not having apparent causes such as inherited bone marrow failure, drugs, hepatitis, and others. Date of disease progression was determined when patients progressed to SAA or became transfusion-dependent from transfusion-independent disease whichever occurred first.

Results: Forty-seven patients were identified and their median age was 9.1 y (range, 2.0-19.5). Thirteen patients (27.7%) had previous history of idiopathic thrombocytopenic purpura. The median Hb level (g/dL), WBC count (x 10⁹/L), platelet count (x 10⁹/L), absolute neutrophil count (ANC, x 10⁹/L), absolute lymphocyte count (ALC, x 10⁹/L), and absolute reticulocyte count (ARC, x 10⁹/L) were 9.4, 3.55, 34, 1.02, 2.11, and 54, respectively. The Kaplan-Meier estimates for progression-free survival (PFS) were 64.6%, 55.1%, and 51.2% at 5 y, 10 y, and 15 y after diagnosis, respectively. Age <10 y (P=0.027), Hb <10 (P=0.004), platelet <20 (P=0.003), % neutrophil <20 (P=0.006), and ARC >50 (P=0.014) were predictive of lower PFS in univariate analysis. In multivariate analysis using Cox proportional hazard model, Hb <10 (P=0.028) and platelet <20 (P=0.046) were the independent risk factors for disease progression. By Spearman correlation analysis, Hb level showed a positive correlation with platelet count (P=0.01), whereas it had no correlation with WBC count (P=0.90) or ANC (P=0.087). The 10-y overall survival was 87.2% and 10 out of the 14 patients who eventually underwent allogeneic hematopoietic cell transplantation are alive disease-free.

Conclusions: Approximately a half of children and adolescents with iNSAA are expected to progress in 15 y from diagnosis. Since a significant proportion of patients with iNSAA had previously been diagnosed as ITP, bone marrow examination should be implemented once other lineage cytopenia develops in patients presumed to have chronic ITP. Unexpectedly, WBC count and ANC did not predict disease progression while lower Hb and platelet counts did. Closer follow-up is needed for those who are more likely to progress.

Key words: non-severe aplastic anemia, children, adolescents, risk factors, progression-free survival





Pediatric blood transfusion practices at a regional referral hospital in Kenya

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Abstract Content

BACKGROUND

Severe anemia in children is a major public health problem in sub - Saharan Africa. In this study we describe clinical and operational aspects of blood transfusion in children admitted to Coast Provincial General Hospital, Kenya.

STUDY DESIGN AND METHODS

This was an observational study where over a 2 - year period, demographic and laboratory data were collected on all children for whom the hospital blood bank received a transfusion request. Clinical data were obtained by retrospective review of case notes over the first year.

RESULTS

There were 2789 requests for blood for children (median age, 1.8 years; interquartile range [IQR], 0.6 - 6.6 years); 70% (1950) of the samples were crossmatched with 85% (1663/1950) issued. Ninety percent (1505/1663) were presumed transfused. Median time from laboratory receipt of request to collection of blood was 3.6 hours (IQR, 1.4 - 12.8 hr). Case notes of 590 children were reviewed and median pretransfusion hemoglobin level was 6.0 g/dL (IQR, 4.2 - 9.1 g/dL). Ninety - four percent (186) were transfused "appropriately" while 52% (120) were transfused "inappropriately." There was significant disagreement between the clinical and laboratory diagnosis of severe anemia (exact McNemar's test; p < 0.0001). Antimalarials were prescribed for 65% (259) of children who received blood transfusions but only 41% (106) of these had a positive blood film.

CONCLUSION

In this setting, clinicians often order blood based on the clinical impression of "severe anemia." This has implications for laboratory workload and the blood supply itself. However, the majority of children with severe anemia were appropriately transfused. The use of antimalarials with blood transfusions irrespective of blood film results is common practice.

ABBREVIATIONS

CPGH

Coast Provincial General Hospital KNBTS

Kenya National Blood Transfusion Services

WAZ

weight - for - age z - scores

Severe anemia resulting in significant morbidity and mortality is common in children in sub - Saharan Africa and urgent blood transfusion is a lifesaving intervention.1, 2, 3, 4 Blood shortages are common in low - and middle - income countries and delays in the acquisition and administration of blood have contributed significantly to in - hospital mortality of children with severe anemia.5

International clinical transfusion guidelines for settings with limited resources are restrictive and reflect historical inadequacies in the blood supply. Since 2005, the World Health Organization (WHO) recommendation has been to reserve transfusion for those children with profound anemia (hemoglobin [Hb] \leq 4 g/dL; Hb \leq 10 g/dL in neonates) and in those where anemia is less severe (Hb 4 - 6 g/dL) only when signs of critical illness are present. Whole blood transfusion of 20 mL/kg is recommended (10 mL/kg red blood cells [RBCs] preferred when available for children with heart failure and severe acute malnutrition) and for children with severe acute malnutrition 10 mL/kg whole blood and furosemide (1 mg/kg intravenously) at the start of the transfusion.6 In contrast, in high - income settings transfusion guidelines for hemoglobin (Hb) thresholds in children and neonates are between 7 and 12 g/dL depending on the clinical context and RBCs are routinely available and used.7, 8

To prevent the transmission of malaria by blood transfusion in endemic countries, international guidelines recommend donor selection.

Keywords: Emman





AN OUNCE OF PREVENTION AND A POUND OF CURE

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Abstract Content

Aim

Carbapenem resistant gram negative bacterial sepsis has emerged as the most significant cause of mortality in pediatric oncology and transplantation units in India. Early detection of their presence in the child's gut by multiplex RT- PCR based Xpert Carba-R assay using a rectal swab can help institute appropriate antibiotic policy implementation and reduce mortality. The aim of our study was to analyze the pattern of Carba R in our cohort and its clinical application in improving outcomes related to sepsis.

Patients and methods

We performed a combined retrospective and prospective study among the children who underwent hematopoietic stem cell transplantation(HSCT) between Jan 2013 and June 2018 in the department of pediatric blood and marrow transplantation at Apollo Cancer Institutes, Chennai. Rectal swab samples were tested for Carba-R genes in all patients who were admitted after June 2015, to screen for the presence of five resistant genes namely VIM, IMP, OXA, KPC and NDM and it cost approximately USD 75. The unit policy was changed in June 2015 to add colistin early in the children with neutropenic fever who had a positive Carba-R and to de-escalate after 48 hours. The results of screening and the outcomes of children in specific relation to septic events were analysed.

Results

Group 1 consisted of children analyzed retrospectively from January 2013 to June 2015 and Group 2 consisted of children analyzed prospectively from June 2015 to June 2018. One hundred and ninety two children were present in Group1 and 310 children in Group 2. The indications for transplantation and the type of transplantation have been compiled in Table 1. Amongst the 310 samples screened, 120(37%) were positive for Carba-R genes. The most common gene was NDM (61%), followed by OXA (24%), VIM (10%) and KPC (5%). Of these 310 children, 62 (20%) had culture proven sepsis. Stool Carba-R was positive in 28 out of the 62 children (45%) and colistin was added early with the onset of septic event during the neutropenic period. The mortality rate due to sepsis was higher in Group 1 at 6% when compared with Group 2 with a mortality rate of 2.9% despite an increase in multidrug resistance both in the community and in the hospital setting.

Table 1 – Patient characteristics

INDICATION	GROUP 1	GROUP 2	
BENIGN	137 (71.4%)	218 (70%)	
MALIGNANT	55(28.6%)	92(30%)	
TYPE OF HSCT			
ALLOGENEIC	182(94.8%)	291(93.8%)	
AUTOLOGOUS	10(5.2%)	19(6.2%)	

Conclusion

Multidrug resistant organisms (MDRO) bacterial infections present a significant challenge to extremely vulnerable children such as HSCT recipients and the incidence of MDRO at the time of admission detected by the presence of NDM, KPC, VIM and OXA strains from the stool samples of children was as high as 42% in our cohort . Prior knowledge of this resulted in early addition of appropriate antibiotics and helped reduce mortality due to bacterial sepsis during the neutropenic phase by 50% from 6% in Group 1 to 2.9% in Group 2. We would recommend this screening tool to help find smart solutions to smart bugs.



Keywords: Carba-R, Rectal swab, multidrug resistant organisms, mortality.

- Line of





Transforming vision in to reality in a resource limited setting: establishing a Pediatric Hematopoietic Stem cell Transplant unit through public private partnership in India

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Abstract Content

Background: Allogenic Hematopoietic Stem Cell Transplantation (HSCT) has been an established curative option for a number of non-malignant and malignant disorders. Unfortunately, most children in our country are unable to avail of this option due to non-affordability and its nonavailability in public sector hospitals. We share our experience of establishing a Hematopoietic Stem Cell Transplant Unit at the Lokmanya Tilak Municipal General Hospital under the aegis of the Muncipal Corporation of Greater Mumbai. To date, over two and half years, we have performed twenty one hematopoietic stem cell transplants for various indications.

Objective: To share the experience and challenges in establishing a HSCT unit in a Public Hospital.

Method: The need for a Hematopoietic Stem Cell Transplant (HSCT) centre was always felt, with indications for HSCT being identified in an increasing number of children. The idea of setting up a HSCT centre, though conceived in 1998, could not materialize till 2012 due to a resource crunch. Once this hurdle was crossed with the donation from a philanthropic organization, the task of administrative approval, space allocation and getting the desired infrastructure in place commenced in 2013. Funds were utilized for building a state-of-the-art 20- bedded Pediatric Hematology-Oncology Unit with an one bedded HSCT unit. The purchase of equipment and staff recruitment was done simultaneously. Training of the selected staff, including the paramedical personnel and team building was initiated. Donor funding was ensured for pre-HSCT workup, process of transplantation and post-transplant care. Patients in whom HSCT was considered curative and who had a matched sibling donor were considered for transplant.

Results: The HSCT unit was operational by August 2015 and 21 patients have been transplanted to date. These include 13 children with Severe Aplastic Anemia (SAA), 5 with Thalassemia Major(TM), 1 with chronic granulomatous disease(CGD), 1 with Griscelli syndrome with hemophagocytic histiocytosis (HLH) and 1 infant with Severe Combined Immune Deficiency- Reticular Dysgenesis (SCID). HSCT with matched sibling donor was done in 19 patients, whereas 2 patients had 9/10 match. Reduced Intensity Conditioning (RIC) consisting of Flu-Cy-ATG was used in patients with SAA and Treo-Thio-Flu-ATG was administered to the baby with SCID. For 4 of 5 TM myeloablative regimen consisting of Bu-Cy-ATG was used, whereas the one thalassemic a regimen with Treo-Thio-Flu-ATG was given. Peripheral blood stem cells (PBSC) was the source of stem cells in all patients except 5 thalassemia major patients, Bone marrow harvest was done for thalassemia major. Twenty of the 21 patients are on follow up, ranging from 30 days to 2 year 8 months. The infant with SCID died of adenoviral infection during immediate post- transplant period during the severely neutropenic phase and 2 thalassemia major patients had secondary graft failure.

Conclusion: It is feasible to set up a HSCT unit in a public sector hospital if one has the vision, passion and commitment. Presently, there are hardly any similar units in the public sector. And of course, the key to success of any HSCT Centre is good team work.

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Donor Lymphocyte Infusion in children – an ounce of prevention provides a pound of cure

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Abstract Content

Background

Donor lymphocyte infusion (DLI) is a form of cellular immunotherapy which may be effective in preventing a relapse due to graft versus leukaemia effect in malignancies and progression of impending graft rejection in benign hematological conditions. There is scant data for the use of DLI in children and we describe the indications and cost effective methods of delivering care at our centre.

Patients and methods

We conducted a retrospective analysis of the children who underwent hematopeitic stem cell transplantation and received DLI either as a part of pre-emptive therapy in leukemia or for mixed chimerism in benign disorders at Apollo Cancer Institutes from January 2011 to May 2018. The first step was withdrawal of immunosuppression and DLI was commenced 7 days later if there was no evidence of graft versus host disease (GVHD). The desired volume of fresh peripheral blood from the donor was infused based on the CD3 count. DLI was given in a graded regimen with the cell dose of 1 x 10*5 CD3 cells/kg, 5 x 10*5 cD3 cells/kg, 1 x 10*6 CD3 cells/kg depending on the graft kinetics and the clinical status of the children. The dose was one log lower in children undergoing haploidentical HSCT starting at 1x10*4/kg.

Results

A total of 569 children underwent HSCT during the study period and DLI was performed in 58 children. The male female ratio was 1.4: 1 and 72.4% were for benign haematological conditions including thalassaemia major, sickle cell anaemia and primary immune deficiency disorders. Reduced intensity conditioning was used in 12% children. The donor was a fully matched family donor in 90%, mismatch family donor in 6%, matched unrelated donor in 4%. A haploidentical family donor was used in 12%. Peripheral blood stem cells were used in 62% and bone marrow in 38% children. DLI was commenced for mixed chimerism less than 95% to prevent graft rejection in 79% and in 21% children it was used as pre-emptive therapy in high risk malignancies to prevent a molecular relapse. In our cohort, 26 children (45%) received single DLI, two DLI in 17 (29%) and three DLI in 13 children. In majority of the children (72%), small aliquots of peripheral blood could prevent graft rejection / relapse. Twenty one children (46%) achieved 100% chimerism, 12 children (26%) had mixed chimerism and were clinically stable. Twenty two children who received DLI developed mild skin and mouth GVHD and gut involvement was seen only in 4 of these children. The mortality was 17% (10/58) due to graft loss, relapse of leukemia and one death attributed to graft versus host disease.

Conclusion

DLI is an effective tool in preventing graft rejection in benign conditions and relapse of leukemia in high risk cases. It is a safe procedure for the donor as the amount of peripheral blood required is graded from 0.1 ml to 75 ml. Careful follow up of graft kinetics and clinical vigilance for grade 4 GVHD makes it an easily applicable tool even in resource constrained settings and in haploidentical HSCT.

Keywords: Donor lymphocyte infusion, graft rejection, graft versus leukemia effect, graded regimen, Graft versus host disease





A Yearly Report of Primary Immunodeficiency Patients Treated with Reduced-Intensity Conditioning Hematopoietic Stem Cell Transplantation at the Largest Iranian Children's Hospital

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Abstract Content

Background: The Hematopoietic Stem Cell Transplantation (HSCT) department of Children's Medical Center (CMC), known as the largest children hospital of Iran and the country's pediatric center of excellence, was founded in the middle of September 2016. During the first year of its activity, nearly 20% of cases treated at this department had primary immunodeficiencies (PIDs).

Methods: In this cross sectional study, a yearly epidemiologic profile of PID patients treated with fludarabine, melphalan and antithymocyte globulin as reduced intensity conditioning regimen for allogeneic HSCT at CMC is presented. The data were extracted from patients' medical records and entered into predesigned checklists.

Results: Nineteen PID patients (68.4% male) with median age of 4 (range: 0.7-13) years underwent HSCT in this department during the study period. Chronic granulomatous disease (6 patients; 31.6%) and severe combined immunodeficiency (5 patients; 26.3%) were the leading indications for HSCT followed by Leukocyte Adhesion Deficiency (3 patients), Wiskott–Aldrich syndrome (2 patients), Familial Erythrophagocytic Lymphohistiocytosis (1 patient), Chediak Higashi (1 patient) and Hyper IgE Syndrome (1 patient). Peripheral blood was the most common source of HSCs (84.2%). The cells were donated by patients' siblings (31.6%), other relatives (52.6%) or unrelated donors (15.8%). Median granulocyte and platelet engraftment time were 10 (range: 1-15) and 10 (range: 9-16) days, respectively. Acute GvHD developed in 9 patients (47.4%), while 4 patients (21.1%) have experienced chronic GVHD, so far. Two patients (10.5%) died, in which the underlying cause was infection in one and graft failure in the other one. In all patients, the parents were blood relatives, i.e., first or second cousins. When compared to 14 acute lymphoblastic leukemia patients treated with HSCT at this department during the same study period, whose only 43.9% of the parents had cousin-cousin marriages, this parameter (consanguineous marriage) bears a significant risk for having a child with inherited PID (P<0.001, RR [95% CI]: 2.3 [1.3-4.3]).

Conclusions: The outcome of PID patients treated at this department was favorable with RIC-based allo-HSCT. In Muslim-majority countries like Iran cousin-cousin marriages are aloud. This put such couples to increased risk for having children with genetic diseases like PIDs. At the same time, this factor provides a higher chance of finding an HLA matched healthy donor among the patients' relatives.

Keywords: Consanguinity; Hematopoietic Stem Cell Transplantation; Immunologic Deficiency Syndromes; Iran





Clinical Manifestations, Genetic Analysis and Outcome of Transplant-Associated Thrombotic Microangiopathy in Children with Neuroblastoma

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Abstract Content

Introduction: Transplant-associated thrombotic microangiopathy (TA-TMA) is an increasing recognized complication of hematopoietic stem cell transplantation (HSCT). TA-TMA is commonly identified following allogeneic HSCT, but is infrequently reported after autologous HSCT. We examined clinical manifestations, genetic analysis and outcome of TA-TMA in pediatric neuroblastoma patients after allogeneic or autologous HSCT in a single medical center in Taiwan.

Methods: Children younger than 18 years old with neuroblastoma who underwent high-dose chemotherapy followed by HSCT at Linkou Chang Gung Memorial Hospital between January 2012 and June 2018 were included. All patients received the uniform high-dose chemotherapy: topotecan, busulfan, and melphalan (Topo/Bu/Mel). The medical records were retrospectively reviewed.

Results: Twenty pediatric neuroblastoma patients underwent 21 HSCTs (13 autologous HSCT and 8 allogeneic HSCT) using Topo/Bu/Mel. Only one (5%) patient was diagnosed with TA-TMA 3 months after autologous HSCT. The 4-year-old patient presented with unexplainable hypertension on day +13. Hematuria, proteinuria, low haptoglobin level, the presence of schistocytes, normal ADAMTS13 activity, and increased CH50 level were detected. TMA was confirmed by renal biopsy. We administered plasma exchange sessions followed by eculizumab therapy. Anti-Factor H autoantibody was negative. Genetic testing revealed two variants in *CFH* and *DKGE* genes. TA-TMA responded to eculizumab therapy with gradual improvement of laboratory test results, and the patient tolerated the therapy well. Unfortunately, he had a full blown relapse of neuroblastoma 4 months after eculizumab therapy. His renal function deteriorated after salvage chemotherapy despite concomitant eculizumab therapy. Consequently, he died of disease progression 6 months after eculizumab therapy.

Conclusions: TA-TMA occurs infrequently in pediatric neuroblastoma patients after HSCT using Topo/Bu/Mel regimen. In addition to endothelial injury caused by high-dose chemotherapy, preexisting genetic variants in the genes coding for complement factors or leading to the prothrombotic status may place them at a greater risk for TA-TMA.

Keywords: Children; Hematopoietic stem cell transplantation; Neuroblastoma; Thrombotic microangiopathy


Topic: Pediatric transplants Abstract No: 8922

A Novel reduced-intensity conditioning regimen containing cladribine for allogeneic hematopoietic stem cell transplantation in pediatric patients with major thalassemia

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Abstract Content

Reduced intensity conditioning before allogeneic stem cell transplantation is an option for pediatric patients with thalassemia. In recent years, cladribine was widely used in conditioning regimen for acute leukemia transplant program. To observe the efficacy and security of conditioning regimen containing cladribine for allogeneic hematopoietic stem cell transplantation(allo-HSCT) in pediatric patients with major thalassemia, We retrospectively analyzed the clinical data of 13 pediatric patients with major thalassemia undergoing allo-HSCT from March 2017 to March 2018. These 13 patients were diagonosed definitely, and the median age at transplantation was 5 years (range:2~13 years), including 9 matched unrelated donors, 2 HLA 6/10 matched related donor, 2 HLA- matched sibing donors. All patients received a new conditioning regimen which was made up of Cyclophosphamide(CTX), Cladribine, Busulfan(Bu) and antithymocytic globulin. The median mononuclear cell(MNC) dose and CD34 positive cell dose were 10.97×108 /kg (range: 5.72~12.49×108 /kg) and 12.2×106 /kg(range: 6.7~21.5×106 /kg). Grafe-versus-host disease(GVHD) was prevented by cyclosporine A(CSA), methotrexate(MTX) and Mycophenolate Mofetil(MMF). ALL 13 patients had successful engraftment. Median time of neutrophil and platelet engraftment was 11 days (range: 8~17 days) and 15 days(range: 10~37 days)respectively. Using the method of short tandem repeat-polymerase chain reaction(STR-PCR) at 30 days after transplantation, 10 patients were considered to be full donor chimerism (FDC), while 3 patients were were considered to be mixed chimerism(MC). By reducing the dose of immunosuppressant drugs and donor lymphocytes infusion(DLI), these 3 patients of MC turned to be FDC 2 weeks later and stayed stable. Five patients developed grades II acute GVHD and 1 patients developed grades IV intestinal acute GVHD 35 days after transplantation, who finally died of severe infection 70 days after transplantation. 3 developed limited chronic GVHD. 30% of the patients developed cytomegaloviremia. None suffered from serious transplantation-related complications, such as hepatic venoocclusive disease(HVOD),hemorrhagic cystitis and septicemia,etc. The median follow-up time was 6 months(range: 3~9months). 12 of the 13 patients survived and became transfusion-independent. The conditioning regimen containing cladribine may be safe and effective for allo-HSCT in pediatric patients with major thalassemia. However, strong immunosuppression may increase the risk of infection and virus activation after transplantation.

Keywords: pediatric patients; thalassemia; allogeneic hematopoietic stem cell transplantation; intensive conditioning regimen.





Haematopoietic Stem Cell Transplantation in Acquired Severe Aplastic Anaemia of Childhood: A Three-Year Experience from Sabah Women's and Children's Hospital

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Abstract Content

Introduction

Aplastic anaemia is a rare life-threatening blood disorder. The incidence varies according to geography and ranges from 2-15 per million per year with the highest incidence in East Asia. First line treatment for severe aplastic anaemia (SAA) in children is haematopoietic stem cell transplantation (HSCT) with a HLA match related donor. The second paediatric HSCT unit in the Ministry of Health Malaysia was established in October 2014 at the Sabah Women's and Children's Hospital (SW&CH) to cater for the multi-ethnic childhood population of Sabah. We analyzed the outcome of children with acquired severe aplastic anaemia undergoing HSCT at SW&CH.

Methods

This is a retrospective review of medical records of children aged 15 years and below who were diagnosed with SAA and underwent HSCT at the HSCT unit of SW&CH. The study period was from 1st. January 2015 till 31st. December 2017.

Results

Nine children with SAA underwent allogeneic HLA match sibling bone marrow transplantation. The female to male ratio was 1:1.25 (4 girls and 5 boys) with a median age of 12.8 years (range: 9.6 - 14.3). The median time from diagnosis to HSCT was 7 months (range: 3 - 8). One patient (11%) had failed treatment with immunosuppressive therapy (IST). The conditioning regime consist of fludarabine, cyclophosphamide and anti-thymocyte globulin (ATGAM). Mini methotrexate at D+1, +3, +6, +11 and ciclosporin were used as GVHD prophylaxis. The median CD34 cell dose was 4.4×10^{6} cells/kg (range: 1.8 - 7.4). The median neutrophil and platelet engraftment were at D+14 (range: 10 - 20) and D+18 (range: 10 - 41) respectively. One patient expired at D0 due to Candida tropicalis fungaemia. Sinusoidal obstructive syndrome (SOS), immune haemolysis, grade III acute GvHD and chronic GvHD occurred in 1 patient (11.1%) each. The D+30 chimerism showed donor chimerism in 4 patients (50%) and mixed chimerism in 3 patients (37%). Chimerism data was unavailable in one patient (13%). At a mean follow-up of 15 months (range: 8 - 28) 8 patients (89%) are alive with normal haematological parameters.

Conclusion

Allogeneic HLA match sibling bone marrow transplantation with fludarabine, cyclophosphamide and antithymocyte globulin (ATGAM) conditioning regimen has a favourable disease free survival outcome in our SAA patients. However long term surveillance is required to detect late graf rejection and long term complications.

Keywords: Severe Aplastic Anaemia; Haematopoietic Stem Cell Transplantation; Fludarabine



Topic: Pediatric transplants Abstract No: 8946

Outcomes of Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency : The Experience from A Single Tertiary Center.

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Abstract Content

We performed a retrospective analysis on the outcome of hematopoitic stem cell transplantations (HSCTs) for primary immunodeficiency disorders in National Taiwan University Children's Hospital in recent 10 years (1997-2008). There were total 20 patients, including 13 males and 7 females. The most common indications for HSCT were severe combined immunodeficiency, Wiskott-Aldrich syndrome, and osteopetrosis. The average diagnostic age was around 1-year-old, and the average time from diagnosis to the date of transplant was 168 days. The mean source of stem cell were matched unrelated donor (6/20) and mismatched unrelated donor (5/20). Five-year overall survival (OS) was 70% of the whole cohort. 8 patients had acute graft versus host disease, and 5 of them were more than grade 2. 3 cases in the cohort had graft failure, 2 of them the source were cord blood, and the other one was haplo-identical. This cohort support the use of HSCT as a curative therapy for primary immunodeficiency disorders.

Keywords: HSCT, primary immunodeficiency disorder



The 23rd Annual Congress of 2018 APBMT

Topic: Pediatric transplants Abstract No: 8977

Autologous Stem Cell Transplant in Pediatric Patients with Atypical Teratoid Rhabdoid Tumor

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Abstract Content

Background:

Atypical teratoid rhabdoid tumor (ATRT) is one of the malignant embryonal brain tumors with poor prognosis, especially in young children. With the use of combining surgery, chemotherapy, and radiotherapy, the outcome of those patients is still unsatisfactory. Autologous stem cell transplant had been reported to improve the outcome in those patients. Herein, we present the results of incorporating autologous stem cell transplant into treatment scheme for pediatric patients with ATRT at our institute.

Methods:

From August 2011 to December 2017, all pediatric patients with ATRT who receive a single or tandem autologous transplant as consolidation were included. Before transplant, ATRT patients less than 3 years of age will not be provided with craniospinal irradiation until progression/relapse. The clinical characteristics, disease status before transplant, stem cell dose, engraftment status, post-transplant complications, and outcome were analyzed.

Results:

There were 11 pediatric patients with ATRT, who received total 18 cycles of autologous stem cell transplant at partial response (PR, n=6), complete response (CR, n=4) and progressive disease (PD, n=1), were enrolled. Six patients received a single transplant, while the other 5 had tandem transplant. The male to female ratio was 5 to 6. Median age at diagnosis and transplant was 1.4 years old (ranged 0.6-7.1) and 2.2 years old (ranged 1.2-7.8). The conditioning regimen included carboplatin/etoposide/ thiotepa in 11 cycles and melphalan-containing regimens in 7. All patients achieved engraftment. The median days for absolute neutrophil count>500/mm³ and platelet>20000/mm³ were 10 (ranged 7-11), and 14 days (ranged 5-42). The most common post-transplant complications included 14 episodes of neutropenic fever, 10 gastroenteritis, and 8 mucositis. During the transplant, one patents developed K. pneumonia sepsis, 4 fungal infections, 2 upper GI bleedings, and 1 CMV viruria. No transplant-related mortality was found. Seven children relapsed and died of disease in 6 and of second glioblastoma multiforme in 1 despite ATRT free after salvage treatment, while 4 are alive with disease free. The overall and progression-free surivival are 22.8 months (ranged 5.0-82.3), and 12.0 months (ranged 3.6-77.4), respectively.

Conclusions:

Our results demonstrated the improving results by incorporating autologous transplant into the standard treatment scheme for pediatric ATRT, in comparison to that of our historical cohorts. However, salvage radiotherapy rarely prevented further relapse in children less than 3 years of age.



Topic: Pediatric transplants Abstract No: 9044

Haplo-identical Bone Marrow Transplantation with post-transplant Cyclophosphamide in pediatric haematological disorders; A ray of hope in a challenging situation

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Abstract Content

Introduction:

Paediatric patients with haematological disorders have Haematopoieitic Stem Cell Transplantation as the only curative therapy. Around 40-50% patients do not have an HLA-matched donor. This intricate situation is complicated further in the developing world where Bone Marrow Donor Registries are non-existent. An answer to this dilemma comes in the form of Haploidentical hematopoietic cell transplantation. This option of transplantation with the administration of Cyclophosphamide in the post-transplant period as a prophylactic against Graft versus Host Disease (GvHD) has given forth encouraging results in patients with haematological disorders.

Methods:

Haploidentical HCT was performed in our institute over a period of 04 years from 2014 to 2017 and included 24 paediatric patients with various haematological disorders. The disorders included Beta Thalassaemia Major, Aplastic anemia, Severe combined immunodeficiency disorder, Fanconi's anemia and Gaucher's Disease in the non-malignant category while Acute lymphocytic leukemia and Acute myelogenous leukemia were the malignant ones.

Results:

The current study reported that mean neutrophil and platelet engraftment was achieved in 14.12±2.85 days and 22.5±13.73days respectively. Our study reported primary and secondary graft failure to be in 20.8% and 16.6% patients. The incidence of grade II-IV acute GVHD and III-IV acute GVHD were 4% and 4% at day 100, respectively. Overall survival rate was 58.3% in our cohort. The majority of participants in our study were Beta thalassaemia patients and had an overall survival was 83.3%.

Conclusion:

Haploidentical BMT is new hope for those patients lacking a full matched donor in hematological non malignancies, bone marrow failure and immunodeficiency disorder.

Keywords: Haploidentical allogeneic stem cell transplant, bone marrow failure, immunodeficiency disorder.



Comparison of FLAMSA based reduced intensity conditioning with Treosulfan/Fludarabine conditioning for patients with acute myeloid leukemia in remission: an ALWP/EBMT analysis.

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Abstract Content

Introduction - Allogeneic stem-cell transplantation (HSCT) is the most effective way to control and treat intermediate and high risk acute myeloid leukaemia (AML). FLAMSA (Fludarabine+Ara-C+Amsacrine ; Schmid et al. *J Clin Oncol* 2005; 23: 5675–5687) chemotherapy followed by reduced intensity conditioning (RIC-Cyclophosphamide 120mg/kg with Bu-4-6mg/kg, or TBI 4-6cGy) is an effective regimen in high-risk older patients with refractory AML, but has not yet been extensively studied for patients in remission. Treosulfan in combination with Fludarabine has been shown (Treo-Flu) to be an effective conditioning regimen for AML including in the higher risk setting, especially in patients above 45 years. Thus, we wanted to compare these two reduced toxicity regimens (FLAMSA/RIC vs Treo-Flu), in patients aged 45-65 years.

Methods - Inclusion criteria included: age 45 to 65y, de novo or secondary AML in CR1 or CR2, transplantation between 2007 and 2016, conditioning with Treo-Flu ($30-42g/m^2$) or FLAMSA/RIC (FLAMSA-TBI, FLAMSA-Bu, Bu 6mg/kg, 4cGY TBI), either with a HLA-matched sibling donor (MSD) or a 9-10/10 HLA-matched unrelated donor (MUD). Patients who received manipulated grafts, or transplant from $\leq 8/10$ HLA-matched donor were excluded.

Results – A total of 629 patients were included (203 with FLAMSA-TBI, 145 with FLAMSA-Bu and 281 with Treo-Flu). Median follow-up was 36, 18 and 18 months in the FLAMSA-TBI FLAMSA-Bu and Treo-Flu groups respectively. As compared to other groups, the FLAMSA-TBI group included younger patients, who were more likely to have received MSD transplant for de novo FLT3-ITD positive AML in an earlier period. Cytogenetics and performance status were comparable among the 3 groups. All three regimen had similar rates of engraftment (97% and 95% and 98% respectively, p=0.3). In the FLAMSA-TBI, FLAMSA-Bu and Treo-Flu groups, two years non- relapse mortality (NRM) was 15%, 25% and 13%; incidence of grade II-IV acute GVHD were 26%, 30% and 19% and 2 year incidence of extensive chronic GVHD were 14%, 9% and 21% respectively. As compared to Treo-Flu, relapse incidence at 2 years was lower in FLAMSA-TBI and FLAMSA-Bu (39% for the Treo Flu vs 20% and 28% for the FLAMSA-TBI and FLAMSA-Bu respectively), the median time being 17, 18 and 14 months respectively. Two year LFS and OS were 48%, 64% and 69%, 47% and 53% in the Treo-Flu, FLAMSA-TBI and FLAMSA-Bu groups. In multivariate analysis, after adjusting for baseline co-variates, there were no significant differences between FLAMSA-Bu and Treo-Flu groups for all outcome parameters. FLAMSA-TBI was associated with a higher incidence of acute GVHD (HR: 2.0, p=0.02), a lower relapse rate (HR 0.44, p=0.003) and a better LFS (HR 0.67; p=0.04) compared to Treo-Flu.

Conclusion- In patients age 45-65 years with AML in CR undergoing allogeneic transplantation from sibling or unrelated donors, FLAMSA-TBI is associated with significantly better LFS and similar OS as compared to Treo-Flu, mainly due to reduction in relapse rates. While FLAMSA-Bu is with similar overall efficacy as compared to Treo-Flu. These data may serve as the scientific background for a well design randomized study comparing the FLAMSA/RIC and the Treo Flu conditioning regimens for AML.



Keywords: allogeneic stem cell transplantation; acute myeloid leukemia; conditioning regimen; complete remission.

ALL PARTY

Evaulation of relapse and its treatment following Allogenic Stem Cell Transplantation (ASCT) for Acute Myeloid Leukaemia (AML)

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Abstract Content

Aim: To evaluate relapse and its treatment following Allogenic Stem Cell Transplantation (ASCT) for Acute Myeloid Leukaemia (AML).

Materials and Methods: 335 (169 female ,166 male) patients, median age 50 (17-68) years, underwent ASCT [301 myeloablative , 34 Reduced intensity(RIST)] between September 2000 -15 for AML (non M3) at a tertiary Canadian facility.

Results: Overall, 166 (49.6%) patients were alive without disease and 111 (33.1%) patients (53 male, 58 female), median age 51 (19-68)years had relapsed. Conditioning was myeloablative in 93(83.8%), RIST in 18(16. 2%). At transplant 87(78.4%) ,12(10.8%) and 12(10.8%) patients were in CR1, CR2 and with disease. Sites of relapse were bone marrow 103(92.8%), extramedullary only 6(5.4%) and Central Nervous system(CNS) only in 2(1.8%). Denovo, Myelodysplasia and therapy related AML constituted 84 (75.7%), 15(13.5%) and 12(10.8%) of relapses. Relapses were early (<1 year post-transplant) in 71(64%) and late (>1 year) in 40(36%). Median survival was 58 days (2-2510 days).

Post relapse the treatment details, patient number (%), median time to relapse post-transplant (days), median overall survival post relapse (days) and number of survivors (with graft vs host disease) were -

Withdrawal of immunosuppression, 44(39.6%), 100(43-2314),57.5(3-2510),1(1), Best supportive care-29(26.1%),266(19-2164),44 (2-618), 0, Chemotherapy-24(21.6%),624.50(96-2743),284(59-2315) 4 (1)

Second transplant-2(1.8%),1543(1288-1799),747(417-1077), DLI- 4(3.6%), 374(189-542), 528.5(132-1432) and Clinical trial- 7 (6.3%),102(13-425),198 (87-448),1 respectively.

Seven patients (2 CNS only) are alive and disease-free post relapse. ELN 2017 risk score (p=.001), Secondary AML(p=.039) and RIST(p=.01), were associated with increased relapse.

Conclusions: More aggressive strategies including second transplants and novel agents are needed in these patients.

Keywords: allogenic transplantation, myeloablative, reduced intensity, acute myeloid leukemia, relapse



Topic: Abstract No: 8678 Transplantation

for

leukemia

AlloHSCT in Adults with Relapsed/Refractory Acute Lymphoblastic Leukemia Treated with Blinatumomab vs Standard-of-Care Chemotherapy from a Randomized Phase 3 Study

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Abstract Content

Introduction: Blinatumomab demonstrated a significantly longer overall survival (OS) vs standard of care chemotherapy (SOC) in adults with relapsed/refractory acute lymphoblastic leukemia (R/R ALL), although the incidence of subsequent allogeneic hematopoietic stem cell transplantation (alloHSCT) was the same at 24% in both arms (*N Engl J Med* 2017;376:836-847). Here we report OS by alloHSCT status from the TOWER study.

Methods: Adults with R/R ALL were randomized 2:1 to receive blinatumomab or SOC. Study treatment consisted of 2 cycles of induction with blinatumomab (4 weeks on/2 weeks off) or SOC followed by consolidation of up to 3 additional cycles. Up to 4 additional maintenance cycles with blinatumomab (4 weeks on/8 weeks off) were allowed for up to 12 months. At any time after the first cycle, patients eligible for alloHSCT (investigator's discretion) could proceed to alloHSCT. Remission was defined as complete remission with full, partial, or incomplete hematologic recovery (CR/CRh/CRi) within 12 weeks of treatment initiation. OS from treatment initiation was estimated using Simon-Makuch and Cox regression methods. The study was not designed to measure the impact of alloHSCT on OS.

Results: Of the 97 patients who received on-study alloHSCT, baseline characteristics were generally comparable between treatment groups. Of these patients, 81% (50/65) treated with blinatumomab and 56% (18/32) treated with SOC had a response prior to transplant (Table 1); 56% (28/50) and 61% (11/18), respectively, were MRD negative. MRD relapse prior to transplant occurred in 14% (7/50) of patients treated blinatumomab and 6% (1/18) treated with SOC. More patients receiving SOC had matched sibling or unmatched donors (100% [18/18]) than did those receiving blinatumomab (86% [43/50]); more patients treated with blinatumomab had haploidentical (10% [5/50]) or cord blood transplants (4% [2/50]) than did those receiving SOC (0% [0/18]). Based on Simon-Makuch estimates, patients had higher survival rates following blinatumomab+alloHSCT than SOC+alloHSCT (last follow-up survival probability 50.9% vs 31.6%) (Figure 1). Using time-dependent Cox regression adjusting for response status, alloHSCT vs no alloHSCT after blinatumomab was associated with a 55% reduction in the risk of death (hazard ratio 0.45 [95% CI 0.24, 0.84]; p=0.012).

Conclusions: AlloHSCT following blinatumomab appears to benefit OS.

Keywords: AlloHSCT; Acute Lymphoblastic Leukemia; Blinatumomab





Long-Term Survival of Adults With B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) After Treatment With Blinatumomab And Subsequent Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract Content

Introduction: In B-cell precursor (BCP) acute lymphoblastic leukemia (ALL), blinatumomab has demonstrated efficacy in two phase 2 trials: MT103-203 (Gökbuget et al, *Blood* 2017) in minimal residual disease (MRD) and MT103-211 in relapsed/refractory (R/R) disease (Topp et al *Lancet Oncology* 2014). We describe the long-term outcomes after blinatumomab followed by allogeneic hematopoietic stem cell transplantation (alloHSCT).

Methods: Survival after blinatumomab and alloHSCT in continuous complete remission (CCR) was evaluated from two phase 2 trials, MT103-203 (MRD trial) and MT103-211 (R/R trial). In the MRD trial, 116 patients were treated with blinatumomab between November 2010 and February 2014. In the R/R trial, 189 patients were treated with blinatumomab between January 2012 and October 2013. For both trials, patients were followed up through 2017.

Results: Patient characteristics and outcomes are summarized in Table. Among blinatumomab patients in CCR, most patients who received alloHSCT in the MRD trial were >35 years of age whereas those in the R/R trial were younger (≤35 years). After a follow-up of at least 3 years, survival of blinatumomab patients with or without alloHSCT in the MRD trial according to age ≤35 years or >35 years was as follows: among patients ≤35 years, 16/26 (62%) patients with alloHSCT in CCR were alive versus 2/9 (22%) patients with no alloHSCT in CCR; among patients >35 yrs, 19/48 (40%) patients with alloHSCT in CCR were alive compared with 13/27 (48%) with no alloHSCT in CCR. Median overall survival (OS) from time of alloHSCT was not reached in patients ≤35 years in either trial (Table).

Conclusion/ summary: These results suggest that in transplant-eligible patients in CCR, alloHSCT following blinatumomab is a potential option.

Keywords: Survival; B-cell precursor; acute lymphoblastic leukemia; blinatumomab; HSCT



Prophylactic donor lymphocyte infusion for patients with advanced acute leukemia after allogeneic hematopoietic stem cell transplantation : an efficacy and safety analysis.

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Abstract Content

Objective: To explore the efficacy and safety of early prophylaxis donor lymphocyte infusion (pDLI) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for prophylaxis of relapse in patients with advanced acute leukemia (AL).

Method: We retrospectively analyzed all the patients with advanced acute leukemia who underwent allo-HSCT during January 1, 2013 to June 30, 2017 and then received pDLI in our center. All the patients received Colony-Stimulating Factor(G-CSF) primed peripheral blood progenitor cells (PBPCs) infusion and a short-term immunosuppressant therapy with low dose of closporine A(CSA) in complete remission(CR).

Result: At a median time of 105.5 (59-355) days after transplantation, 62 patients received pDLI. The median of CD3⁺ cells infused were 3.95 (0.4-7.6) x10⁷/kg. After a median follow-up of 23.0 (3.4-52.7) months, 42 patients stay alive in CR, 17 patients relapsed, 16 patients died and 3 of them died of infection or graft versus host disease (GVHD) in CR. The 2-year probability of overall survival (OS) and leukemia-free survival (LFS) was 71.5% (95%CI: 59.0%-84.0%) and 66.1% (95% CI: 53.6 %-78.6%) respectively. The cumulative incidence of relapse was 28.3% (95% CI:27.7%-28.9%) at 2 years. The 2-year cumulative incidence of III-IV grade of acute graft versus host disease (aGVHD) was 9.7% (95% CI: 9.5%-9.9%). The 2-year cumulative incidence of moderate and severe chronic graft versus host disease (cGVHD) was 30.9% (95%CI: 30.1%-31.7%). The 2-year cumulative incidence of GVHD-free and relapse-free survival (GRFS) were 36.9% (95%CI: 24.2%-49.6%). The 2-year cumulative incidence of treatment-related-mortality (NRM) was 5.7% (95% CI: 5.5%-5.9%). Mutivariate analysis showed that patients with cGVHD obtained better outcome and lower relapse rate (Figure 1). Older donor (≥40 years old) was independent risk factor for both OS (P=0.012) and GRFS (P=0.038). The patients who developed aGVHD before DLI were more likely to develop II-IV grade aGVHD after DLI (P=0.007). The occurrence of aGVHD after DLI (P=0.002) and higher hematopoietic cell transplantation-comorbidity index (HCT-CI) (P=0.028) were associated with higher cumulative incidence of moderate and severe cGVHD.

Conclusion: prophylaxis donor lymphocyte infusion following allogeneic hematopoietic stem cell transplantation may effectively decrease the relapse rate and improve the survival outcome of patients with advanced acute leukemia, without increasing GVHD morbidity and treatment-related-mortality (NRM).

Keywords: allogeneic hematopoietic stem cell transplantation; prophylaxis donor lymphocyte infusion; advanced acute leukemia





The efficacy analysis of allogeneic hematopoietic stem cell transplantation in 48 leukemia patients with central nervous system leukemia

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Abstract Content

Objective To investigate the efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the treatment of leukemia patients also suffering from central nervous system leukemia. MethodsA total of 48 leukemia patients with central nervous system leukemia admitted to our hospital from May 2012 to December 2017 were retrospectively analyzed. The criteria for enrollment: TLeukemic cells were seen in cerebrospinal fluid morphology; 2 Intracranial or intraspinal spaceoccupying, pathologic diagnosed with leukemia cell infiltration or leukemic treatment is effective; ③patients with clinical symptoms and signs, disappear after sheath injection or systemic treatment. Including, 21 cases of acute myeloid leukemia, 22 cases of acute lymphocytic leukemia, and 5 cases of chronic myelogenous leukemia. Before transplantation, 19 patients were evaluated for complete remission in their bone marrow, and 29 patients without remission. The pretreatment regimen used TBI (200 cGy 2 times/day, total 6 times) as the main protocol, and 3 patients were combined with whole brain and total spinal cord radiotherapy, 2 patients were combined with Cyber knife treatment, and children were treated with modified IDA combined with BUCY. ResultsAll 48 patients were successfully transplanted, the median time for leukocyte engraftment was 14 (10-23) days, the median time for platelet transplant was 16 (6-70) days. Bone marrow was evaluated 28 days after transplantation, all 48 patients reached complete remission, and DNA testing confirmed that they were all full donor chimcrism. The median follow-up time was 14 (2-69) months. Of these patients, 29 cases survived, 10 cases relapsed and three of them had recurrence of central nervous system leukemia after transplantation. One year after Allo-HSCT, the overall survival (OS) was 77.3±12.9%, the disease-free survival rate (DFS) was 77.6±9.9% in the remission group, and in the non-remission group the OS rate was 61.2±9.2%, the DFS rate was 57.7±9.3%. ConclusionAllogeneic hematopoietic stem cell transplantation is safe and effective for leukemia patients with central nervous system leukemia. TBI-based pretreatment regimen combined with whole-brain and total spinal cord radiotherapy or intracranial regional radiotherapy can further reduce the recurrence rate and enable patients to obtain Long-term survival.

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Keywords: Leukemia, Central nervous system, Systemic radiotherapy, Hematopoietic stem cell transplantation



Adult acute megakaryoblastic leukemia: rare association with cytopenias of undetermined significance and p210 and p190 BCR-ABL transcripts, prior to allogeneic stem cell transplantation

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Abstract Content

Acute megakaryocytic leukemia (M7-AML) is a rare form of acute myeloid leukemia (AML), which is associated with poor prognosis. The case presented in the current report is a statement for the difficult diagnosis and clinical management of M7-AML in the context of a previous hematologic disorder of undetermined significance and associated genetic abnormalities. Probably, following the complete hematologic remission and further with induction chemotherapy plus tyrosine kinase inhibitor therapy, the clinical management of this case will be followed by a allogeneic bone marrow transplantation, the only proven therapy to improve overall survival. Cytopenias of undetermined significance of the presence of BCR-ABL transcripts have yet to be presented in AML, but in chronic myeloid leukemia (CML), this scenario could be associated with aggressive disease. Abnormal BCR-ABL transcripts might prevent the protein from interacting with small G proteins, as presented by Colla et aligin AML or blast crisis of CML. By using dasatinib, which has previously been shown to be efficient in the blast crisis of CML,^a that has a clinical evolution similar to that of AML and is accompanied by cytopenias, we present for the first time a case that we consider to have a negative prognosis (BCR-ABL transcripts and cytopenias of unknown significance) and that is treated successfully and creates a bridge toward stem cell transplantation. Such clinical cases may be aggressive at presentation, but using modern combination chemotherapy with small molecule-based therapy and cellular therapies, the patient outcome might be improved. Still, we should emphasize that this manuscript is a case report and should be considered as such with all its limitations. Systematic recordings and long-term follow-ups are required to confirm our results.

Keywords: BCR-ABL transcript, acute megakaryocytic leukemia, bridge to transplant



Prognostic impact of cytogenetic abnormalities on outcome of allogeneic hematopoietic stem cell transplantations for adults with acute myeloid leukemia – a single institute analysis of 320 recipients

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Abstract Content

<Introduction>

In acute myeloid leukemia (AML), diagnostic karyotype is one of the most powerful independent prognostic factors for disease response and survival, but the clinical impact of karyotype evolution during therapy remains uncertain, especially on outcome of allogeneic hematopoietic stem cell transplantation (Allo-HSCT).

<Methods>

We retrospectively analyzed the outcome of 462 consecutive AML patients who underwent Allo-HSCT for the first time at Toranomon Hospital between 2008 and 2016. Patients who were diagnosed with therapyrelated AML (n=23), were ECOG PS of 3 or more, had serious active infection at the time of transplantation (n=60), or lacked information on diagnostic karyotype (n=59) were excluded. Cytogenetic abnormalities at diagnosis and just before transplantation were categorized based on the revised Medical Research Council (MRC) classification.

<Results>

Three hundred and twenty patients were included in this study. The median age at transplantation was 59 (range, 17-74) years, with a median HCT-CI score of 2 (0-7). 261 (82%) were not in remission. Underlying diseases were AML-NOS in 102, AML with recurrent genetic abnormalities in 37, and AML-MRC in 181. 248 (78%) received umbilical cord blood transplantation (UCBT), 31 (10%) did related, and 40 (13%) did unrelated HSCT. Patients were categorized into three groups, adverse (n=83), intermediate (n=215), and favorable (n=22), according to the cytogenetic abnormalities at diagnosis.

With a median follow-up of 26 (range, 1-103) months, 3-year probabilities of OS, PFS, relapse rate and NRM for entire population were 41.3%, 36.8%, 33.7, and 29.6%, respectively. Patients in adverse group showed a higher incidence of relapse (46.3% vs. 29.2%, P < 0.01) and a lower OS (27.1% vs. 45.3%, P < 0.01) compared with those in intermediate/favorable group.

Among adverse group, patients with monosomal karyotype (MK) showed a higher incidence of relapse (59.0% vs 29.8%, P = 0.01) and a lower PFS (20.0% vs 37.5%, P = 0.04) compared with those without MK, both of which were confirmed in multivariate analysis. CBT showed lower relapse rate compared with the other sources (38.7% vs 85.6%, P = 0.01), which was also confirmed in multivariate analysis, whereas CBT did not improve PFS because of its higher rates of NRM.

We also compared cytogenetic abnormalities at diagnosis and just before transplantation in non-remission patients (n=261). Patients who lacked information on karyotype before transplantation (n=72) were excluded. 18 patients (10%) were re-categorized from intermediate to adverse group before transplantation, and they showed a higher incidence of relapse compared with those remained intermediate group (64.7% vs 24.9%, P = 0.01), which was also confirmed in multivariate analysis.

<Conclusion>



This retrospective study demonstrated that diagnostic karyotype is an independent prognostic factor following Allo-HSCT in AML patients. MK adversely affected PFS by increased incidence of relapse. In non-remission patients, cytogenetic abnormalities just before transplantation predicted outcome of Allo-HSCT more accurately than diagnostic karyotype.

Keywords: cord blood transplantation, acute myeloid leukemia, karyotype



High risk disease status significantly influences the clinical outcomes of acute leukemia patients who experienced relapse and receiving chemotherapy plus donor lymphocyte infusion after haploidentical hematopoietic stem cell transplantation

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Abstract Content

Introduction: Post-transplant relapse remains the most important causes of transplant failure after haploidentical hematopoietic stem cell transplantation (haplo-HSCT). Chemotherapy plus donor lymphocyte infusion (Chemo-DLI) can significantly improve the outcomes of patients who relapsed after haplo-HSCT compared with those received chemotherapy alone. This is the first study that we aimed to investigate the prognostic value of disease characteristics in patients who experienced relapse and received Chemo-DLI after haplo-HSCT.

Methods: This study included acute leukemia patients who experienced relapse after haplo-HSCT (n=108) at the Institute of Hematology, Peking University, Beijing, China between August 2003 and June 2015. Chemotherapy sensitive before haplo-HSCT was defined as achieving complete remission (CR) within 2 induction chemotherapies, and the others were defined as chemotherapy resistant. Subjects with acute leukemia were considered to be at standard risk before haplo-HSCT if they were in first or second CR prior to HSCT. Patients were classified as high risk if they had acute leukemia in its third CR or greater, relapse, or non-remission prior to HSCT. Early relapse after haplo-HSCT was defined as relapse within 1 year after haplo-HSCT, and late relapse was defined as relapse \geq 1 year after haplo-HSCT.

Results:

Chemotherapy sensitivity and the clinical outcomes after Chemo-DLI

A total of 52 (66.7%) and 14 (46.7%) patients in chemotherapy sensitive and resistant group, respectively, achieved CR after Chemo-DLI (P=0.056). The 2-year cumulative incidence of NRM was 7.5% versus 22.7% (P=0.034) in chemotherapy sensitive and resistant groups. The 2-year probabilities of PFS and OS were significantly better in chemotherapy sensitive group compared to those of chemotherapy resistant group (Figure 1A-B). Chemotherapy resistant was associated with higher risk of NRM after Chemo-DLI.

Disease status prior to HSCT and clinical outcomes after Chemo-DLI

A total of 62 (67.4%) and 4 (25.0%) patients in standard and high risk groups, respectively, achieved CR after Chemo-DLI (P=0.001). The 180-day cumulative incidence of PD was 49.8% versus 75.0% (P=0.009) in standard and high risk groups. The 2-year probabilities of PFS and OS were significantly better in standard risk group compared to those of high risk group (Figure 1C-D). High-risk disease status prior to haplo-HSCT was associated with poorer survival after Chemo-DLI.

Time from HSCT to relapse and clinical outcomes after Chemo-DLI

A total of 39 (51.3%) and 27 (84.4%) patients in early and late relapse group, respectively, achieved CR after Chemo-DLI (P=0.001). The 2-year cumulative incidence of PD was 73.4% versus 50.4% (P=0.004) in early and late relapse groups. The 2-year probabilities of PFS and OS were significantly better in early relapse group compared to those of late relapse group (Figure 1E-F). Relapse within 1 year after haplo-HSCT was significantly associated with higher risk of PD and poorer survival after Chemo-DLI.



Conclusion: our findings suggested that some disease characteristics can predict the outcomes of patients experienced relapse and received Chemo-DLI after haplo-HSCT, and Chemo-DLI could not overcome the poor prognostic significance of a high-risk status of acute leukemia prior to haplo-HSCT. New therapeutic strategy should be further identified to improve the clinical outcomes of these patients.

Keywords: donor lymphocyte infusion; graft-versus-leukemia; chemotherapy resistant; acute leukemia





The Treatment Outcomes of Hematopoietic Stem Cell Transplantation According to Donor Types in Elderly Patients with Acute Myeloid Leukemia

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Abstract Content

Introduction

Few studies have reported data on the efficacy of hematopoietic stem cell transplantation (HCT) from alternative donors in elderly acute myeloid patients (eAML).

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Methods

This retrospective study included 100 consecutive eAML aged >60 years who underwent an autologous (auto-HCT, n=18) or allogeneic HCT (allo-HCT) from either a matched sibling (MSD, n=30), unrelated (MUD, n=24), or haploidentical (haplo, n=28) at the Catholic Blood and Marrow Transplantation Center (May 2005–February 2016). Reduced-intensity conditioning was used in all but two patients with allo-HCT. MUD and hapo donors received antithymocyte globulin.

Results

Patients were in first (n=84) or second (n=13) complete remission or relapse (n=3) with a median age of 62 years (range, 60–69). With a median follow-up of 48.2 months (range, 4.5–142.2), the 4-year cumulative incidences (CIs) of nonrelapse mortality (NRM) and relapse were $51\%\pm10\%$ and $13\%\pm7\%$ for MSD, $25\%\pm9\%$ and $13\%\pm7\%$ for MUD, $21\%\pm9\%$ and $15\%\pm7\%$ for haplo, and $22\%\pm10\%$ and $40\%\pm12\%$ for auto-HCT (P=0.067; P=0.151). The corresponding 4-year overall (OS) and disease-free survival (DFS) were $40\%\pm10\%$ and $23\%\pm12\%$, $67\%\pm10\%$ and $63\%\pm10\%$, $64\%\pm10\%$ and $64\%\pm10\%$, and $37\%\pm12\%$ and $37\%\pm12\%$, respectively (P=0.104 and P=0.084). Regarding allo-HCT, the 1-year CI of moderate-to-severe chronic graft-versus-host disease (GVHD) was significantly increased in MSD ($57\%\pm9\%$) compared to MUD ($42\%\pm10\%$) and haplo ($11\%\pm6\%$, P=0.001). In multivariate analysis, donor type was associated with chronic GVHD, NRM, DFS, and OS, while no influence was seen on relapse and acute GVHD.

Conclusions

These data suggest an encouraging role of alternative donor HCT to improve long term survival rates in eAML, and a need for strengthening of GVHD prophylaxis to reduce chronic GVHD for MRD HCT.

Keywords: elderly AML, hematopoietic stem cell transplantation, donor type



Haploidentical Hematopoietic Stem Cell Transplant for Acute leukemia: A Single Center Experience

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Abstract Content

Introduction: Allogeneic hematopoietic stem cell transplantation continues to be the most potent antileukemic treatment for patients with high-risk or chemo-refractory acute leukemia. It is now not limited to those recipients who have an available matched-sibling donor or matched-unrelated donor as haploidentical stem cell transplant seems to be a promising option. Over recent years in the absence of a HLA matched donor, haploidentical donors have been increasingly adopted as a source of stem cells for allogeneic HCT. Haploidentical related donor is one of the most important alternative sources for those without HLA identical sibling donor

We report our experience with haplo identical HSCT in patients with high Acute leukemia.

Material and methods: Forty consecutive patients diagnosed with High risk acute leukemia including refractory or relapsed Acute Lymphoblastic leukemia (ALL) or Acute Myeloid Leukemia (AML) who underwent 41 Haploidentical HSCT between Nov 2012 and June 2018 were included in this retrospective study. Out of 40 patients, 23 patients had AML and 17 patients had ALL (Table 1). One patient underwent 2nd haplo HSCT for primary graft failure. G-CSF mobilized peripheral blood stem cell graft was used in all transplants. All patients received standard bacterial/ viral/ fungal and VOD prophylaxis and treated in HEPA filtered room.

Of the 41 transplants non myeloablative (NMA) conditioning was used in 27 patients (66%) and 14 patients (34%) had received myeloablative regimen(MA). Detail of conditioning regimen as follow: NMA in 27: Flu/Cy/TBI (Fludarbine 30 mg/m² X 5 days, Cyclophosphamide 14.5mg X 2 days and 200 cG TBI); MA : Bu/Flu/Cy in 11 (Busulfan 3.2 mg/kg X 4 days, Fludarbine 25mg/m² X 5 days, Cyclophosphamide 14.5 mg X 2 days); Thymoglobulin/Flu/Thiotepa/MeI in 2 (Thymoglobulin 1.5 mg/kg X 3 days, Fludarabine 40mg/m² X 4 days, Thiotepa 10mg/kg X 1 day, Melphalan 70 mg/m² X 2 days) and Flu/Cytarabine/Idarubicin/MeI in one (Fludarabine 30mg/m² X 5 days, Cytarabine 2gm/m² X 5 days, Idarubicin 8mg/m² X 2 days, Melphalan 200mg/m² X 1 day). GVHD prophylaxis included PTCy 50 mg/kg/day on D3 and 4, Tacrolimus and Mycophenolate from D5 in 39 transplants. Two patients received T cell depletion graft.

Results: The median age of patient's was 30 years (range 5 years-55 years). Median neutrophil and platelet engraftment was on day +15 and day +22 respectively. Median CD34 cell dose was 6.9 x 10⁶ cells/kg. At median follow up of 134 days (range 12-1667) the leukemia free survival; overall survival and transplant related mortality were 30%, 40%, and 60%, respectively (Table 2). Twenty patients (50%) developed CMV reactivation post transplant .Ten patients (25%) developed acute GvHD grade 2-4. Ten patients (25%) on follow up developed chronic GVHD. Twenty four (60%) patients expired and the cause of death was predominantly infection (50%) followed by persistent disease in 38% and GvHD in 12%.

Conclusion: Haploidentical HSCT may be considered as a valid option for patients with high-risk leukemia lacking HLA identical donor preferably in the early disease status. T cell replet HSCT does provide good antileukemic activity aginst high risk acute leukemia.

Keywords: haploidentical, outcome, acute leukemia



Impact of gene mutations on overall survival of allogenic hematopoietic stem cell transplantation for high risk acute myeloid leukemia in complete remission

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Abstract Content

Introduction: Gene mutations (such as FLT3-ITD, ASXL1, TET2, DNMT3A, RUNX1, PHF6, NRAS, KRAS, TP53 etc.) that are generally considered to have poor prognosis have significant impact on survival in patients with acute myeloid leukemia (AML). In present study, gene mutations on overall survival (OS) of allogeneic hematopoietic stem cell transplantation (HSCT) for high risk (according to NCCN-2018 risk stratification) AML was investigated. Methods: Between April 2012 to December 2016, 140 high risk AML patients who underwent allo-HSCT in our center were included, all of them were in complete remission (CR) status before HSCT .The median age was 22 (range, 2 to 58) years old. Male to female was 78 to 62. The median disease course was 6 (1-52) months. Transplants at CR1, CR2 were 114 (83.8%), 26 (19.1%) respectively. Donor sources were matched sibling donor (MSD) in 26 (19.1%), matched unrelated donor (MUD) in 22 (16.1%) and haploidentical donor (HID) in 92(67.6%). Conditioning regimens were Busulfan(Bu) plus Cyclophosphamide(Cy) in 132 (82.6%) and total body irradiation(TBI) plus Cy in 8(17.4%). Antithymocyte globulin was used in MUD and HID HSCT. Cyclosporine, short-term methotrexate, and mycophenolate mofetil were employed for GVHD prophylaxis. Results: The surviving patients had a median follow-up 36 (range, 18 to 73) months with an OS of 73.1%. Univariate analysis showed that FLT3-ITD(with vs without ,65.2%vs 72.3%,P=0.919); type of gene mutations (single FLT-ITD vs FLT3-ITD with other mutations vs other type of mutations vs none,68.3%vs 65.6%vs 69.7%vs 78.4% ,P=0.497); number of gene mutations (one vs two vs three or more vs none,74.4%vs 78.7%vs 56.0%vs 87.5%,P=0.081)and cytogenetics (intermediate risk vs high risk , 62.8%vs 73.1%,P=0.910) had no significant effect on OS. OS was also not related to patient's age (?18 y vs ≥18 y,P=0.762); donor's age (?36y vs ≥36y, P=0.624); conditioning regimen?BU-based vs TBI-based,P=0.072?; type of donor(MSD vs MUD vs HID,P=0.479); Donor-patient sex match(M-M vs M-F vs F-F vs F-M,P=0.975);Median MNC count(×10⁸/kg) (?4.47 vs ≥4.47,P=0.549);Median (?8.06 vs ≥8.06,P=0.158);Median CD34⁺count(x10⁶/kg) CD3⁺count(×10⁸/kg) (?1.55vs ≥1.55,P=0.781);acute graft versus host desease(aGVHD) (grade 0-?vs ≥ grade?-?, P=0.959). On the other hand, the CR status before HSCT(CR1 vs CR2,P=0.027)?minimal residual disease (MRD) detected by multiparameter flow cytometry (MFC) before HSCT (negative vs positive,P=0.041)?extramedullary lesion (with vs without,P=0.046)?HCT-CI (0 vs ≥1,P=0.043)?chronic GVHD (with vs without,P=0.013)?disease type (primary vs secondary,P=0.003)?WBC count at diagnosis (<10×10⁹/L vs ?10×10⁹/L,P=0.057)?ABO blood type match (matched vs major mismatched vs minor mismatched vs different, P=0.005) had significant effect on OS. The multivariate analysis risk factors for OS were only adversely associated with secondary AML (P=0.005) and WBC count more than 10×10⁹/L at diagnosis(P=0.002). Relapse was associated with CR status before HSCT(CR1 vs CR2 P=0.005). Patients with grade ?-? aGVHD (P=0.042) and secondary AML at diagnosis(P=0.033) were the risk factors for transplantation related mortality. Conclusion: Under our HSCT protocol, allogenic HSCT has attenuated the influence of gene mutations on OS in high risk AML patients.

Keywords: Gene Mutation;AML;High Risk;Allo-HSCT





Comparable outcomes of myeloablative conditioning regimen without antithymocyte globulin in CBT for pediatric patients with hematological malignancies with a weight of more than 30 kilograms vs. less than 30 kilograms

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Abstract Content

Purpose

Cord blood transplantation (CBT) is an effective option for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and myelodysplastic syndrome (MDS), but children with heavier weight (weighing more than 30kg) always have inferior outcomes than children with lighter weight. This article aims to identify the outcomes of myeloablative conditioning regimen (MAC) without antithymocyte globulin (ATG) in CBT for pediatric patients with different weight.

Methods

We conducted a retrospective analysis including 142 pediatric patients weighing less than 30kg and 130 pediatric patients weighing more than 30kg from May 2008 to September 2017 in our center. All the children were given a combination of cyclosporine (CsA) and mycophenolate mofetil (MMF) without ATG for graft-vs.-host disease (GVHD) prophylaxis. Most of the lighter children and two third of the heavier children were given busulfan(Bu) based MAC while another one third of the heavier children were given total body irradiation (TBI) based MAC.

Results

Children with different weight had no difference in gender, disease status, disease risk, and blood type. However, heavier children were older and had more loci of human leukocyte antigen(HLA) mismatch (P=0.000 and P=0.016). More children weighing more than 30kg suffered ALL than children weighing less than 30kg (P<0.05). The cumulative neutrophil engraftment rate by 42 days and the platelet engraftment rate by 120 days were almost the same in heavier children group and lighter children group (97.7% vs. 94.4% and 86.2% vs. 86.6%, p=0.284 and p=0.313, respectively). Non-relapse mortality (NRM) and relapse rate were also similar in these two groups (16.3% vs. 12.3% and 22.0% vs. 21.9%, p=0.345 and p=0.923, respectively). While the incidence of chronic GVHD (cGVHD) was higher in heavier children group (17.9% vs. 9.4%, P<0.05), but not grade II to IV acute GVHD (aGVHD) nor grade III to IV aGVHD. Three years of overall survival (OS), disease-free survival (DFS) and GVHD-free/relapse-free survival (GRFS) showed no significant difference in these two groups.

Conclusions

This study is the first to demonstrate the similar curative effect of myeloablative conditioning regimen without antithymocyte globulin in CBT for pediatric patients with different weight. A large-scale prospective study is needed.

Keywords: Pediatric patients; Cord blood transplantation; ATG; Hematological malignancy



The comparison between Umbilical cord blood transplantation and HLA-identical sibling allo-PBSCT in the treatment of MDS-EB and AML-MRC

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Abstract Content

Abstract: Objective To analyse and evaluate the clinical effects of Umbilical cord blood transplantation (UCBT) and HLA-identical sibling allo-PBSCT for patients with Myelodysplastic syndrome with increased progenitor cells (MDS-EB) or AML-MRC. Methods A retrospective analysis on 39 cases receiving UCBT and 28 cases receiving HLA-identical sibling allo-PBSCT in the Department of hematology, the first affiliated hospital of University of Science and Technology of China from August 2011 to December 2017. Results The hematopoietic system were successfuilly reconstructed in 36 cases receiving UCBT. The median time of absolute neutrophil count (ANC) > 0.5 x 109 / L was 17.5 (12 ~ 31) d .The disease-free survival was performed in 30 patients and the median survival time was 19 (1 ~ 76) months. With the remaining 9 patients all died, median survival time was 4 (0.5 ~ 30) months. 2 of them died of relapse, 3 of aGVHD, and 4 of Multiple organ dysfunction syndrome. The hematopoietic system were successfully reconstructed in all cases receiving HLA-identical sibling allo-PBSCT. The median time of absolute neutrophil count (ANC) > 0.5 x 109 / L was $11(10 \sim 20)$ d .22 patients realized the disease-free survival and the median survival time was 23(1~82)months. The remaining 6 patients all died, median survival time was 6.5(2~18) months. 2 of them died of relapse, 1 of aGVHD, 2 of pulmonary infection and 1 of thrombotic microangiopathy(TMA).Conclusion Allogeneic hematopoietic stem cell transplantation (AllO - HSCT) is the only way to cure MDS for the moment.UCBT is taking seriously for its weak immunogenicity and lower cGVHD effect. It can be used as an effective method for treatment of high-risk patients with MDS if the compatriot donor with all coincident is absenced.





FLT3 -ITD positive is an independent risk factor for adverse outcomes after allogeneic hematopoietic stem cell transplantation in AML

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Abstract Content

Introduction : FLT3-ITD mutation in AML produced a negatively impact on the prognosis of patients if treated with chemotherapy only. Methods: To explore its influence on AML patients after allogeneic hematopoietic stem cell transplantation (HSCT), we conducted a retrospective study of 239 AML patients who underwent allogeneic HSCT in our center from January of 2014 to December of 2017, all of whom had undergone FLT3-ITD mutation testing at AML diagnosis. Results: 50 patients (21%) was demonstrated with FLT3-ITD positive, and the baseline was comparable in the two groups apart from FLT3-ITD positive patients had higher median marrow blasts percentage in the AML diagnosis (77.64%VS 58.25%, P=0.01) compared with FLT3-ITD negative AML patients. The estimated 3 years overall survival (OS) and disease-free survival (DFS) are respectively 70% and 81.9% in all patients. The estimated three years OS in FLT3-ITD positive patients and FLT3-ITD negative patients was similar (58.2%VS 72.9%, p=0.33). In contrast, patients with FLT3-ITD mutation had a significantly lower estimated three years DFS (69.3% vs 84.4%; P=0.02) because of a higher relapse rate for the three years cumulative incidence of relapse (30.3%VS14.1%, p=0.015), and in multivariate analyses, FLT3-ITD mutation (HR, 2.62, 95%CI 1.20 to 5.75, p=0.016) contributed independently to the risk of relapse. Conclusion: These data demonstrate high risk of relapse after allogeneic HCT for FLT3-mutated AML that translates into adverse disease-free and overall survival outcomes.

Keywords: acute myeloid leukemia; FLT3-ITD; allogeneic hematopoietic stem cell transplantation





Allogeneic Hematopoietic Stem Cell Transplantation for Refractory /Relapsed B-Cell Acute Lymphoblastic Leukemia after CART Cell Therapy

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Abstract Content

[Introduction] Anti-CD19 CART cell therapy has shown promising results in refractory /relapsed B-cell acute lymphoblastic leukemia (B-ALL). However, whether allogeneic hematopoietic stem cell transplantation (allo-HSCT) should be performed after CART therapy to achieve durable complete remission (CR) is still undefined. Some studies have reported CD19 negative relapse at 3 to 6 months after CART therapy if those patients did not be bridged to allo-HSCT; while the others have shown a similar overall survival (OS) at 6 months for the patients with or without allo-HSCT after CART therapy (79% versus 80%). But the studies mentioned above had only a few cases (4-13) bridged to allo-HSCT.

[Methods] Between August, 2017 and April, 2018, thirty-six cases with relapsed/refractory B-ALL who underwent allo-HSCT after achieved CR or CR with incomplete count recovery (CRi) by anti-CD19 (30 cases) or anti-CD22 (6 cases) CART cell therapy were enrolled. The median age was 8 years (1year10months-42years). Nine patients (25%) had poor cytogenetic or molecular abnormalities, including 4 with TP53 mutation/deletion, 1 with FLT3-TKD mutation, 1 with BCR-ABL1, 1 with MLL-AF4, 1 with complex karyotype and 1 with monosomal karyotype. The median time from CART cell infusion to allo-HSCT was 53 (34-98) days. Majority of the cases (28/36, 77.8%) received allograft from related haploidentical donors, 6 from matched siblings and 2 from matched unrelated donors. Myeloablative conditionings with either total body irradiation -based or busulfan-based regimen were used. OS and leukemia-free survival (LFS) were performed by Kaplan-Meier method.

[Results] Seven cases (19.4%) developed CMV viremia, and 6 patients (16.7%) had EBV viremia. Eleven cases (30.6%) presented with hemorrhagic cystitis. The incidence of acute graft-versus-host disease (GVHD) was 25% (5 cases in grade I , 3 cases in grade II and 1 case in grade II). Two cases developed limited chronic GVHD. With a median follow-up time of 200 (105-353) days, 34 cases were still alive. The 6-month OS rate was 96.9% (95%CI=79.8%-99.6%). Five cases (13.9%) had relapse post allo-HSCT, 2 patients died from relapse, and 2 cases received anti-CD22 CART infusion and obtained CR again. The 6-month LFS rate was 91.7% (95%CI=76.3%-97.2%).

[Conclusion] Our preliminary clinical results have shown that with current strategy, a high 6-month OS (96.9%) and LFS (91.7%) rates have been achieved. We consider a quick bridging to allo-HSCT after CR with CART therapy and our established transplant protocol for haploidentical HSCT are key factors resulting in good transplant outcomes. Long-term follow up is warranted.

Keywords: allogeneic hematopoietic stem cell transplantation;refractory /relapsed B-cell acute lymphoblastic leukemia;CART therapy;overall survival;leukemia-free survival



Progress of allogeneic transplantation at our hospital for 40 years; increasing of older patients but decreasing in the rate of non-relapse mortality

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Abstract Content

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has curative potential against hematological malignancies for almost 4 decades. Expanding indications for allo-HSCT, advances in treatment for complications, introduction of reduced intensification transplantation and increased availability of alternative graft sources have resulted in a growing number of HCT survivors. However, detailed analysis of these progress have not been studied. Here we performed a retrospective single-center study to assess changes in outcomes after allo-HSCT over 4 decade's periods. We separated the ear of transplantation as 1977-1989, 1990-1999, 2000-2009 and 2010-2017. The number of patients were 58, 207, 356 and 387, respectively (total 1008). Median age is increasing from 29 years old in 1977-1989 to 45 years old 2010-2017. There is no significant difference in the rate of disease risk. The rates of 5-year overall survival (OS) were 41.4%, 45.8%, 42.9% and 48.6%, respectively, without significant difference. One-year non-relapse mortality (NRM) were 36.2%, 28.9%, 24.6% and 17.0%, respectively, with significant difference (p<0.01). In the past 40 years, the age to receive allo-HSCT has been rising, but the risk of patients has been constant. The rate of OS remained unchanged, but that of NRM decreased significantly. Taken together, it is due to the progress of transplant technology that the NRM rate is decreasing despite older patients becoming transplanted in the last 4 decades.

Keywords: non-relapse mortality, over all survival



Topic: Abstract No: 8860 Transplantation

for

leukemia

Treatment of refractory/relapsed acute myeloid leukemia (AML) with CLAG regimen followed by allogeneic hematopoietic stem cell transplantation: A report of three clinical cases

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Abstract Content

Treatment of refractory/relapsed acute myeloid leukemia (AML) with CLAG regimen followed by allogeneic hematopoietic stem cell transplantation: A report of three clinical cases

Introduction: Patients with refractory/relapsed AML have very poor prognosis. There are limited treatment options for them worldwide. Our study aimed to explore the efficacy and safety of CLAG-based conditioning regimen followed by hematopoietic stem cell transplantation (allo-HSCT) for refractory/relapsed AML.

Methods: From July 2017 to March 2018, three patients with refractory/relapsed AML received salvage allo-HSCT at our center. Two men and one woman. The median age was 30 (range 27-35) years old. One patient underwent matched sibling donor (MSD) allo-HSCT, one patient underwent haploidentical related donor (HRD) allo-HSCT, and one patient underwent 9/10 HLA matched unrelated donor (URD) allo-HSCT. At the time of transplantation, all patients have relapsed for the first time. The bone marrow blasts were 6.5%, 49.5% and 61.5%. All patients were given myeloablative conditioning regimen. For the patient receiving MSD-HSCT, the conditioning regimen consisted of cladribine(5mg/m²/d) intravenously on days -12 to -10, cytarabine(2g/m²/d) intravenously on days -12 to -10, busulfan(3.2mg/kg/d) intravenously on days -7 to -4, cyclophosphamide(60mg/kg/d) intravenously on days -3 to -2, ATG(4.5mg/kg) total dose intravenously on days -3 to -1; MeCCNU(250mg/m2/d) orally on day -1. For the patient receiving URD-HSCT, the conditioning regimen consisted of cladribine(5mg/m²/d) intravenously on days -11 to -9, cytarabine(2g/m²/d) intravenously on days -11 to -9, busulfan(3.2mg/kg/d) intravenously on days -7 to -4, cyclophosphamide(60mg/kg/d) intravenously on days -3 to -2, ATG(6mg/kg) total dose intravenously on days -4 to -1, MeCCNU(250mg/m²/d) orally on day -1. For the patient receiving HRD-HSCT, the conditioning regimen consisted of cladribine(5mg/m²/d) intravenously on days -15 to -11, cytarabine(2g/m²/d) intravenously on days -15 to -11, busulfan(3.2mg/kg/d) intravenously on days -8 to -5, cyclophosphamide(60mg/kg/d) intravenously on days -4 to -3, ATG(6mg/kg) total dose intravenously on days -5 to -2, MeCCNU(250mg/m²/d) orally on day -2. All patients received the same GVHD prophylaxis consisting of cyclosporin, methotrexate, and mycophenolate mofetil. The median mononuclear cell count and CD34+ cell count patients received were 18.33 x 108/kg and 9.351x 106/kg.

Results:The median follow-up for all patients was 139 (range 119-357) days, and all patients achieved engraftment successfully. The median time of neutrophil and platelet engraftment were 11 days and 12 days. All three patients got complete remission (CR) after transplantation, two patients received prophylactic donor lymphocyte infusion (DLI). One patient suffered Grade I aGVHD at days +23, one patient suffered Grade II aGVHD at days +13. One patient relapsed 4 months after transplantation, then he received chemotherapy and DLI and achieved CR again. Two patients remained sustaining CR.

Conclusion:For treatment of refractory/relapsed AML, we applied CLAG-based conditioning regimen followed by allo-HSCT, all patients engrafted successfully and achieved CR without severe GVHD. Our preliminary result showed CLAG regimen followed by allo-HSCT might be a well-tolerated and effective regimen for patients with refractory/relapsed AML. A clinical trial with more patients and long-term follow-up is required to verify the conclusion.

Keywords: CLAG;relapsed;allo-HSCT;AML;conditioning regimen



Long-term outcomes in patients with Acute Lymphoblastic Leukemia post allogeneic transplant

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Abstract Content

Curative therapy for eligible patients with high risk Acute Lymphoblastic Leukemia (ALL) necessitates an allogeneic transplant. However, many patients who survive the initial transplant eventually succumb to complications. There is paucity of data on the long-term outcomes of these patients. We therefore aim to look at the overall survival, relapse-free survival and complications in our cohort of patients after the initial transplant period.

Patients who were diagnosed with ALL and underwent allogeneic transplant 8 years ago were identified from our institutional disease registry. The characteristics of the patients, survival time, time to relapse, complications including graft-versus host disease (GVHD), infections, endocrinopathies, post-transplant lymphoproliferative disease (PTLD) and secondary malignancies post allogeneic transplant were collated. STATA (version 11.0) was then used to analyse the data collected.

37 patients who were diagnosed with ALL and underwent allogeneic transplant from January 2005 to December 2010 were identified. The median follow-up time following transplant was 7 years (range 11 days – 15 years). The median age at diagnosis was 28 (range 17-67), 30 (81%) patients had B-ALL, 6 (16%) had T-ALL and 1 (3%) unknown. 23 patients (62%) died, with the 2 year and 5 year and 10-year overall survival being 50.5% (SE 8.5), 41.3% (SE 8.5) and 27.8% (SE 9.9) respectively. The main causes of death were infection (43%) and GVHD (8.7%). 4 patients (11%) relapsed post-transplant, and subsequently demised, with the 2-year and 5-year relapse free-survival being 55% and 41% respectively. All relapses occurred within 2 years of the initial transplant. 23 patients (62%) had GVHD, of which, 9 (24%) had acute GVHD, 12 (32%) had chronic GVHD and 3 (8%) had both. 33 patients (89%) had infections, including cytomegalovirus infections, fungal and bacterial sepsis. 9 patients (24%) had endocrinopathies including steroid induced hyperglycemia, adrenal insufficiency and hypogonadism. 1 patient (3%) had PTLD, and none had secondary malignancies.

As all disease relapses occurred within the first 2 years post-transplant, it highlights the need for close followup and increased vigilance in the early years post-transplant. Following the initial post-transplant period, the long-term non-relapse mortality remains high. As such, the need for continued follow-up and screening of complications post-transplant remains relevant.



Busulfan-containing conditioning regimens in allogeneic hematopoietic stem-cell transplantation for acute lymphoblastic leukemia: Single tertiary center experience in Taiwan

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Abstract Content

The allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is viewed as the ultimate cure for acute lymphoblastic leukemia (ALL). An essential component of allo-HSCT is the conditioning regimen administered before the hematopoietic stem-cell infusion. This study is aimed to compare outcomes of ALL patients receiving either a busulfan with cyclophosphamide (BuCy) or a total body irradiation(TBI)-based regimen. We retrospectively analyzed data from National Taiwan University Hospital (NTUH) institute registry. We enrolled 206 adult patients with ALL who received allo-HSCT between 1997 and 2016 and compared outcomes of patients receiving either a BuCy-based or a TBI-based regimen. There were more B-cell ALL than T-cell ALL (70.5% vs 29.5%). A total of 36 patients among the 165(21.7%) with known cytogenetics carried the Philadelphia chromosome(Ph) while 26 patients (16.3%) carried complex karyotype. Before the allo-HSCT, 157(76.2%) patients achieved first or late complete remission(CR). The main source of stem-cell was from peripheral blood (71.8%), followed by bone marrow (30.4%). Siblings comprised 49.1% of the donors. A total of 128 patients (62%) received BuCy-based conditioning, either myeloablative(MA) or reduced intensity stem cell transplantation (RIST) and 74 patients (36%) received TBIbased regimen. The mean dose of stem cell was 3.71 + 1.32 x106/Kg CD34+ cells. We use cyclosporine and mycophenolate mofetil for prophylaxis of graft-versus-host disease (GvHD). In results, patients received BuCy-based regimen performed as well as TBI-based group in terms of overall survival (50.8% vs 35.1%, p=0.107). As to relapse-free survival(RFS), BuCy group had slightly better result, albeit p value didn't reach significance (p=0.069). In this study, all regimen groups yielded similar treatment-related mortality(TRM), (p=0.277) and incidences of grade 3-4 acute GVHD at day+100, (p=0.474). In conclusion, patients received BuCy-based regimen or TBI-based regimen as conditioning had similar results in terms of OS, RFS, TRM, and GVHD.

Keywords: Transplantation; allogeneic; lymphoblastic; leukemia; busulfan





Impact of Remission Status on the Outcome of Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

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Abstract Content

Objectives: Hematopoietic stem cell transplantation (HSCT) remains a curative option for AML. Treatment outcome is superior in patients achieving complete remission (CR) or CR with incomplete blood count recovery (CRi) before transplantation. This retrospective study examined the impact of CRi on the outcome of AML patients undergoing HSCT.

Methods: Patients with de novo AML achieving CR/CRi with conventional chemotherapy who underwent first allogeneic HSCT from sibling or matched-unrelated donors in Hong Kong were recruited from January 2012 to July 2017. Data were censored on 31 July 2018 to allow a minimal possible follow-up time of 12 months before analysis. CRi was defined by bone marrow blasts less than 5% with hemoglobin <10 g/dL, platelet <100x10⁹/L or neutrophil <1x10⁹/L. Leukemia-free survival (LFS) and overall survival (OS) were evaluated by Kaplan-Meier analysis and compared by the log-rank test. Cox proportional hazard model was used in univariate and multivariate analyses.

Results: 168 patients (74 men, 94 women, median age at HSCT 46 years) were analyzed. Fourteen (8%), 92 (55%) and 62 (37%) patients were classified into good, intermediate and adverse risk groups according to the 2017 European LeukemiaNet (ELN) recommendations. 128 patients received myeloablative whereas 40 received reduced-intensity conditioning HSCT from sibling (N=88, 52%) or matched unrelated (N=80, 48%) donors. (Table 1). 125 patients received HSCT at CR (CR1=75, CR2=44, beyond CR2 = 6) and 43 at CRi (CRi1=22, CRi2=15, beyond CRi2=6). Acute and chronic graft-versus-host disease (GVHD) occurred in 34% and 38% of the HSCT recipients. 113 patients were still alive at the end of the study after a median follow-up of 36 (range, 12-74) months. Overall, their LFS at 1, 2 and 5 years were 76, 69 and 58% (median not reached) and the respective OS were 81, 73 and 63% (median not reached). In univariate analysis, adverse risk group, absence of cGVHD and CRi were associated with poor LFS and OS after HSCT (Table 2). These factors remained significant in multivariate analysis.

Conclusion: ELN defined adverse risk group, absence of cGVHD and incomplete hematological recovery at HSCT have a negative impact on transplantation outcome in *de novo* AML. Nevertheless, HSCT remains a curative treatment option for more than forty percent of these patients.

Keywords: AML, CR, CRi, HSCT



Medium-dose VP-16 intensified conditioning regimen is effective in allogeneic stem cell transplantation for acute lymphoblastic leukemia in CR1

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Abstract Content

Abstract

Objective: Retrospectively analysing the outcome of additional medium-dose etoposide (VP-16 30mg/kg) in allogeneic hematopoietic stem cell transplantation (allo-HSCT) for acute lymphoblastic leukemia (ALL) in CR1 (complete remission).

Methods: From 2010.10.1 to 2018.6.30, forty-five ALL patients in CR1 received allo-HSCT in Shandong provincial hospital. Fourteen patients were conditioned with medium-dose VP-16 (VP-16 group), and thirty-one patients were conditioned without medium-dose VP-16 (control group). The basic conditions of the primary disease, treatment-related toxicity, leukemia-free survival (LFS), overall survival (OS), graft-versus-host disease (GVHD) and relapse-free survival (GRFS), non-relapse mortality (NRM), relapse incidence (RI), GVHD and so on were compared between the two groups.

Results: The VP-16 group was associated with improved 3-year-LFS (82.1% vs. 61.1%, p=0.263) and 3-year-OS (79.1% vs. 64.2%, p=0.449), although there was no statistical difference. Moreover, the additional of VP-16 lead to reduced incidence of aGVHD (II, III, IV) (0% vs. 26.3%, p=0.052) and cGVHD (11.1% vs 21.4%, p=0.437), resulting in improved GRFS (71.8% vs. 51.9%, P=0.208). Meanwhile, the addition of VP-16 enhanced the intensity of conditioning regimen, its RI and NRM were relatively lower than control group (RI: 17.9% vs. 28.1%, p=0.507; NRM: 0% vs. 13%, p=0.257).

Conclusion: The intensified conditioning regimen with medium-dose VP-16 did not increase NRM and GVHD, with tendency to increase OS and LFS, may become an effective pre-treatment scheme in allo-HSCT for ALL in CR1.





Low toxicity conditioning with Total Body Irradiation and Fludarabine with post-transplant cyclophosphamide for allogeneic stem cell transplantation in Acute lymphoblastic Leukemia

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Abstract Content

Introduction

Total body irradiation (TBI) based regimes are preferred for allogeneic stem cell transplantation in ALL patients owing to higher EFS as compared to Busulfan based regimes. We aim to study the efficacy and safetyof Fludarabine (Flu) with TBI based low toxicityconditioning regimen with peripheral blood stem cell graft and post-transplant cyclophosphamide based GvHD prophylaxis approach in patients with high risk ALL at our centre.

Methods

Medical records of all ALL patients who received matched sibling alloSCT using T cell replete peripheral blood stem cells after conditioning with Flu (30 mg/m² for 3 days) & TBI 800-1200 cGy in 8 fractions and post-transplant cyclophosphamide (PTCy) 50mg/kg on day +3and +4 followed by oral Tacrolimus dose adjusted to achieve a trough level of 5-15ng/ml from day +5 till day +180 as GVHD prophylaxis at our centre during the period of January 2014 till March 2018 were reviewed to capture the clinical profile and safety outcomes. The patients were followed up till 4th August 2018 for outcome.

Results

Seventeen ALL patients in complete remission, median aged 27 (15-48) years with male to female ratio of 4.25:1 were eligible for the study. Eight patients (47%) were detected positive for philadelphia chromosome (t9; 22). Nine (53%) patients were in first complete remission (CR1) while 8 were in > CR1 (CR2 = 3, CR3 =1, primary induction failure = 4) at transplantation.

Engraftment was observed in 15(88.2%) patients at a median of 14 days (11-29), while one patient had graft failure and one had early death because of sepsis at day+14. Incidence of transplant related complications like febrile neutropenia, and mucositis (grade II- IV) were 94.1% (n=16), and 58.8%, [n=10 (oral =6, GI= 3, oral + GI=1)] patients respectively during first 100 days of AlloSCT, which were managed conservatively. Six (35.3%) patients had CMV reactivation at a median of 29.5 (17-98) days which got resolved with the treatment with injection ganciclovir and none progressed to CMV disease. One patient developed pulmonaryTB infection at day+76 which was treated successfully. Acute GvHD (overall grade II-IV) involving GIT (n=2), GIT and skin (n=1), and skin (n=1) developed in 4 patients (23.5%) at a median of 69(15-75) days. Chronic GvHD (limited =3, extensive =3) developed in 6 (35.3%) patients at a median of 120 (83-571) days.

Major events occurred were relapse, n=5, graft failure, n=1 and NRM, n=1 [at day +14]. Overall mortality was 5/17 (29%) with cause of death being relapse (n=4) and NRM (n=1). At a median follow up of 22.3 months,OS , PFS and EFS at 2 years is $61.4\pm14.7\%$, $53.4\pm14.6\%$ and $50.1\pm14.1\%$ respectively. No significant difference was found in the OS, PFS,and EFS between patients in CR1 versus >CR1 and those who received 1200 cGy versus 800 cGy of TBI (Table 1).

Conclusions

In conclusion, Flu-TBI-PTCy for patients with ALL is an effective regimen with low toxicity.



Keywords: Flu-TBI based conditioning; ALL; Allogeneic Stem Cell Transplantation; Myeloablative Conditioning

ALS POR





Study of Haploidentical Stem Cell Transplantation for Philadelphia/BCR-ABL Positive Acute Lymphoblastic Leukemia

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Abstract Content

Introduction: We are presenting our data of haploidentical stem cell transplantation (HaSCT) in Ph+ALL.

Methods: We retrospectively reviewed, data of Ph+ALL patients who received Haploidentical Stem Cell Transplantation (HaSCT) from 1-Jan-2013 to 31-Dec-17 at our centre. The follow-up was censored at 30-Jun-2018.

Results: Out of 58 Ph+ ALL patients during study period 10 (males 60%) were found to receive HaSCT and eligible for the study with a median age of 27.5 years (17-42 years). All patients were CNS-1. Cytogenetics was available for 7/10 (70%) patients out of which 6 patients had Ph+ chromosome including 4 with additional cytogenetics abnormalities and 1 patient had normal cytogenetics. All patients had BCR-ABL detected by PCR (p190 in 8, p210 in 2).

All patients received induction and consolidation chemotherapy along with TKI (Imatinib in 1, Dasatinib in 9/10 patients) to achieve remission. Five (50%) patients were taken in CR1 and 5 (50%) in CR2. Seven (70%) patients had major molecular remission (BCR-ABL <0.01%) at the time of transplant.

Five (50%) donors were males and median age was 41.5 years (19-60 years). Matched, minor mismatched and bi-directional donor recipient blood group was seen in 6, 3 and 1 patients respectively. Four patients had 3/6 HLA matched, 2 patients had 8/10 HLA matched while 1 each patient had 4/6, 5/10 6/10, 7/10 HLA matched. Seven (70%) patients had donor positive-recipient positive CMV sero status while donor positive-recipient negative and donor negative-recipient positive were seen in 1 (10%) and 2 (20%) patients respectively.

Conditioning was non-myeloablative (FluCyTBI200cGy, n=7); Myeloablative (BluFluCy, n=2) and RIC (FluTBI800cGy, n=1). All patients received mobilized Peripheral Blood Stem Cells (PBSCs) 5×10^{6} /kg (3.85 x 10^{6} /kg -6.2 x 10^{6} /kg) from HLA haploidentical family donors. Post-transplant cyclophosphamide (day +3 and+4), followed by MMF and Tacrolimus were used for GvHD prophylaxis.

Acute (grade II-IV) and limited chronic GvHDs were observed in 4 and 3 patients respectively. Three patients required 2^{nd} line agent for steroid refractory acute GvHD. CMV reactivation was observed in 9/10 (90%) with 1 patient dying of CMV pneumonia at day +30. Four patients had possible invasive fungal infections. Four bacterial cultures (gram negative n=4) were recorded. One patient each had Mycobacterium Tuberculosis (oesophagus) and primary syphilis.

Major events were relapse (n=2, CNS and bone marrow), graft rejection (n=1) and infection deaths (n=2, CMV pneumonia and bacterial sepsis one each). At a median follow up of surviving patients of 22 months (4-33), 6 (60%) patients are alive in CR (5/5 of CR1 while 1/5 of CR2 cohorts) and 5 (50%) patients had an event (1/5 in CR1 while 4/5 in CR2 cohorts). The estimated 2 year OS and EFS of entire cohort is $56\% \pm 17\%$ and $47\% \pm 16\%$ respectively. The EFS of patients transplanted in CR1 versus patients transplanted in CR2 is p=0.11 (log-rank test). The OS of patients transplanted in CR1 is found to be significantly better than patients transplanted in CR2 (p=0.01 log rank test).

Conclusion: HaSCT is a feasible option for Ph+ ALL patients specially when offered to patients in CR1.





Retrospective Study of Philadelphia Positive Acute Lymphoblastic Leukemia – A Single Centre Experience

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Abstract Content

Introduction-

We are presenting our retrospective study of patients with Ph+ ALL treated on chemotherapy and TKI with or without Allo-SCT.

Material and Methods -

We retrospectively reviewed medical records of 327 ALL patients who were diagnosed and treated at our center during Jan-2011 to Dec-2017 at our centre. Follow-up was censored at 30-Jun-2018.

Results –

Sixty-one (males =36, females = 25) out of 327 patients were eligible for the study. Median age was 38 yrs (14-76 yrs) (table-1 for baseline characteristics). Post induction 55 (90.1%) patients achieved complete remission (CR) while1 (1.6%) had induction mortality due to infection,4 (6.5%) were refractory and 1 (1.6%) patient discontinued treatment. Dasatinib (n=52) and imatinib (n=9) were combined with chemotherapy.

Fifty-three (86.8%) patients received further treatment with TKI+CNS directed therapy and thereafter the consolidation therapy with Allo-SCT (n=19, 35.8%) and chemotherapy with TKI (n=34, 64.1%).

Patients in Allo-SCT group received matched related donor allograft (n=14) with myeloablative and reduced intensity regime in 11 and 3 patients respectively and Haploidentical family donor allograft (n=5/19) with non-myeloablative and reduced intensity regime in 4 and 1 patients respectively.

Chemotherapy related complications:overall 47 episodes of febrile neutropenia were recorded. There were 35 culture positive bacterial infections (gram positive=16; gram negative=19), 2 patients had cryptosporidium in stool, 1 patient had TB, 13 possible invasive fungal infections. Non-infectious complications were vincristine induced neuropathy (n=20, grade-1/2) and dasatinib induced pleural effusion (n=4).

Transplant related complications:Grade 2-4 acute GVHD (n=8), CMV reactivation (n=12) All patients had febrile neutropenia with blood stream infections (n=3), urinary tract infections (n = 9). Six patients had invasive fungal infections. One patient had graft rejection. 1 patient each had pulmonary TB and oesophageal TB. Herpes zoster and BK virus infection were seen in 2 and 1 patients respectively.

Outcome: Overall mortality was 13.1% (n=8/61) including 7 TRM (GVHD=3 and infection=4) and 1 induction mortality. No treatment related mortality observed in chemotherapy group. Median duration of follow-up of entire cohort was 22 months (5-66 months). Thirty seven percent (n=15) of patients had a relapse (Allo-SCT- n=1 and chemotherapy- n=14). The estimated 5 year progression free survival (PFS) of entire cohort was $52\%\pm10\%$. The estimated 5 year event free survival (EFS) and overall survival (OS) was $36\%\pm8\%$, and $48\%\pm14\%$ respectively.

The PFS, EFS and OS were analyzed for age, WBC count, cytogenetics, preconsolidation Major Molecular Response (MMR) and with or without Allo-SCT in CR1(table-2). Patient who received Allo-SCT in CR1 had a better PFS ($85.7\% \pm 13.2\%$) as compared to chemotherapy only group ($40.7\% \pm 10.8\%$) (p=0.01). The 5 years estimated EFS and OS for Allo-SCT versus chemotherapy was $43.7\% \pm 15.7\%$ vs. $33.5\% \pm 9.3\%$ (p=0.25) and $54.7\% \pm 18\%$ versus $43\% \pm 15.8\%$ (p=0.12)respectively.



Conclusion -

Allo-SCT in CR1 is associated with better PFS as compared to chemotherapy consolidation, though the OS and EFS were similar owing to high TRM in Allo-SCT group.

Keywords: Philadelphia Positive ALL; Allogeneic Stem Cell Transplantation



Mutation analysis of six post-transplant relapsed acute myeloid leukemia and suggestions for future incorporation of nextgeneration sequencing (NGS) into precise diagnosis and treatment decision

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Abstract Content

Introduction: Next-generation sequencing (NGS) enables the detection of genomic landscape of acute myeloid leukemia (AML), which, in turn, has raised new diagnostic challenges as well as challenges to the precise treatment.

Method: Since July 2017, targeted NGS to detect the mutations in 21 genes was carried out in patients with AML at diagnosis or at the timing of relapse. Between July 2017 and Mar 2018, a total of 159 adult AML patients underwent NGS testing, of whom 125 patients were tested at diagnosis, 11 at relapse, and 23 during the treatment course. In this study, we centered on mutation profile that was observed in six relapsed AML patients after allogeneic hematopoietic stem cell transplantation (HSCT).

Result: Before a diagnosis of relapse, all 6 patients received 8 allogeneic HSCTs from family donors, in which matched sibling donors (n=5) and haploidentical family donors (n=3) were included. The median duration from last allogeneic HSCT to relapse was 13.5 months (range, 7.5 to 73.8 months), and 2 patients underwent two allogeneic HSCTs before NGS testing at relapse. At least one mutation was detected in 4 out of 6 patients (66.7%), and mutations of 6 genes (variants allele frequency, ranged from 5.25% to 47.22%) were identified in 4 patients. Composition of mutated genes in these 4 patients were as follows; mutations in <u>GATA2</u> and WT1 in case 1, <u>DDX41</u> in case 2, DNMT3A in case 3, <u>RUNX1</u> and SF3B1 in case 4. Of genes mentioned above, GATA2, DDX41 and RUNX1 were the genes involved in predisposition to inherited hematologic malignancies. Because we could not perform germ line genetic testing in these 4 patients and their related donors, we did not know exactly whether these mutations were germline, and where these relapsed leukemic cells were originated from.

Conclusion: Genomic testing using NGS seems to be helpful to understand the molecular basis of AML by patients. We suggest that NGS can be utilized in clinical practice with broad applications, which in part include detection of genetically predisposed AML patients and donor selection to avoid transplantation from potential donor at risk.

Keywords: Next generation sequencing; acute myelolid leukemia; relapse; allogeneic hematopoietic stem cell transplantation




A Success Allogeneic Sibling Peripheral Blood Stem Cell Transplantation in A 76-year-old Patient with Acute Myeloid Leukemia in Second Remission

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Abstract Content

Introduction: Ageing is the emerging problem worldwide. How to treat the elderly properly is simulatingly important. In the past 20 years, chemotherapy drugs involving treating acute leukemia change little, so as conditioning regimens for either myeloablating transplant and reduced-intensity transplant. However, concepts of nutrition, supportive care system, and complication prevention are improving. We want to challenge the oldest aged patient who is capable of completing allogeneic sibling reduced intensity hematopoietic stem cell transplantation.

Methods: We select a 76-year-old female patient who went through 30%-off-dosage of "3+7" induction of acute myeloid leukemia smoothly except pulmonary aspergillus infection which was controlled well by voriconazole in September, 2015. Consolidation of 4-cycles of high-dose cytarabine were also smooth but minimal residual disease (MRD) which was detected by flow cytometry was still there after the consolidation. Disease relapses in October, 2016 and second remission without MRD was achieved in November, 2016 by "FLAG" regimen reinduction. Her HST comorbidity index is 1 (diabetes). Her younger sister who is 60 years ago, having history of 2 times of pregnancy, 2 times of labor is the HLA-matched donor. Both the donor's and the recepient's CMV-IgG are positive.

Results: The conditioning regimen is fludarabine (30mg/m2 for 5 days) plus busulfex (3/2mg/kg/day for 2 days) plus cyclophosphamide (30mg/kg/day for 1 day) and anti-thymocyte globulin (rabbit 2.5mg/kg for 2 days). Peripheral blood stem cell amount is 6.47 x 10⁶/kg. Graft-versus-host disease (GVHD) prophylaxis includes calcineurin inhibitor and methotrexate. Anti-bacteria, anti-fungus, anti-virus are prescribed for prophylaxis as our unit routine. The patient tolerates the regimen with grade I diarrhea and fatigue. Both white cell and platelet engraftment achieve on day 11 after stem cell infusion. She is discharged 8 days after engraftment. No GVHD is observed till now. Neither cytomegalovirus nor aspergillus activation is detected so far.

Conclusions: Allogeneic hematopoietic stem cell transplantation is a safe and effective option for carefully selected patient age over 70. A donor who is over 50 years can still provide enough stem cells to complete transplant.

Keywords: Transplant Leukemia Elderly



Topic: Transplantation for leukemia Abstract No: 8953

The efficacy and safety comparison between HLA-matched and HLA-haploidentical allogeneic hematopoietic stem cell transplantation in adult acute leukemia

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Abstract Content

Objective:

This study compared the safety and efficacy between HLA-matched and HLA-haploidentical allogeneic hematopoietic stem cell transplantation (allo-HSCT) in adult acute leukemia.

Method:

Medical records of 80 acute leukemia patients (median age: 43.0 years) who underwent allogeneic HSCT from two medical centers in Taiwan from 2010 to 2017 were retrospectively reviewed. Patients were stratified into HLA-haploidentical donor group (n=21, 26.3%), matched sibling donor group (n=41, 51.3%), and matched unrelated donor group (n=18, 22.5%), respectively. All patients achieved complete hematological remission before their allo-HSCT.

Results:

Regarding patients' characteristics, 39 patients were men (48.8%), and 41 patients were women (51.3%). 98.7% (78/80) of the patients belonged to intermediate or high risks. 70% (56/80) of the patients were diagnosed to have acute myeloid leukemia (AML). Acute lymphoid or ambiguous leukemia was diagnosed in 24 patients. The 100-day mortality rate in HLA-haploidentical donor group, matched sibling donor group, and matched unrelated donor was 0%, 9.8%, and 5.6%, respectively (p= 0.321). The cytomegalovirus (CMV) reactivation rate was 85.7%, 39.0%, and 55.6%, in these three groups of patients (p= 0.002). Graft failure due to CMV viremia occurred in two patients who had undergone HLA-haploidentical allo-HSCT. Second allo-HSCT were performed in these two patients.

Conclusion:

Comparing to allo-HSCT from matched sibling and unrelated donors, HLA-haploidentical HSCT provides similar efficacy and safety. However, CMV reactivation could be a critical issue. Intensive CMV surveillance and treatment would be important for acute leukemia patients who undergo HLA-haploidentical allo-HSCT.

Keywords: HLA-haploidentical allogeneic hematopoietic stem cell transplantation, acute leukemia



Topic: Transplantation for leukemia Abstract No: 8965

A Retrospective Analysis of Allogeneic Hematopoietic Stem Cell Transplantation for Chronic Myeloid Leukemia in TKI Era in Single Center

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Abstract Content

Taking TKI drugs such as imatinib, nilotinib, dasatinib, bosultinib, and ponatinib has become standard treatment for chronic myeloid leukemia (CML) patients. and some abl gene mutations will occur during that course. How these factors affect the outcome of allo-HSCT are need to be answered. Clinical characteristics of 44 patients with CML who underwent allo-HSCT in our center between May 2012 and May 2016 were retrospectively analyzed. All patients received TKI drugs and 18 of the 44 patients developed ABL gene mutations before transplantation. Abl kinase mutations were T315I (n = 5), F317L (n = 4), Y253H (n = 3), G250E (n = 2), F359V (n = 2), E255K (n = 1), E459K (n = 1), M244V (n = 1), E453A (n = 1), F3791 (n = 1), V299L (n = 1), Q252H (n = 1) and W478R (n = 1). 6 patients had two types abl gene mutations simultaneously. 24 were males and 20 were females. Median age was 28.5(8-55) years old. Before transplant, 9 patients were in chronic phase 1 (CP1), 22 patients were in CP2, 8 patients were in accelerated phase (AP) and another 5 patients were in blast phase (BP). The median time from diagnosis to HSCT was 24(4-352) months. Patients underwent matched sibling donors HSCT (MSD-HSCT)(n=8), unrelated donor HSCT (URD-HSCT)(n=10), and haploidentical HSCT (Haplo-HSCT)(n=26). The conditioning regimens are based on BU/Cy (n=35), BU/FLU (n=6),TBI/Cy (n=2) or TBI/FLU (n=1).GVHD prophylaxis consisted of ATG,CSA, MMF and MTX. The number of mononuclear, CD34+ and CD3+ cells was (8.26±1.42)×10⁸/kg, (4.31±1.1)×10⁶/kg,and (1.9±0.32)×10⁸/kg, respectively. White blood cells were successfully engraftment in all patients and the median time of ANC≥0.5×10⁹/L was day 14(11-25). Median time of platelet≥20×10⁹/L was day 13(9-10) except 1 case. The cumulative incidence of grade II - IV aGVHD was 25%, and the incidence of cGVHD was 23%. Five-year overall survival(OS) rate was 100%, 72.7%, 83.3% and 60% in CML-CP1,CP2,AP,BP . The 5-year OS of MSD-HSCT, URD-HSCT and Haplo-HSCT was 72.9%, 90% and 75.8% . The 5 year OS for ABL gene mutation positive and negative patients were 64% and 83%. No abl gene mutation developed in CP1 patients. Whereas, 2 of the 5 BP patients had ABL kinase domain mutations. The mortality rate was 4.5% within 100 days. The causes of death were TMA(n=2), IV aGVHD(n=1), and relapse(n=5). 4 of 5 patients who relapse and died had ABL gene mutations. Our study shows that donor selection and disease status are still important factors affecting the outcome of CML allo-HSCT during TKI era, and the patients who developed ABL gene mutation before transplantation will have relatively poor outcomes.

Keywords: chronic myeloid leukemia, ;allogeneic hematopoietic stem cell transplantation ;ABL gene mutations





Clinical outcome of CLAG chemotherapy plus modified Bu/TBI conditioning regimen for allogeneic hematopoietic stem cell transplantation patients with acute leukemia and myelodysplastic syndrome

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Abstract Content

[Introduction]We retrospectively evaluated the efficacy and safety of the conditioning regimen consisting of cladribine, cytarabine(Ara-C), and granulocyte colony-stimulating factor(G-CSF), which abbreviated as CLAG, followed by busulfan(BU)/TBI and cytoxan(Cy), in patients with acute myeloid leukemia(AML), myelodysplastic syndrome(MDS), and acute lymphoblastic leukemia(ALL).

[Methods] Between 2015 and 2018, 25 patients received allo-transplantation were enrolled, among which 19 with acute myeloid leukemia(AML), 1 with myelodysplastic syndrome(MDS), and 5 with acute lymphoblastic leukemia(ALL). 64% patients were males, the median age was 30(16-40)years, and the median follow-up was 12(26.5-23)months. Stratificated by cytogenetics at diagnosis: 3(12%) favorable risk AML, 5(24%) intermediate risk AML, 1(4%) high risk MDS, 4(16%) high risk ALL, and 12(48%) high risk AML. Before transplantation, 10 patients were at first complete remission(CR1), all stratificated in high risk group, 4 at second complete remission(CR2) or more, and 11 at non-remission(NR). 4 patients were transplanted from HLA-matched sibling donors(MSD), 3(12%) from 10/10 unrelated donors(UCD), 1(4%) from 9/10 UCD, 18 from Haplo-identical donors, and 1 from Collateral related donors(CRD).

[Result]All patients achieved white blood cell(WBC) and platelet(PLT) recovery, and the time to engraftment of WBC and PLT was 12(10.5-17) and 13.5(11.25-19.5) days respectively. The incidence of acute graft-versus-host-disease(aGVHD) was 96%:5 patients developed Grade I aGVHD, 18 developed Grade II, and 1 developed Grade IV. 14(56%) patients developed chronic GVHD(cGVHD), with 12 mild, and 2 severe. 6 patients relapsed, in which 2 patients died due to relapse, besides, 5 patients died due to non-relapsed mortality(NRM). The estimated 3-year overall survival(OS) and leukemia-free survival(LFS) were 70.96%±10.45%, and 63.5%±14.05%. In univariate analysis, patient age was associated with OS and LFS. **[Conclusion]**CLAG sequential with modified BU/TBI-Cy may be an effective and well-tolerated conditioning regimen for acute Leukemia and myelodysplastic syndrome patients.

Keywords: CLAG; conditioning regimen; allogeneic stem cell transplantation





An Artificial Intelligence Approach for Predicting Allogeneic Hematopoietic Stem Cell Transplantation Outcome by Detecting Pre and Post-Transplant Minimal Residual Disease in Acute Myeloid Leukemia Using Flow Cytometry Data

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Abstract Content

Introduction

Flow cytometry (FC)-assisted minimal residual disease (MRD) detection is known to have clinical significance for disease status monitoring for recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute myeloid leukemia (AML).

However, current interpretation requires experienced manual gating, which is time consuming as well as suffering from inter-physician idiosyncrasies. In this study, we developed an algorithm using artificial intelligence (AI) technology in supporting physicians to conduct rapid and reliable pre and post-HSCT MRD detection for AML patients.

Methods

A total of 5028 retrospective FC data of AML patients from 2009 to 2017 for MRD detection at the National Taiwan University Hospital were enrolled. Each of the samples had a 12-tube test on 100,000 cells, measured in 6 fluorescent channels within 1 tube.

To investigate the prognostic impact, 337 FC data conducted within day -60 to 60 of allo-HSCT were assigned into the Outcome set. The rest of the FC data were 4:1 randomized into the Training set and the Validation set, consisting 3753 and 938 MFC data respectively. The Training set was used to develop and tune the AI algorithm, and final concordance was estimated on the Validation set. An algorithm for AML vs. normal classification was developed, according to previous manual interpretation of FC data.

The numerical values of each tube were first statistically-modelled with a multivariate Gaussian mixture model, then encoded into a Fisher representational vector and vectors of each tube were concatenated as the final high-dimensional input to the supervised machine learning classifier, i.e., a support vector machine with linear kernel. In addition, ANOVA-based feature selection was also conducted throughout the experiments.

For outcome predicting analysis, we included 177 AML patients with available pre or post-allo-HSCT FC data. Their clinical parameters, relapse-free survival (RFS) and overall survival (OS) after allo-HSCT are recorded and analyzed with a median follow-up of 39.9 months.

Results

The average concordance rates of AI algorithm with manual analysis in differentiating AML vs. normal achieved 89.7%. Interestingly, the algorithm developed from only two tubes (CD56, CD38 & CD45 and CD16, CD13 & CD45) achieved performance of 0.910 while algorithms developed from all tubes achieved 0.937 by area under the ROC curve (AUC). Moreover, this AI approach is 100 times faster than the manual gating in interpreting one FC data (7 secs vs 30 mins).

The characteristics for 177 AML patients underwent HSCT were illustrated (Table 1). Those with normal AI Diagnosis on pre-HSCT flow had significantly longer post-HSCT RFS (median RFS 35.0 vs 4.7 months,



p<0.0 01) (Figure. 1a) and OS (median OS 46.9 vs 7.7 months, p<0.0001) (Figure. 1b). Pre-HSCT normal FC also predicted longer post-HSCT OS. Similar findings were observed in post HSCT RFS and OS stratified by post-HSCT flow AI Diagnosis (Figure. 1c & 1d).

Conclusions

This study demonstrated that AI could be an efficient and reliable tool for flow MRD detection in AML. In the future, we like to incorporate other test results simultaneously measured for those patients as our next phase of advancing the AI system.

Keywords: Artificial Intelligence, Flow cytometry, Transplantation, Minimal Residual Disease





Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients

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Abstract Content

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The feasibility and efficacy of high-dose melphalan followed by autologous hematopoietic stem cell transplantation in newly diagnosed elderly patients with multiple myeloma during three years in kermanshah BMT center in west of Iran analyses. Fifty-six multiple myeloma patients, aged 65 years or over, from KUMS center were studied. The induction therapy was bortezomib-based in combination with dexamethasone and either thalidomide , for 4–6 cycles. Peripheral blood stem cells were collected after high-dose cyclophosphamide plus G-CSF or G-CSF alone ,with plerixafor if needed. The conditioning regimen consisted of melphalan at 140 mg/m2 in 18 patients (36%) and 200 mg/m2in 32 (64%).

Two months post autologous hematopoietic stem cell transplantation, a maintenance phase with either thalidomide plus ASA combination therapy was given. The treatment-related mortality was 0% at 100 days post transplantation. The best response achieved was 40% complete response, 36% very good partial response, and 18% partial response.

After a median follow up of 21 months (range 6–31), the estimated progression-free and overall survival rates at two years were 76% [95%CI: (61.6–94.1)] and 88% [95%CI: (76.7–100)], respectively. The higher dose of melphalan (200 mg/m2) afforded superior progression-free and overall survival rates. This prospective study provides evidence for the safety and efficacy of autologous hematopoietic stem cell transplantation as a first-line treatment approach in elderly multiple myeloma patients.

Keywords: Myeloma – Autologous – Melphalane - Bortezomib



Successful management with tandem auto-allo hematopoietic stem cell transplantation for a double-hit diffuse large B cell lymphoma with primary treatment failure

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Abstract Content

The majority of diffuse large B cell lymphoma could be cured with combination treatment with rituximab plus chemotherapy. Achieving complete remission is a requisite for cure and is achieved after initial therapy in approximately 70-95% of patients. (Costa LJ 2017). Costa et al., reported dismal outcome for patients with primary treatment failure, defined as primary progression while on upfront chemoimmunotherapy (PP), residual disease at the end of upfront therapy, or relapse less than 6 months from end of therapy. PP, *MYC* (+) lymphoma, and NCCN-IPI intermediate/high at time of PTF, constitute the ultra-high risk (UHR) features with 2-year OS of only 13.6% vs. 57.6% for patients with PTR with no UHR features.

We reported a 43-yr-old woman with double-hit diffuse large B cell lymphoma characterized by PTR with UHR features was successfully treated with multimodality treatment, including chemoimmunotherapy, autologous peripheral blood stem cell transplantation, local radiotherapy, and MUD-allogeneic PBSCT. She was in CR and still survive with no evidence of disease 12 months after MUD-allo PBSCT.

Keywords: Lymphoma; tandem hematopoietic stem cell transplantation; primary treatment failure







Hematopoietic Stem Cell Transplantation for Mantle Cell Lymphoma in Taiwan

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Abstract Content

Background

This is a retrospective analysis of outcome of mantle cell lymphoma patients underwent hematopoietic stem cell transplantation in Taiwan.

Method

We analyze patients undergoing autologous and allogeneic stem cell transplantation from TSBMT data base.

Results

Forty-six patients underwent autologous and nine allogeneic stem cell transplantations between Feb 2004 and Mar 2016 and median age at diagnosis was 54 with range 35 to 74. Fifty-three of them (97%) were advanced stage and 20% had extranodal disease. The disease status before transplantation were 28 (51%) in CR1, 8 (15%) in CR2, 18 (33%) in PR, and 1 (2%) in relapsed refractory. The median time interval between diagnosis and transplantation was 0.78 years with range 0.42 to 7.34 years. Three and five years progression free survival were 42% and 19%, and overall survival were 84% and 59%, respectively. There was no significant difference of overall survival between patients transplanted in CR1, CR2, or PR before transplantation. However, we can see the survival plateaue of 48% at 5 years in allogeneic transplant patients. In 20 patients relapsed after autologous transplant, 2 in leptomeningeal relapse, 2 in bowel, 1 in skin, 1 in bone marrow, 1 in lung, 5 in nodal, 2 never remission achieved, and 6 were systemic. One patient died of secondary myelodysplastic syndrome with blast excess (MDS-RAEB 2). Six patients underwent second transplant and 2 of them survived. In 17 patients died in this study, 11 died of relapsed refractory disease, 2 died of infection, 2 died of HBV reactivated fulminant hepatitis, 1 died of second malignancy, and 1 undefined cause.

Conclusion

High dose chemotherapy and autologous stem cell transplantation is feasible in both frontline and salvage settings in mantle cell lymphoma patients. Allogeneic stem cell transplantation could be a curative treatment for selected patients.

Keywords: hematopoietic stem cell transplantation (HSCT), mantle cell lymphoma (MCL)





Bendamustine as a salvage therapy in peritransplant setting in hodgkin lymphoma - a single institutional experience

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Abstract Content

Introduction:

Hodgkin lymphoma (HL) being most curable hematolymphoid malignancy has treatment failure rates of 30% to 35%. The standard option that can lead to long-term disease-free survival is salvage chemotherapy followed by autologous stem cell transplantation (ASCT) while allogeneic hematopoietic stem cell transplantation (AlloSCT) represents a potential curative option for patients with multi relapsed or refractory HL. The role of bendamustine as salvage chemotherapy has been explored. We analysed the outcome of our patients with HL who have received bendamustine during peri transplant period.

Materials and Methods:

All patients who received bendamustine either prior to or after autologous or allogeneic transplant for HL were included in this retrospective analysis. The study period was between 1st January 2014 – 31st December 2017. Patients who received bendamustine pre transplant received at least 2 lines of chemotherapy prior to receiving bendamustine. Bendamustine was given as 120 mg/m2 on D1 and D2 every 4 weeks. PET-CT was done for all patients after 2 or 3 cycles of bendamustine. Response was evaluated according to Cheson's response criteria. Toxicity by CTCAE version 4. Over all survival (OS) was calculated from the date of start of 1st cycle of bendamustine to the date of last follow up or death. Progression free survival (PFS) was calculated from the date of start of 1st cycle of bendamustine to date of disease progression, death or last date of follow up if in remission...

Results:

Fifteen patients were included in this retrospective analysis. The median age was 24 yrs (range - 10 to 54). There were 8 male and 7 female patients. The median number of previous lines of chemotherapy prior to bendamustine was 2 (range 1 to 5). Among 15 patients, 6 patients had primary refractory disease and 9 patients had relapsed disease. Of the 15 patients, 6 patients received bendamustine salvage after auto transplant and 9 patients received bendamustine as a bridge to transplant (8 - ASCT and 1 –AlloSCT). The median number of cycles of bendmustine received pre transplant were 2 and post transplant were 3.The overall response rate (ORR) to bendamustine was seen in 11 (73.3%) patients (complete response - 8, partial response- 3). Stable disease was seen in 2 (13.3%) and 2 patients (13.3%) had progression to bendamustine. Four (66 %) of 6 patients who received bendamustine after relapse from auto transplant had either complete or partial response to it. At a median follow up of 7 months (range, 1-23), the PFS was 45.1% and OS was 75.7% at 12 months. Four patients (26.7%) had grade III/IV febrile neutropenia, 3 patients (20%) had grade III/IV thrombocytopenia and 1 patient (6.7%) had grade III skin rash.

Conclusion:

Single agent bendamustine is an effective salvage therapy in peritrasnplant setting (post transplant relapse as well as bridge to stem cell transplant) with reasonable response and manageable toxicities. A large prospective study is warranted.

Keywords: Bendamustine;Hodgkin lymphoma;Stem cell transplant



Optimal chemo-mobilization for peripheral blood stem cell collection in multiple myeloma

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Abstract Content

For successful autologous stem cell transplantation, collection of the sufficient number of hematopoietic stem cell is essential after induction therapy for transplant candidates in multiple myeloma (MM). In this study, we compared the efficacy and safety of stem cell mobilization with etoposide (VP-16; 375 mg/m² on days 1 and 2) and cyclophosphamide (CY; 3.0 g/m² on day 1) in patients with MM. Granulocyte-colony stimulating factor (G-CSF, 10 mg/kg/day, subcutaneously) was administered from the development of neutropenia to the final collecting day. Sixty-five patients were mobilized with CY and G-CSF and 63 were mobilized with VP-16 and G-CSF. All patients were mobilized within 7 months from the beginning of frontline treatment. The median total collected CD34+ cell count was significantly higher in VP-16 mobilization group (27.6 x 10⁶ CD34+/kg vs. 9.6 x 10⁶ CD34+/kg, P<0.001). The rate of mobilization failure which was defined as total collected number of CD34+ cell < 2.0 x 10⁶ CD34+/kg in three apheresis procedures was lower in VP-16 group (1.6% vs. 10.8%, P=0.062). Severe infections during mobilization period were frequently developed in CY group compared to VP-16 group (18.5% vs. 7.9%, P=0.117). In conclusion, intermediate dose of VP-16 with G-CSF appears to be effective and tolerable chemo-mobilization method compared to CY and G-CSF, especially when it is difficult to use plerixafor in MM.

Keywords: Myeloma, Mobilization, Etoposide





The Safety and Efficacy of Plerixafor and G-CSF for Autologous Stem Cell Mobilization in Patients with Malignant Lymphoma and Multiple Myeloma

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Abstract Content

[Introduction] This study evaluates the safety and efficacy of plerixafor in mobilizing hematopoietic stem cells for autologous stem-cell transplantation in malignant lymphoma and multiple myeloma patients.

[Methods] This is a retrospective study in a single center of Kyoto university hospital. Patients with malignant lymphoma and multiple myeloma requiring an autologous hematopoietic stem-cell transplantation were eligible. Patients in Plerixafor and G-CSF (P+G) group received daily subcutaneous G-CSF (10µg/kg or 400µg/m²). Beginning on evening of day 4 and continuing daily for up to 3 days, patients received subcutaneous plerixafor (240 µg/kg). Starting on day 5, patients began daily apheresis for up to 3 days. Patients in Chemotherapy and G-CSF (C+G) group received standard chemotherapy for malignant lymphoma or high dose cyclophosphamide for multiple myeloma. During bone marrow recovering phase, patients started to receive G-CSF and continued until stem-cell apheresis. The primary end point was the time to collect optimal CD34+ cells and the proportion of patients reaching 2x10⁶ CD34+ cells/kg in 4 or fewer apheresis days. The secondary outcome was incidences of serious adverse events.

[Results] From January 1, 2013 to May 31, 2018, a total of 51 patients (15 P+G; 6 multiple myeloma, 9 malignant lymphoma, 36 C+G; 12 multiple myeloma, 24 malignant lymphoma) were included. The numbers of prior chemotherapies were significantly large in P+G group; 2 (13%) vs 18 (50%) underwent apheresis after 1st line chemotherapy, 8 (53%) vs10 (28%) after 2nd line chemotherapy, 5 (33%) vs 8 (22%) after more than 2 line chemotherapy, in P+G group and C+G group, respectively (p=0.04). Overall the other patient baseline characteristics were similar between these 2 groups. The number of patients reaching 2x10⁶ CD34+ cells were 11 (74%) vs 14 (39%) on the first day of apheresis (p=0.03), 14 (94%) vs 26 (72%) on the second day (p=0.14), 14 (94%) vs 29 (81%) on the third day (p=0.41), in P+G group and C+G group, respectively. The median number of collected CD34+ cells was 3.78x10⁶ cells/kg (range, 1.75 to 13.10) for P+G group and 3.62x10⁶ cells/kg (range, 0.30 to 20.50) for C+G group. The overall incidences of non-hematological serious adverse events were 0 in P+G group and 13 (36%) of neutropenic fever in C+G group.

[Conclusion]Combination use of Plerixafor and G-CSF were well tolerated and resulted in a significantly higher proportion of patients with multiple myeloma and malignant lymphoma achieving the optimal CD34+ cell target for transplantation in fewer apheresis days, even after greater cycles of chemotherapy, compared with chemotherapy and G-CSF.





The First 12 Months Transplant Activity and Outcome Report at The 1st National Haematopoetic Stem Cell Transplant (HSCT) Centre in Sri Lanka

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Abstract Content

Introduction

Sri Lanka is a developing country in South East Asia with a population of 21 million. We describe the establishment of an HSCT centre at National Cancer Institute (NCI) of Sri Lanka. NCI is the largest tertiary cancer centre with universal health coverage. Absence of HSCT was a major deficiency as most patients cannot afford transplant abroad. In 2013/14 its clinicians decided to establish the 1st national HSCT centre in collaboration with National Blood Transfusion service (NBTS). This was enthusiastically supported by the Government, local and expat sponsors. Collaboration between NCI and St Vincent's Hospital Sydney (SVHS) followed by infrastructure development, mentorship and training and setup of protocols resulted in the first Autologous HSCT (AHSCT) in December 2016. We present our model of establishing public HSCT programme in Sri Lanka and outcome of AHSCT in the first year.

Methodology

Pre-transplant: NCI constructed a new HSCT facility and upgraded pathology facilities. NBTS undertook apheresis, stem cell processing and cryopreservation.

A team of 16 consisting of clinicians, pathologists, nurses, scientists and pharmacist were trained at SVHS. This was followed by regular internet-based mentoring, establishing protocols, and on-site trainings by voluntary SVHS staff.

Transplant eligibility: Multiple myeloma (MM) in CR or PR, relapsed Non-Hodgkin's lymphoma (NHL), Hodgkin lymphoma (HL) patients < 65 years, with good Performance status were selected included.

Autologous HSC mobilised with Cyclophosphamide and GCSF. HSC products were cryopreserved and postthawed samples checked for viability and contamination before product infusion.

Melphalan was the conditioning regime for MM and BEAM for HL and NHL. Patients were kept under intensive monitoring peri-transplant. Immediate commencement of antibiotics, fluid management, blood component transfusions were instigated as per protocols. Engrafted patients discharged and managed regularly at Clinic.

Results

20 autologous transplants were done in the first year. Mean age was 47 years (Range: 17–62) and M: F 3:2. There were 17 MM and one each of NHL, HL and POEMS syndrome.

Median CD34 stem cells collected was 12.72 x 10⁶/kg (Range: 3–31.7). 60% of the patients needed single apheresis. Median infused cell dose was 4.07 x10⁶/kg (Range: 2–7.4).

Median engraftment day was 13 (Range: 11-19). Median Hospitalisation was 16 days (Range: 14-20). All developed febrile neutropenia (7 had positive cultures). All developed Grade III thrombocytopenia needing platelet transfusions (Median platelets packs 12). Zero transplant related mortality (TRM) and acceptable morbidity achieved.



At the median follow-up of 47 weeks (to 31/5/2018), the overall survival is 100%. 11 (65%) multiple myeloma patients were in remission.

Conclusion

2 ½ years after initial planning of the HCT centre, 20 transplants were performed in our first year of operation with an overall survival of 100%.

This encouraging transplant outcome was attributed to, commitment by trained multi-disciplinary team complemented by partnership with an experienced and dedicated voluntary mentoring team, meticulous planning, adequate equipment and infrastructure, support from government, local and expat philanthropists.

We plan to initiate allogeneic programme in NCI and to commence assisting the setting up of other HSCT centres in the country.

Keywords: Haematopoetic, Transplant, Myeloma, SriLanka,



The benefit of thalidomide maintenance in patients with non-Hodgkin's lymphoma after autologous stem cell transplantation: a single-center retrospective study

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Abstract Content

Introduction

At present, there is no standard of care for patients with relapsed/refractory non-Hodgkin's lymphoma (NHL) after autologous stem cell transplantation (ASCT). Though, rituximab maintenance has been reported in patients with relapsed/refractory follicular lymphoma(FL) and mantle cell lymphoma (MCL) after ASCT. Thalidomide is a kind of immunomodulatory drug (IMiD) and has been proved to be effective in various NHLs, but the value of IMiD maintenance after ASCT remains to be discussed. In this study, we retrospectively analyzed the efficacy of thalidomide maintenance(TM) in patient with relapsed/refractory NHL after ASCT, comparing with historical controls of patients without TM.

Patients and Methods

Between January 2013 and December 2017, one hundred and ninety-eight patients with advanced or relapsed/refractory NHL undergoing TM after ASCT at the Sun Yat-sen University Cancer Center (SYSUCC) were reviewed. As historical control, two hundred patients without TM after ASCT during January 2006 to December 2012 were compared for analyses. All patients achieved CR before ASCT. Patients with transplantation related deaths and patients lost to follow-up were excluded. TM were given 100mg daily for one year. The latest follow-up was updated to June 30th, 2018. Clinical and laboratory information was collected. The survival analyses were calculated in different histological subtypes, including diffuse large B-cell lymphoma(DLBCL), peripheral T-cell lymphoma (PTCL), and MCL.

Results

Overall, a total of 311 patients(170 DLBCL, 105 PTCL, 36 MCL) were available for final analyses after exclusion of ineligible patients. Patients with PTCL were consisted of 20 patients with PTCL-NOS, 46 patients with natural killer/T-cell lymphoma, 25 patients with anaplastic large cell lymphoma, and 14 patients with angioimmunoblastic T-cell lymphoma. In the TM group(81 DLBCL, 59 PTCL and 23 MCL) and the non-TM group(89 DLBCL, 46 PTCL and 13 MCL), the median age were 44 years (range, 19–72) and 40 years (range, 17–76) respectively, the proportion of male were 55% and 62% respectively, and the median follow-up time were 24 months(range, 6–68 months) and 79 months(range, 5–160 months) respectively.

The 3-year overall survival (OS) comparisons were as follows: DLBCL: 77.8% vs. 64.0% (P = 0.037), MCL: 93.3% vs. 83.9% (P=0.433), and PTCL: 74.1% vs. 60.0% (P=0.219), in the TM group and the non-TM group, respectively. The 3-year progression-free survival (PFS) comparisons were as follows: DLBCL: 69.8% vs. 61.4% (P = 0.094), MCL: 93.3% vs. 61.5% (P=0.028), and PTCL: 57.9% vs. 51.5% (P=0.447), in the TM group and the non-TM group, respectively. In multivariate analysis, TM and age(>60 years) were independent prognostic factors for OS in DLBCL, and TM was the only independent prognostic factors for PFS in MCL.

The major toxicities observed in the TM group were as follows:, thrombocytopenia(73.2%), leucopenia(50.0%), constipation(53.5%), fatigue(58.5%), Somnolence (38.7%), rash(25.0%), edema(23.0%), and peripheral neuropathy(8.3%).



Conclusions

Despite the retrospective nature and other limitations of this study, it is suggested that TM might be associates with promising survival benefit in patients with high-risk DLBCL and MCL after ASCT. It warrants further prospective studies to confirm the efficacy of IMiD maintenance in NHL.

Keywords: maintenance; non-Hodgkin's lymphoma; thalidomide; transplantation



Acute GVHD following Autologous Stem Cell Transplant for Multiple Myeloma: A case series

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Abstract Content

Introduction: Graft-versus-host disease (GVHD) has rarely been reported after autologous SCT (ASCT). Acute GVHD after ASCT can involve the gastrointestinal tract and rarely skin and liver and presents with diarrhea, skin rash and jaundice respectively. Early recognition and prompt treatment can reduce disease progression, morbidity and mortality. We report here four patients of multiple myeloma who developed acute gut GVHD following ASCT.

Case series: A total of 225 patients underwent ASCT at Bone Marrow Transplant centre of BLK Superspeciality Hospital from Jan 2010 to June 2018, out of which 146 had multiple myeloma were retrospectively analysed. Autologous acute GVHD developed in 4 patients all of whom had multiple myeloma. Patient details and outcomewere in table 1. All patients received melphalan 200mg/m² as conditioning regimen. All patients developed green colored, large volume, watery loose stools after engraftment (median 13.5 days of ASCT) clinically suggestive of acute gut GVHD. Patients were evaluated for infective causes of diarrhea including stool examination for Clostridium difficile and blood CMV-PCR and all were negative. Sigmoidoscopy was done in all patients and histopathology of the specimens showed evidence of gut GVHD with apoptosis in crypts, cryptitis and crypt loss in focal areas (Figures 1. a-c).

The patients were treated with intravenous methylprednisolone 2mg/kg as first line treatment. One patient also required second line treatment with etanercept. All patients recovered with the treatment after a median of 3.5 days (range, 2- 6 days). The steroids were tapered over 2 weeks. After a median follow up of 12 months (range 6-20 months), 3 patients are in remission for GVHD and one patient has developed limited chronic oral GvHD.

Discussion: Autologous GVHD is a rare condition which has been reported in patients undergoing autologous stem cell transplant for multiple myeloma. Out of 146 patients who underwent ASCT for multiple myeloma at our centre over 8 years period, four patients (3%) developed acute gut GVHD. All these patients presented early after ASCT with copious watery diarrhea clinically suggestive of gut GVHD. Biopsy and histological examination in all cases revealed features consistent with gut GVHD and patients showed dramatic response to systemic steroids. Patient should be simultaneously evaluated for mucositis, bacterial, viral and drug induced diarrhea.

Patients undergoing ASCT do not have HLAmismatch and therefore pathophysiology of GVHD after ASCT is mainly due to diminished self-tolerance secondary to an altered immune system. Newer drugs used for multiple myeloma treatment like immunomodulators and proteasome inhibitors, both of which our patients had received, have been postulated to alter regulatory T cell function that could potentially lead to GVHD in these patients. The prevalence has been found to be consistently higher among patients with multiple myeloma compared to lymphoma. The diagnosis and management of autologous GVHD is similar to that of acute GVHD after allogenic SCT. These cases highlight the need for high index of suspicion of autologous GVHD and timely treatment.

Keywords: Autologous, GvHD



Clinical outcomes of allogeneic stem cell transplantation with reduced intensity conditioning method with FluMel-TBI regimen in refractory or relapsed non-Hodgkin lymphoma

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Abstract Content

INTRODUCTION

Since the development of novel targeted therapies including of well-known rituximab, approximately 60-80% of patients with various heterogenous non-Hodgkin lymphoma (NHL) might be cured dramatically. However, therapeutic options for patients with primary refractory/ relapsed NHL to conventional chemotherapy was limited, and long-term follow-up studies after auto-HSCT suggested that progression-free survival (PFS) was still being debated in some cases. We recently reported the acceptable survival outcomes in allo-HSCT for patients with relapsed or refractory NHL who underwent uniformed regimen with fludarabine (Flu), melphalan (Mel), and TBI (FMT). In this present study, we examined retrospective analysis for survival outcomes with single institute based-standard reduced intensity conditioning (RIC) method with FMT regimen for relapsed or refractory aggressive NHL which was the more larger cohorts and extended follow-up duration retrospectively, and another objective of this study was to identify transplant outcome predictors undergoing FMT regimen.

IPATIENTS AND METHODS

From. 2007 to 2017, 89 patients with refractory or relapsed NHL who underwent allo-HSCT received RIC regimen (FMT), including of fludarabine 30mg/m2 for six consecutive days (in total 180 mg/m2) plus melphalan 70 mg/m2 for one day with additional TBI of 800cGy in four fractionated doses for two days as a standard conditioning regimen in our center.

RESULTS

There were 42 patients with B-cell NHL, 42 of T-cell NHL, and 5 of NK cell lymphoma. The majority of patients (n=67, 75%) was in the advanced Ann-Arbor stage and a half of patients (n=40, 44.9%) had bone marrow involvement at initial diagnosis. At the time of allo-HSCT with RIC regimen. 49 patients (55.1%: 29 patients of CR and 20 of PR) had chemosensitive disease, and 40 patients (44.9%: 14 patients of SD and 26 of PD) revealed chemorefractory disease. During a median follow-up of 31 months (range 7-135 months) in survivors, the estimated 3-year OS and DFS for the entire cohort were 47.1% (95% CI, 36-57%) and 45.4% (95% CI, 35-56%) respectively. And cumulative incidence of NRM at 1-year and 3-year were 10.0% (95% CI, 4.4-18.4%) and 13.8% (95% CI, 6.6-23.5%) respectively, then most causes of TRM were acute graft-versus-host disease (GVHD) and infection. Grade II-IV of acute GVHD and the extended (moderate to severe) chronic GVHD were identified 11 (12.4%) and 16 (18%) patients respectively, and there was no cause of overlap disease. In analysis for the risk factors affecting transplant-survival outcomes with FMT regimen, chemorefractory status at transplant (HR=2.30; 95% CI: 1.28-4.15, p=0.006), the presentation of grade III-IV acute GVHD (HR=10.57; 95% CI: 3.90-28.64, p<0.001), and no mild chronic GVHD (HR=0.37; 95% CI: 0.15-0.89, p=0.026) were independently significant predictor of poor OS, while chemorefractory status at transplant (HR=2.02; 95% CI: 1.14-3.59, p=0.016) and the presentation of grade III-IV acute GVHD 95% CI: 2.66-17.19, p<0.001) were significantly associated with poor DFS. (HR=6.76; Conclusion

In relapsed or refractory NHL, this long follow-up study showed that FMT regimen as RIC method showed the favorable survival outcomes with acceptable TRM and relapse incidence. It especially showed the group of chemosensitive disease prior to allo-HSCT and manageable chronic GVHD.



Allogeneic hematopoietic stem cell transplantation for multiple myeloma: A single-center experience

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Abstract Content

Background The role of allogeneic hematopoietic stem cell transplant (allo-HSCT) in multiple myeloma in the era of new agents is controversial. Predictive factors for the outcome of allogeneic transplantation in patients with myeloma remain undetermined.

<u>Methods</u> We retrospectively evaluated single-institute outcomes of allo-HSCT for multiple myeloma from 1993 to 2015. Overall survival (OS) and disease-free survival (DFS) were analyzed using the Kaplan-Meier method. Cox proportional hazards model was used to examine the association of variables with outcomes of HSCT. Variables included for analysis were as follows: age at allo-HSCT, time period between transplantation and diagnosis, ISS and Durie-Salmon Staging, disease stage at allo-HSCT, myeloma subtypes, number of previous autologous hematopoietic stem cell transplants (ASCT), upfront tandem auto-allo-HSCT, donor type, HLA incompatibility, KIR-ligand incompatibility, missing of recipient KIR-ligand C1, and conditioning regimen. Fine and Gray competing risk regression models for survival analysis were carried out to assess cumulative incidence of relapse and NRM.

Result Twenty-two patients were included. Median age at transplant was 53.5 years (range: 39-66 years), 68.1% of patients aged 50 years and older. Disease stage at time of transplant was early (first CR) in 7 patients (13.8%), intermediate (second CR, PR, or SD) in 12 patients (54.6%), and late (refractory or PD) in 3 patients (13.6%). The median number of treatment regimens received before allo-HSCT was 3 (range: 1-6). Most patients (86.4%) had received ASCT before allo-HSCT; 14.3% of patients had a second ASCT prior to allo-HSCT. 31.8% of patients underwent upfront tandem auto-allo-HSCT. The Kaplan-Meier estimate of OS was 50%, 45%, 35%, and 25% at 1 year, 2 years, 3 years, and 5 years; DFS was 50%, 31%, 21%, and 16% at 1 year, 2 years, 3 years, and 5 years, respectively. Five patients survived more than 5 years, 3 of them were disease-free at the end of follow-up (survival: 100, 107 and 112 months). The only factor affecting OS when estimated by multivariate cox regression model is disease stage (late vs. early or intermediate; HR 7.6 [1.40 - 41.71], p=0.019). There was no impact of disease stage, ISS, DSS, myeloablative conditioining, KIR-ligand incompatibility, or upfront tandem auto-allo-HSCT on DFS or risk of relapse. Early NRM was 13% and 26% at 3 months and 6 months. Risk factors for NRM in multivariate analysis include unrelated donor (unrelated vs. sibling donor; HR 3.8 [1.07 - 13.23], p=0.038) and missing of recipient KIRligand C1 (C1Cx vs. C2C2; HR 2.2 [Cl: 1.02 - 4.62], p=0.044). Notably, 18.2% of patients (n=4) developed second malignancy during follow-up period, including PTLD (n=2), esophageal SCC (n=1), and colon adenocarcinoma(n=1).

<u>Conclusion</u> The results suggest allo-HSCT has the potential to offer long-term remissions in a small proportion of patients. However, the application of allo-HSCT for MM is limited by high risk of NRM and high relapse rates. Refractory or progressive disease at time of allo-HSCT is associated with grave transplant outcomes. Upfront tandem auto-allo-HSCT did not improve OS and DFS. The role of allo-HSCT in MM remains investigational and controversial.

Keywords: Allogeneic hematopoietic stem cell transplantation, multiple myeloma





Outcomes of patients with multiple myeloma who underwent autologous stem cell transplantation: A single-centre experience

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Abstract Content

Introduction

Autologous stem cell transplantation (autoSCT) is considered as standard of care in the treatment of patients with symptomatic multiple myeloma (MM) who are eligible for transplantation. Here, we report the results of a retrospective analysis of MM patients who underwent their first autoSCT at our center.

Aim

The aim of our study is to determine the transplant-related complications and the contributing factors, as well as the survival outcomes in our patient cohort.

Methods

This is a single-center retrospective study. The clinical records of all newly diagnosed MM treated with autoSCT between 1st Jan 2014 to 31 December 2017 were reviewed. Data was available for 75 patients and their clinical courses were analyzed.

Results

Mean age of patients who underwent autoSCT was 60 years. High dose melphalan (N=63) was the most commonly used conditioning regimen. The dose of melphalan was adapted according to the patient's age and renal function. 1 patient with disease involving the central nervous system received melphalan combined with thiotepa (5mg/kg x 2 days). Another patient developed angioedema after receiving one day of melphalan and conditioning regimen was switched to busulphan (3.2mg/kg x 2 days). The most common transplant-related adverse events were febrile neutropenia (76%), \geq grade 3 diarrhoea (12%) and \geq grade 3 mucositis (8%). 1 transplant-related death due to pneumonia occurred. The mean cell dose was lower among patients who developed \geq grade 3 mucositis compared to those who did not develop \geq grade 3 mucositis (4.85 x 10⁸ cells/kg, 95% CI 2.6-7.1; SD=2.1 versus 6.3 x 10⁸ cells/kg, 95% CI 5.7-7.0; SD=2.1) although this did not reach statistical significance, p =0.18. Univariate analysis showed no significant association of age and cell dose with transplant related febrile neutropenia, \geq grade 3 mucositis or diarrhea. 2-year progression free survival (PFS) after autoSCT was 63.6% (95% CI=49.0% - 75.1%, SE=0.067). Median PFS was 37.7 months (95% CI = 23.1 months – 48.3 months, SE = 7.25). Median overall survival (OS) was not reached.

Conclusion

From our analysis, febrile neutropenia was the most common adverse event. There was a trend towards lower cell doses among patients who developed \geq grade 3 mucositis. Our analysis did not show correlation of lower cell doses or increased age with other common transplant related adverse events of febrile neutropenia or \geq grade 3 diarrhoea. 63.6% of MM patients who underwent post autologous stem cell transplant at our centre remained progression free for 2 years post transplant.

Keywords: multiple myeloma; autoSCT; adverse events; survival outcomes





Thiotepa-Carmustine-Etoposide as Conditioning Therapy Before Autologous Stem Cell Transplantation for Central Nervous System Non-Hodgkin Lymphoma

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Abstract Content

Introduction

The treatment of primary central nervous system lymphoma (PCNSL) has evolved through the years from whole brain radiotherapy (WBRT) alone to high-dose methotrexate (MTX) in combination with various other chemotherapeutic agents followed by consolidation WBRT. The addition of chemotherapy, particularly MTX improved survival from less than 5% to about 22% at 5 years. Delayed neurotoxicity with WBRT in about a third of patients remains a major barrier to long-term survival. Emerging data showed high dose therapy in PCNSL and secondary CNS lymphoma (SCNSL) as consolidation have similar efficacy as compared to WBRT while avoiding long term neurotoxicity. From 2013, we changed our consolidation strategy from WBRT to high-dose chemotherapy using CNS-penetrating agents – thiotepa (TT), carmustine (BCNU), and etoposide (VP16) followed by autologous stem cell transplant (ASCT) in all CNS lymphoma patients. Herein we report their outcomes.

Aim

To evaluate clinical outcomes of PCSNL and SCNSL patients conditioned with TT-BCNU-VP16 followed by ASCT.

Method

This is a retrospective analysis of consecutive PCNSL and SCNSL patients who underwent ASCT from December 2013 to April 2018 using TT-BCNU-VP16 conditioning at two large transplant centers in Singapore. The conditioning regime is as followed: BCNU 400mg/m² was delivered once on D-5, VP16 150mg/m² once daily from D-5 through D-3, and TT 5mg/kg Q12hourly on D-4 and D-3. Baseline characteristics and toxicity events were summarized using frequency counts and descriptive statistics. Kaplan-Meier estimates of event free survival (EFS) and overall survival (OS) were performed.

Result

A total of 8 patients were included with baseline characteristics as shown in Table1. Transplant outcome (Table2) and toxicity profile (Table3) as shown. The EFS and OS after 6 months median follow up (2-32 months) post-transplant, are 75% and 87.5% respectively. Three of the patients had PCNSL while five had relapse DLBCL with isolated SCNSL. All patients were successfully harvested and five were in CR before transplant. Median stem cells dose was 6.65 million/kg (4.25 – 20.99mil/kg). The response to treatment improved further post-transplant to 100% CR, which showed the efficacy of the conditioning regime. One patient relapsed 4 months post-transplant and underwent whole brain radiotherapy. One patient died at 2 months post-transplant with disease in remission due to pseudomonas infection. He had poor premorbid and was heavily pretreated with four lines of chemotherapy. Median day of neutrophil and platelet engraftment are 12.5 and 15.5 respectively. All patients had neutropenic fever, two with bacteremia. The study is limited by the small number of patient and short median follow up.

Conclusion

TT-BCNU-VP16 conditioning is effective and well tolerated for PCNSL and SCSL. Further studies with more subjects and longer follow up are warranted.





Trends in the use of autologous stem cell transplantation and survival after transplant in multiple myeloma: A population-based study in Taiwan

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Abstract Content

Background: Autologous hematopoietic stem cell transplantation (ASCT) is standard treatment for selected patients with multiple myeloma (MM). Limited available data describe ASCT usage and survival in patients with MM living in Asia. We aimed to describe trends in ASCT usage, treatment patterns and survival in patients with MM in Taiwan.

Methods: We conducted a retrospective cohort study utilizing the Taiwan National Healthcare Insurance claims database. All newly diagnosed confirmed MM patients in the catastrophic illness files during January 1, 2007 to December 31, 2012 were enrolled. Patients with any primary cancer other than MM were excluded. All eligible patients were followed up until death or the end of the observation period (December 31, 2013), whichever occurred first. Death was confirmed by the death status in the catastrophic illness files. Main analyses were purely descriptive, and exact method was used to calculate 95% confidence intervals (CIs).

Results: Of 1969 newly-diagnosed MM patients included in the cohort analysis of whom 254 (13%) underwent ASCT. Gender distribution and geographic region were similar in the transplanted and non-transplanted cohorts (Table). Overall, 3.9% of transplanted patients were aged 65+ years, versus 67.2% of non-transplanted patients (p<0.0001). Transplants in 65+ year-olds increased from none in 2007-2008 to 5.8% in 2011-2012. Transplanted patients were significantly less likely to have renal impairment, anemia or pneumonia (p<0.0088), and had a lower Charlson Comorbidity Index score at diagnosis (0.7) than non-transplanted patients (1.4). Median time from diagnosis until ASCT decreased from 0.82 years in 2007-2008 to 0.68 years in 2011-2012 (p=0.00005). Frequently used first-line treatment regimens in transplanted patients included thalidomide (59.8%), and/or bortezomib (16.9%), compared with melphalan (51.9%), and/or thalidomide (51.1%) in non-transplanted patients. Median overall survival (OS) was 6.46 years in transplanted patients versus 1.92 years in non-transplanted patients (Figure). Five-year OS was 58% and 23%, respectively. Two-thirds of patients received maintenance regiments within 90 days after ASCT; 67% included thalidomide, 18% included bortezomib, 18% were steroids alone. Four patients died within 90 days after the transplantation procedure.

Conclusion: Patients with MM in Taiwan who undergo ASCT have improved survival compared with nontransplanted patients. ASCT may be underutilized in Taiwan, but longitudinal data suggest its' use in older adults may be expanding.

Keywords: Autologous hematopoietic stem cell transplantation; multiple myeloma; taiwan; overall survival





Outcome of Autologous stem cell transplantation in Multiple Myeloma, in the Era of Novel agents: A Single centre Experience

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Abstract Content

Abstract

BACKGROUND:

Multiple myeloma (MM) is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. In the last decade the major advance in the management of MM has been the introduction of novel agents into the therapeutic armamentarium. The novel agents along with ASCT have markedly improved the rate of complete remission, which has important implications in overall outcomes.

Patients and methods:

We retrospectively analysed the data in patients with MM who were transplanted at our centre from 2012to 2017. Aim was to analyse the influence of pre transplant characteristics and post transplant treatment modalities on progression free and overall survival.

Results:

A total of 50 MM patients with median age of 55 yrs(38 to 67 years) were transplanted between 2010 and 2015. Male to Female ratio was 1.27:1 with 28(56%) male and 22(44%) females In all, 38(76%) patients had IgG, 7(14%) had IgA and 2(4%) had light chain. Twelve (24%) patients were classified as ISS I whereas 25(50%) were ISS II and 13(26%) were ISS III. At the time of ASCT, 34(68%) of patients were in complete remission (CR), 14(28%) in Very good partial remission (VGPR) and 2(4%) patients were in Partial remission (PR). Prior to autograft, 76%(38) of cases had received VTD regimen whereas 24%(28) had received VCD regimen. Conditioning with melphalan 200mg/m² was given in 44(88%) of patients, remaining 6(12%) patients received 140 mg/m² in view of renal failure.

Following ASCT 48(96%) patients achieved CR/VGPR at 3 months excluding 2(4%) patients who had TRM. All patients were advised at 3 months post-Transplant for maintenance therapy with Thalidomide/Lenalidomide. Over amedian follow up period of 46 months, 28(56%) of the patients were alive and disease free, 11 (22%) were alive with relapse, and 9 (18%) had disease related mortality. Median OS and PFS from the date of transplantation were 40 and 26 months respectively. Median OS from diagnosis was 46 months.

Discussion:

First-line use of proteasome inhibitors and immunomodulatory drugs for transplant and nontransplant patients has yielded higher RR, PFS and OS.

Long-term follow-up studies of high-dose therapy with transplantation show that approximately 50% of patients with MM are alive at 5 years after transplantation. We have confirmed these data; in our group of 50 patients, 56% of them are alive, with a median follow-up 46 months and also Median OS, PFS from the date of transplantation were 40 and 26 months respectively.

Because ASCT is not curative in myeloma, the use of various posttransplantation maintenance therapies to prolong the duration of disease control is logical, but the benefit of these strategies is unclear. An exception is the maintenance therapy with thalidomide/ lenalidomide, which probably does improve survival.



Based on our data, we can confirm the importance of these novel drugs for the prolongation of survival in patients after autoSCT, as reported previously by other authors.

Conclusion:

ASCT in combination with novel drugs is an effective strategy in patients with MM to improve depth of response, PFS, and overall survival.

Keywords: MULTIPLE MYELOMA, AUTOLOGOUS STEM CELL TRANSPLANT, IMMUNOMODULATORY DRUGS



The efficacy of G-CSF mobilized, non-cryopreserved stem cell collection in the same admission with autologous stem cell transplantation for multiple myeloma

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Abstract Content

Introduction: Autologous stem cell transplantation (ASCT) is the standard treatment for multiple myeloma (MM). Stem cell mobilization can be performed by either G-CSF alone or chemotherapy combination with G-CSF. Cryopreserved process is the major step after stem cell collection but may be difficult to access in limited resources. Previous studies showed that stem cell storage at 4 centigrade was possible and safe. This was a prospective pilot study aimed to evaluate the efficacy, cost effectiveness of G-CSF mobilized and non-cryopreserved stem cell in the same admission with ASCT for MM.

Methods: This study was performed during July 2014 to December 2017. MM patients who achieved at least very good partial response underwent stem cell mobilization with G-CSF alone (10 ug/kg/day) for 5 consecutive days before admission (day 1-5). The first day of stem cell collection was performed on day 6 with cryopreserved techniques and kept for 2nd ASCT. The second day of stem cell collection was conducted with non-cryopreserved techniques and stored at 4 centigrade. A day after stem cell collection, patients underwent ASCT with melphalan 200 mg/m² in 2 consecutive days. On the next day, non-cryopreserved stem cell was transfused.

Results: There were eighteen patients with a median age of 56 years. The majority was female (75%). The mean stem cell dose was 4.72×10^6 /kg (2.08 - 14.8 x 10⁶/kg). The mean stem cell viability was 97% (73-99%). No bacterial contamination was detected from all stem cell bags. The median time for neutrophil and platelet engraftment was 12 (8-20), 20 (10-31) days, respectively. The average hospitalization length was 23 (17-36) days. There was no transplant related mortality. All patients achieved complete response and stringent complete response after transplantation procedure. The cost of treatment was cheaper compared to the average cost in the whole country. [357,990 baht (11,186 US dollar) vs. 506,062 baht (15,814 US dollar)].

Conclusion: This alternative way of stem cell collection for MM is feasible in term of safety and efficacy. Moreover, the treatment cost is cheaper and can be performed in the hospital lacking cryopreserved facilities.

Keywords: stem cell; autologous stem cell transplantation; multiple myeloma



Long-term Outcome of Hematopoietic Stem Cell Transplantation, a Two-decade Retrospective Cohort in Phramongkutklao Hospital.

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Abstract Content

Introduction

It has been more than 50 years that hematopoietic cell transplantation (HCT) has been a curative modality of treatment several disorders both non-malignancy (i.e.severe combined immunodeficiency, refractory autoimmune disease) and malignancy (solid tumors and hematologic malignancy). The Worldwide Network for Blood and Marrow Transplantation Group (WBMT) reported number of patients (pts) underwent HCT which increased from 46,563 pts in 2006 to 68,146 pts in 2012 (increased by 46%). In 1986, HCT was initiated in Thailand. Approximately 120 -150 transplanted Thai pts were reported at that time but current transplanted rate markedly increased to 600 – 700 transplanted pts annually. At the present, there are 13 hospitals capable of performing HCT but only 4 hospitals can perform allogeneic HCT. Budget limitation is one of the most important obstacles of HCT service in Thailand. Established in 1998, our Bone Marrow Transplant unit has served as one of those 4 transplant centers in Thailand capable of performing allo-HCT. This study aims to report survival outcomes in transplanted patients for 20 years of our service.

Methods

The study was a retrospective cohort included pts of age older than 15 years old underwent HCT between January 1998 and December 2017. Indications of HCT and overall survival (OS) were collected. OS was analyzed by Kaplan-Meier method.

Results

195 transplanted patients were collected. The median age was 43 years (17 – 67 years), 117 (60%) patients were male. Indication of HCT were acute myeloid leukemia (AML) 36 (18%) patients, lymphoma 42 (22%) patients, chronic myeloid leukemia (CML) 29 (15%) patients, multiple myeloma (MM) 57 (29%) patients and others 31 (16%) patients. The median follow-up was 10 years. 186 patients were capable of analysing by survival analysis. 5-year and 10-year OS of entire cohort was 62% (95% confidence interval; CI: 53.9-69.6) and 51% (95%CI: 40.6-59.6), respectively. The subgroup analysis of survival according to 4 main disease indications for HCT was shown in Figure 2.

Conclusion

This study reported long-term outcomes of 195 transplanted patients during 1998 – 2017. MM is the most frequency of indications for HCT particularly in the 2nd decade of our service. For the entire cohort, 5-year OS was 62% (95%CI: 53.9-69.6) and 10-year OS was 50.5% (95%CI: 40.6-59.6). These results produced comparable transplant outcomes.

Figure 1 Overall survival of the entire cohort.

Figure 2 Overall survival (A), and relapse-free survival (B) according to diseases indicated for HCT

Keywords: Long-term Outcome;Hematopoietic Stem Cell Transplantation;Survival



Analysis of the efficacy and prognostic factors of 67 patients with multiple myeloma after undergoing autologous peripheral hematopoietic stem cell transplantation

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Abstract Content

Objective: To explore the efficacy and prognostic factors of autologous stem cell transplantation (ASCT) for multiple myeloma (MM) patients.

Methods: A total of 67 MM patients who received induction treatment followed by ASCT between July, 2009 and October 2017 were enrolled in the retrospective .study.

Results: After ASCT, all (100%) patients achieved partial response (PR), and 59.1% patients achieved complete remission (CR). During a median follow-up of 28 months, 31 patients relapsed after transplantation and 16 patients died. 1 patient died of the second tumor, the remaining patients died of disease progression, and 3 patients were lost to follow-up. The median progression-free survival (PFS) was 55.6 months, the median OS was not achieved. In 64 patients with revised International Classification System (R-ISS), 11 cases (16.4%) had stage I, 23 cases (34.3%) had stage II, 8 cases (11.9%) had stage III, with median PFS of I,II,III stage was 85.4 (n=11), 51.9 (n=23) and 20.9 (n=8) months,respectively (P=0.047). There was a significant difference in median OS (not yet reached, 60.9 and 22.9 months for R-ISS I and II, and III,respectively, P=0.007) among the three stages of R-ISS. We also found that patients belonging to R-ISS II and having high-risk chromosomal abnormalities (CA) had a significant shorter median PFS and OS than those with R-ISS II without CA. MRD negative status by flow cytometry (defined as <10⁻⁴) at 3 months post-ASCT (n=15) showed a better PFS (95.07 months, P=0.049). The pre-transplant efficacy, pretreatment regimen, post-transplant efficacy, and maintenance treatment subgroup analysis showed that there was no significant difference in median OS and PFS between groups. Cox analysis showed that R-ISS was independent prognostic factors for OS.

Conclusion: Induction therapy followed by ASCT is a safe strategy for MM patients, and also significantly improve their outcome. The R-ISS and low level MRD are reliable prognostic tools for estimating survival in transplant myeloma patients.

Keywords: multiple myeloma; autologous peripheral stem cell transplantation; risk factors; survival analysis



High-dose Chemotherapy Followed by Autologous Stem Cell Transplantation for Patients with Multiple Myeloma – Experience of a Single Medical Center in Taiwan

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Abstract Content

Introduction

Mutiple myeloma (MM) is an incurable plasma cell malignancy. In the era of novel agents, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains the recommended treatment for newly-diagnosed fit patients with MM. We aimed to review the outcome of MM patients treated with high-dose chemotherapy followed by ASCT in Chang Gung Memorial Hospital at Linkou, Taiwan.

Methods

We retrospectively reviewed patients with MM treated with high-dose chemotherapy followed by ASCT from 2000 to September 2017. Basic demographic data, disease characteristics, induction treatment before ASCT, response after induction treatment and after ASCT, progression-free survival (PFS) and overall survival (OS) after ASCT were collected. Comparisons of treatment outcome were made according to clinical characteristerics.

Results

There were 153 cases with 75 females and 78 males. The median age was 54 (range 30 to 66). At diagnosis, most of the patients was Durie-Salmon stage (DSS) III (78.4%) and International Staging System (ISS) III (41.3%). Anemia with Hb \leq 10 g/dL was observed in 97 cases (63.4%), hypercalcemia with corrected serum calcium level > 10 mg/dL in 53 cases (35.1%) and elevated serum creatinine > 2.0 mg/dL in 36 cases (23.5%). Induction treatment included chemotherapy (N=39, 25.5%), thalidomide plus steroid (N=31, 20.3%), and bortezomib-based regimen (N=83, 54.2%). Responses after induction treatment were partial response (PR) or less in 45 cases (29.4%), very good partial response (VGPR) in 54 (35.3%) and complete response (CR) in 54 (35.3%). Responses after ASCT were PR or less in 17 (11.2%) cases, VGPR in 42 (27.6%) and CR in 93 (61.2%). Treatment-related mortality was found in one patient (0.7%). Patients with DSS I/II, Hb > 10 g/dL, CR after induction treatment, and CR after ASCT had better PFS (P = 0.008). Patients with Hb > 10 g/dL, CR after induction treatment, and CR after ASCT had better OS. By multivariate analysis, only CR after ASCT had better OS. By multivariate analysis, only CR after ASCT had better OS. By multivariate analysis, only CR after ASCT had better OS.

Conclusion

Patient with MM treated with high-dose chemotherapy and ASCT had good PFS and OS and also a low treatment-related mortality rate in our series.

Keywords: multiple myeloma; autologous stem cell transplantation; progression-free survival; overall survival





Autologous stem cell transplantation in multiple myeloma: posttransplant outcomes of Taiwan Blood and Marrow Transplantation Registry

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Abstract Content

Background/Purpose

Multiple myeloma (MM) is a monoclonal plasma cell malignancy. The primary choice of treatment for MM is induction therapy followed by autologous stem cell transplantation (ASCT). This study aimed to analyze the treatment efficacy of ASCT in a Taiwan cohort and evaluate possible prognostic factors.

Methods

From the database of the Taiwan Blood and Marrow Transplantation registry, data on 396 MM patients who underwent ASCT were reviewed.

Results

The average age was 54.8 years, and the proportion of male patients was greater than female patients (57.6% vs. 42.4%). Most of the patients were diagnosed as having IgG-type myeloma (52.4%), followed by IgA-type (23.2%) and light-chain type (21.4%). Patients with Durie Salmon Staging System (DSS) III comprised 61.9% of the study cohort, while 23.7% had stage II and 14.4% had stage I. The median progression-free survival (PFS) and overall survival (OS) after ASCT was 46.5 months and 70.4 months, respectively. DSS III was a poor prognostic factor affecting both PFS and OS with a duration of 35.9 months and 69.0 months, respectively, compared with the other two stages (p=0.006 and p=0.03, respectively). In addition, patients with better treatment response before ASCT had better PFS and OS compared with those who did not show a response (both p<0.0001). The overall incidence of organ toxicities associated with transplantation was low.

Conclusion

In conclusion, our cohort showed that myeloma patients with early DSS and better treatment response before ASCT had better long-term survival outcome.



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Keywords: Multiple myeloma, transplantation, survival



Diagnostic challenge: Primary bone marrow diffuse large B-cell lymphoma mimicking systemic autoimmune disorders.

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Abstract Content

Introduction

Primary bone marrow lymphoma (PBML) is a rare entity of non-Hodgkin's lymphoma (NHL) with aggressive disease progression and poor prognosis. Although PBML was documented in the literature since 1977, its diagnostic criteria or clinical features are not clearly defined. With poor survival, timely and accurate diagnosis of PBML is essential. It has been reported that combining chemotherapy with stem cell transplantation could be promising strategy for PBML. Unfortunately, atypical symptoms in the absence of tumor mass and lymphadenopathy can make the diagnostic procedure extremely challenging, leading to missing the window of opportunity. Here, we present PBML patient with systemic inflammatory symptoms mimicking autoimmune disorders.

Case Report

A 53-year-old man visited the outpatient clinic of neurosurgery department due to lower back pain starting 15 days before. He presented with symptoms of spinal cord compression; left leg weakness, urinary urgency, urge incontinence, constipation and erectile dysfunction. Initial MRI of spine showed T2 hyperintense lesion in cornus medullaris and spinal myelitis (SM) was the first impression. After 2 weeks, his neurologic symptom has expanded to right leg weakness and sensory change of left leg. He was immediately admitted to neurologic department and treated with steroids based on CSF study revealing inflammatory condition with lymphocytic pleocytosis. Brain MRI showed no abnormality, PET-CT revealed systemic inflammatory status involving spinal cord, lungs, spleen, renal cortex and prostate. Peripheral lymphadenopathy was not noticeable from imaging studies. Among systemic autoimmune markers, anti-nuclear antibody and anti-Ro/SSA antibody were detected. However, patient didn't meet the diagnostic criteria of Sjögren syndrome. Bone marrow (BM) study due to newly developed thrombocytopenia revealed mature B-cell neoplasm, most likely diffuse large B-cell lymphoma (DLBCL). 2 days after BM diagnosis was confirmed, patient developed a metabolic acidosis, hypotension, respiratory failure and expired.

Discussion

Primary bone marrow DLBCL is a rare entity of extranodal NHL. The diagnostic challenges of this disease include overlapping features with intravascular large B-cell lymphoma (IVLBCL), absence of disease-specific clinical symptoms and lack of unified diagnostic criteria. Several studies made attempts to overcome these challenges. Ponzoni et al. have suggested a random biopsy in uninvolved organs would be a useful confirmatory strategies for distinguishing IVLBCL from primary bone marrow DLBCL. Martinez et al. have proposed the diagnostic criteria of PBML; (1) isolated bone marrow infiltration regardless of peripheral blood involvement; (2) no evidence of lymph node, spleen, liver, or other extra marrow involvement on physical examination or imaging studies; (3) absence of localized bone tumors; (4) no evidence of bone trabeculae destruction in the bone marrow biopsy; and (5) exclusion of leukemia/lymphoma cases that are considered to involve primarily the bone marrow.

Retrospective review of our patient revealed his laboratory results strongly correlates with primary bone marrow DLBCL. However, clinicians had difficulty diagnosing because of atypical manifestations such as spinal myelitis, lack of cytopenia and symptoms of autoimmune disease. In this paper, we report extremely rare clinical symptoms of primary bone marrow DLBCL and try to draw the attention of clinicians to this disease entity.





Stem cell transplantation increases survival probability of patients with multiple myeloma, but may decrease the bortezomib-related survival advantages – an experience in a single institution

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Abstract Content

Introduction: Both bortezomib and stem cell transplantation have been proved to increase survival advantages on patients with multiple myeloma. This retrospective analysis is to find any addition of benefit when both procedures are applied on patients.

Methods: From 2007 to 2016, there are 126 patients with multiple myeloma treated partially or completely at KF-SYSCC and registered in KF-SYSCC Cancer Registry data office. All patients are selected for survival analysis.

Results: In 126 patients, median age is 60 (52-68), male is slightly predominant (M:F ratio is 1.14). 3-year and 5-year estimated survivals are 53% and 38%, respectively. 42 patients have been treated with bortezomib and 84 have not. 3-year and 5-year estimated survivals with bortezomib treatment are 71% and 60%, and without bortezomib are 40% and 23% which are significant different. 20 out of 126 patients have received stem cell transplantation. 3-year and 5-year survivals are 83% and 77% which are significantly higher than the survivals of the cohort without transplantation. Within 20 transplant patients, 15 have received bortezomib and the other 5 have not. 3-year and 5-year survivals in bortezomib cohort are 83% and 74%, while those in non-bortezomib cohort are 80% and 80%.

Conclusion: Bortezomab has positive impact on survival of patients with multiple myeloma. Stem cell transplantation increases the survival probability on year 3 and 5. The positive impact on survival from bortezomib is decreased by stem cell transplantation. Further prospective study may be needed to confirm this finding.

Keywords: Myeloma; Transplantation; Bortezomib





Stem cell transplantation for T-cell lymphoma: data from Taiwan Society of Blood and Marrow Transplantation

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Abstract Content

In Taiwan, according to the Taiwan Cancer Registry, there are about 330 new cases of T-cell lymphoma every year which accounted for 10%-15% of non-Hodgkin lymphoma, and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (28%), natural killer/T-cell lymphoma (NKTCL) (18%), and angioimmunoblastic T-cell lymphoma (AITL) (14%) represent the most common three subtypes of T-cell lymphomas. T-cell lymphomas are generally aggressive malignancies with poor prognosis. There are no established standard treatment guidelines for T-cell lymphomas, and the timing of stem cell transplantation (SCT) is not well known.

In this study, we investigated the outcomes of Taiwanese patients with T-cell lymphomas after SCT. From database of Taiwan Society of Blood and Marrow Transplantation, we retrospectively analyzed 131 patients with T-cell lymphomas who received SCT (autologous: 90, allogeneic: 41) from 2009 to 2014. More autologous ST recipients were in complete remission (CR), and more allogeneic recipients had advanced disease. 56 patients who were sensitive to chemotherapy underwent SCT as upfront setting. The 2-year PFS and OS rates were 67.0% and 64.5%, respectively. Regarding disease status before transplantation, patients with CR1 had the best outcomes, with 2-year PFS and OS rates of 80.5% and 66.0%, respectively. Among different subtypes, patients with NKTCL showed the worst outcomes, with 2-year PFS and OS rates of 44.9% and 23.5%. The PFS and OS rates for the other three major subtypes were as follows: 57.1% and 72.9% for anaplastic large-cell lymphoma; 84.7% and 75.0% for AITL; and 51.6% and 51.4% for PTCL-NOS. As for the rarer subtypes of lymphoma, such as adult T-Cell leukemia/lymphoma (n=9) and subcutaneous panniculitis-like T-cell lymphoma (n=7), data from our study as well as previous reports show that SCT can be beneficial.

We concluded that CR1 is a strong predictor of longer survival. As for up-front SCT, autologous SCT seemed to be feasible and safe, but the benefits of more aggressive allogeneic SCT are still not clear. Future research into allogeneic SCT should aim to reduce non-relapse mortality and improve OS at the same time. Considering the poor outcomes of SCT in patients with relapsed disease, early referral should be considered for high risk patients. Among different histological subtypes, the poor outcomes of patients with NKTCL cannot be overcome by either autologous or allogeneic SCT.





Survival Analysis through Mantle Cell Lymphoma Risk Stratification and Stem Cell Transplantation in the Era of Target Therapy – an observational cohort study in Taiwan

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Abstract Content

Mantle cell lymphoma is a B cell non-Hodgkin lymphoma mostly with advanced stage and non-nodal tissue involvement. Long-term survival is not achieved through the remission after induction chemotherapy. In recent years small molecule inhibitors and target therapy were developed for obtaining optimal disease control whereas high-dose chemotherapy with autologous stem cell rescue (HDC-SCR) and allogeneic stem cell transplantation (allo-SCT) still serve as effective consolidation or salvage treatment for this disease. In this longitudinal observational study, pretreatment parameters and therapy modalities were investigated retrospectively in hope for gaining insights in prospective clinical trial design. In this single-institute cohort spanning from 1999 to 2018, medical records of 103 patients (male: 85 vs. female: 18) were systematically reviewed, with a 38-month median follow-up duration. The median age at diagnosis was 62 years old. The Ann Arbor staging at diagnosis was mostly stage 4 (80.6 %) and blastoid variant comprised of 9.7 %. Using MIPI scores, patients could be stratified as low risk (<5.7) 27 %, intermediate risk (between 5.7 and 6.2) 36 %, and high risk (³6.2) 37 %. In treatment, CHOP-like induction chemotherapy was given to 76% of this cohort. The number of patients receiving consolidative HDC-SCR and allo-SCT were 35 (34%) and 6 (5.8%), respectively. In recent years, bortezomib and ibrutinib were added to the treatment armamentarium for salvage therapy in this cohort, given to 31 (30.1%) and 16 (15.5%) patients, respectively.

The median overall survival was 82 months. In further analysis, the overall survival differences between MIPI risk groups were significant (median OS 51 vs. 82 vs. 146 months, p=0.01). Negative immunohisotochemical stain of Cyclin D1 did not poses a survival risk. Besides, overall survival was significantly shorter in patients with blastoid variant (median survival 15 vs. 82 months, p=0.003). Patients who were older than 60-year-old also had poorer outcome (median survival 54 vs. 144 months, p=0.01). In the multivariate analysis for OS, blastoid variant, advanced-stage, and higher MIPI scores were independent adverse risk factors while allo-SCT had protective effect. Two subgroups of patients might benefit from allo-SCT for long-term survival. For patients younger than 60 years of age, allo-SCT conferred an overall survival advantage (median survival 31 months vs. no death reported, p=0.118). Likewise, patients of non-blastoid variant also benefitted from allo-SCT (median survival 31 months vs. no death reported, p=0.188).

In contrast, HDC-SCR did not result in significant overall survival advantages (median OS 73 vs. 147 months, p=0.063). Interestingly, for advanced-stage patients not receiving HDC-SCR, ibrutinib might contribute to a better overall survival (median OS 34 months vs. not achieved, p=0.274) with a median follow-up duration of 71 months. In conclusion, for aggressive type of mantle cell lymphoma, allo-SCT still might be a viable option for subgroups of mantle cell lymphoma patients. Longer follow-up would be needed to address the role of novel therapy in this disease.

Keywords: Mantle cell lymphoma, stem cell transplantation, single-institute, overall survival, risk stratification





Outcome of Bendamustine-Replacing BCNU as Conditioning Regimen for Autologous Hematopoietic Cell Transplantation for Patients with Lymphoma

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Abstract Content

Introduction

Carmustine(BCNU)-based chemotherapy regimens (BEAM, BEAC) are viewed as the standard conditioning chemotherapy for lymphoma patients undergoing autologous hematopoietic cell transplantation (aHCT). However, pulmonary toxicity and availability prompt us search for bendamustine for substitution. We report our experience of Bendamustine-replacing BCNU (BeEAM) as the conditioning regimen for aHCT for patients with lymphoma.

Patients and Methods:

We retrospectively reviewed medical records of lymphoma patients who had undergone BeEAM as conditioning chemotherapy for aHCT from Sep 2013 to Aug 2018 in our institution. There were 15 patients with median age of 52 years old [Range:27-68]. Their clinical characteristics, disease status before transplantation, treatment responses, time of engraftment and survival were analyzed.

Results

The different types of lymphoma included 7 with diffuse large B cell Lymphoma, 3 with Hodgkin Lymphoma, 2 with mantle cell Lymphoma. Marginal Zone Lymphoma, anaplastic large cell Lymphoma and peripheral T cell Lymphoma was in each one patient. Before aHCT, there were 2 patients with first complete remission, 6 patients with second complete remission, 3 patients with partial response after first relapse, and 4 patients with partial response. Median stem cell yield was 6.29 x106 cells/ul [Range, 1.65-45.39 x106 cells/ul]. Median dosage of Bendamustine was 186mg/m2 [Range, 94-201 mg/m2]. Neutrophils recovered greater than 0.5 x 109/L after a median of 10 days [Range, 7-14 days], and the median time until platelets greater than 20 x 109, and 50 x109 /L was 14 days [Range, 7–21 days], and 19 days [Range, 1.2–58 days], respectively. At last follow-up, a median follow up time after aHCT was 29.9 months [Range, 0.5-57.3 months], 7 (46.7%) patients were in CR, 1 (6.7%) patient was partial remission, 4 (26.7%) patients were relapsed, and three patients (20%) were dead, including two patients with disease progression and the other one patient with transplant-related complication. The median progression free survival and overall survival were not reached.

Conclusion

Our study suggests the BeEAM regimen as conditioning chemotherapy for lymphoma patients with aHCT therapy was efficacious and safe

Keywords: Lymphoma; Autologous Hematopoietic Cell Transplantation; Bendamustine; Conditioning



Choosing the Induction Chemotherapy of Multiple Myeloma underwent Autologous PBSCT in Surabaya: Effect on CD34+ Count, Engraftment Period and Length of Stay

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Abstract Content

Introduction : Autologous Peripheral Blood Stem Cell Therapy (PBSCT) on Multiple Myeloma (MM) patients had a higher response rate and becoming a standard of care after primary therapy for eligible patients. CD34+ count is essential marker of stem cells prerequisite for the PBSCT in MM patient. Choosing an induction chemotherapy for eligible patients becoming very important step in order to achieve optimal CD34+ count. Several guidelines suggested that Bortezomib were superior than VAD, unfortunately only VAD were covered by government health insurance (BPJS) in Indonesia. This study aimed to know the effect of induction chemotherapy on premobilization CD34+ count, engraftment period, and length of stay.

<u>Methods</u>: Ten MM patients underwent induction chemotherapy and achieved CR with plasma cell < 2.5% in Dr.Soetomo Hospital Surabaya during 2014-2017. Five patients had VAD (Vincristin 0.4 mg/m², Doxorubicin 9 mg/m², Dexamethasone 40 mg/day on d1-4, d9-12, d17-20) for 6 cycles, and the other 5 patients had Bortezomib (1.3 mg/m² on d1, d4, d8, d11) for 6 cycles as an induction chemotherapy. We observed premobilization CD34+ count, engraftment period, and length of stay of these patients.

<u>Result</u>: The mean of premobilization CD34+ count of 5 MM patients who had VAD as an induction chemotherapy was $72.92 \pm 78.65 \times 10^6$ while 5 patients who had Bortezomib was $179.48 \pm 177.90 \times 10^6$. Engraftment period on VAD and Bortezomib patients group happened with the mean of 20.2 ± 6.0 and 18.4 ± 10.8 days after PBSCT performed. The VAD patients group had mean length of stay of 48.2 ± 2.5 days, while on Bortezomib patients group had 52.2 ± 8.7 days. The kruskal wallis study was performed and showed that there was no difference between VAD and Bortezomib as an induction chemotherapy on premobilization CD 34+ count (p = 0.347; p> 0.05). The T-test study that had been done also revealed there was no difference between VAD and Bortezomib as an induction chemotherapy on engraftment period and length of stay at the hospital (p = 0.754 and p = 0.357; p> 0.05).

Conclusion : The premobilization CD34+ count, engraftment period and length of stay at the hospital was relatively the same in MM patients who had VAD or Bortezomib as an induction chemotherapy for autologous PBSCT. VAD was still giving good result on premobilization CD34+ count, having engraftment period and length of stay similar to Bortezomib and furthermore it was covered by government health insurance (BPJS) in Indonesia.

<u>Keyword</u>: Premobilization CD34+ count; Engraftment period; Length of stay; Induction chemotherapy; Autologous PBSCT; Multiple Myeloma

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Keywords: Premobilization CD34+ count; Engraftment period; Length of stay; induction chemotherapy; Autologous PBSCT; Multiple Myeloma





Allogeneic Hematopoietic Stem Cell Transplant for Myelofibrosis: A Single-Center Experience in the Philippines

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Abstract Content

Introduction

Myelofibrosis (MF) is a myeloproliferative neoplasm with a debilitating symptom profile that affects quality of life and survival. Hematopoietic stem cell transplant (HSCT) is the only curative option. Despite this, MF is still a rare indication for HSCT. The Asia Pacific Blood and Marrow Transplantation Group reported that myeloproliferative neoplasms accounted for only 1% of transplant indications in the Asia Pacific area in 2015. Currently, there are no studies on the outcomes of Filipino patients with MF who have been treated with HSCT. We present our experience.

Methods

All patients undergoing HSCT for MF between January 2010 to June 2018 at the St. Luke's Medical Center – Global City (n=4) were included. The median age was 46 years old. All patients were diagnosed to have primary myelofibrosis. Three patients were stratified as intermediate-2 risk, and one patient was stratified as high-risk according to the Dynamic International Prognostic Scoring System (DIPSS) – Plus. Two patients underwent haploidentical HSCT, and two patients had human leukocyte antigen (HLA) identical sibling donors. All patients were given reduced intensity conditioning and received peripheral blood stem cells. The conditioning regimen used for haploidentical HSCT included fludarabine, cyclophosphamide, total body irradiation, followed by post transplant cyclophosphamide. The conditioning regimen used for the patients with HLA-identical sibling donors included fludarabine and melphalan. Engraftment was noted to occur at a median of 15 days.

Results

Engraftment analysis at day 100 was noted to be 100% donor chimerism for two patients and mixed chimerism for one patient. One of the patients had secondary graft failure at day +41. Patients received graft versus host disease (GVHD) prophylaxis with a combination of tacrolimus, mycophenolate mofetil \pm prednisone. One patient developed acute GVHD of the skin (stage 3) and gut (stage 1). One patient had acute GVHD of the gut (stage 2) only. One patient developed chronic GVHD of the skin manifested by hypopigmentation and exfoliation of the skin which was confirmed by biopsy. One patient had chronic GVHD of the first patient was noted to have bicytopenia and peripheral blood blasts of 16% at 31 months. Leukemic transformation was considered. The patient expired at 31 months. The second patient stayed in complete remission. She was last seen at 35 months. The third patient developed pancytopenia and a repeat engraftment analysis was 100% recipient at 29 months. Immunosuppressive medications were discontinued and she is now scheduled for a second HSCT. The fourth patient was noted to have hemolytic anemia and

Conclusion

Our case series revealed successful transplant outcomes in three out of four patients, with noted transfusion independence and improved quality of life for these three patients for a period of over 2 years. HSCT must be considered for patients with intermediate-2 and high-risk disease, as well as patients who have transfusion-dependent anemia, peripheral blood blasts, and adverse cytogenetics.

leukopenia on day +41. Immunosuppressive medications were discontinued, and engraftment analysis was 100% recipient. He underwent a second full match HSCT however he expired from septic shock on day +16.

Keywords: Myelofibrosis; Hematopoietic Stem Cell Transplant; Philippines





Hematopoietic stem cell transplant for aplastic anemia: A retrospective analysis from a tertiary care center

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Abstract Content

Introduction: Acquired Severe aplastic anemia is serious medical condition leading to high mortality if not treated immediately. Hematopoietic Stem cell transplant (HSCT) is the only definite curative treatment for these patients especially under 40 yrs of age.

Materials and methods:

Eighty nine patients who underwent stem cell transplant between March 2008 to June 2018 were included in this retrospective study at our centre. Informed consent was taken from all patients and the study was approved by institutional review board. Transplant type: Matched sibling donor (MSD) HSCT: 63; Haploidentical HSCT: 24 and matched un-related donor (MUD) HSCT in 2 patients. Conditioning regimens: For MSD and MUD transplant Fludarabine & Cyclophosphamide with or without ATG and for Haplo HSCT Fludarabine - Cyclophosphamide -TBI with or without ATG. Graft source: Bone marrow in 16 patients & G-CSF Mobilised PBSC in 69 patients. GvHD prophylaxis: for MSD and MUD: Cyclosporine and mini Methotrexate and for all Haplo HSCT PTCy and Tacrolimus and MMF was used. All patients received standard bacterial/ viral/ fungal and VOD prophylaxis and treated in HEPA filtered room.

Results: Out of 89 patients 58 were male and 31 females with median age of 17 yrs (range 2-60 yrs). There were 50 patients below 18 yrs of age. Median CD34 cell dose was 5.96×10^6 cells/kg. Median neutrophil and platelet engraftment was on day +13 and day +18 respectively.

Twenty one patients developed acute GvHD, out of which 17 patients had grade 2-4. Chronic GVHD was seen in fifteen patients including extensive chronic in 5 patients. Graft failure was seen six patients including 2 primary graft rejections. Transplant related mortality was in twenty four patients (27%) including four patient expired before receiving stem cell graft. The cause of death was sepsis in 20/24 patients (83%) and severe GvHD was in 4/24 patients (17%). At median follow up of 780 days (range -3 to 3781) the disease free survival, overall survival and transplant- related mortality after transplant were 66%, 73%, and 27%, respectively. Thirteen patients had CMV reactivation post transplant.

Discussion: Allogenic stem cell transplantation is the treatment of choice for severe aplastic anemia patients less than 40 years age. We compared our results with the western data and found nearly similar overall and disease free survival rates. The OS in our study was 73% and the TRM was 27%. The most common cause of death was infection. Acute and chronic GVHD developed in % each which is similar to that reported in western literature.

Conclusion: Sepsis is predominate cause of mortality in severe aplastic anaemia patients especially in developing world, thus allogenic stem cell transplant should be offered to patients who are eligible for allogenic stem cell transplant as soon as possible. Alternate donor especially haplo identical donor has expanded the pool of donor to facilitate transplant on urgent basis.

Keywords: Severe Aplastic Anemia, HSCT





HEMATOPOIETIC STEM CELL TRANSPLANT FOR SICKLE CELL DISEASE: SINGLE CENTER EXPERIENCE FROM INDIA

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Abstract Content

Introduction: Sickle cell anemia (SCA) remains associated with high risks of morbidity and early death. Even best of supportive care fails to improve quality of life. Hematopoietic stem cell transplant is the only curative treatment for selected group of patients. In the long run it is not just economical but also substantially improves quality of life. We report our experience with HSCT in a group of children affected by SCA.

Material and Methods: Thirty three consecutive patients suffering from SCA who underwent HSCT between March 2014 and June 2018 were included in the study. Transplant type: Eighteen matched sibling donor HSCT, 13 haplo-identical HSCT, one mismatched unrelated donor HSCT and one matched sibling cord blood transplant. Conditioning regimens as follow: For HLA matched and mismatch transplants: By/Cy/ATG (Busulfan 3.2 mg/kg/day x 4 days, Cyclophosphamide 50mg/kg/day x 4 days, hATG 30mg/kg/day x 3 days), in 10 haploidentical HSCT rATG/Thiotepa/ Flu/Cy/TBI (Thiotepa 10mg/kg x 1 day, fludarabine 30mg/m2 x 5 days, cyclophosphamide 14.5 mg/kg/day x 2 days, TBI 2Gy single dose, rATG 1.5 mg/kg/day x 3 days); three patients with haplo HSCT received rATG/Bu/Flu (Thymoglobulin 1.5 mg/kg/day x 3 days, Busulfan 3.2mg/kg/day x 4 days, Fludarabine 35 mg/m2 x 6 days). GvHD prophylaxis for match sibling and mismatch donor was cyclosporine 3mg/kg/day in 2 divided doses starting D-3 and methotrexate 10/m2 on D+1 followed by 7mg/m2 on day 3, 6 and 11 post HSCT; Cyclosporine and methylprednisolone was used for CBT. For Haplo HSCT GVHD prophylaxis was PTCy 50 mg/kg/day on D3 and 4, Tacrolimus & Mycophenolate starting from D5. All patients received standard bacterial/ viral/ fungal and VOD prophylaxis and treated in HEPA filtered room.

Results: The median age of patient's was 8 years (range 10 mo -29 years). All patients who underwent HSCT had history of severe veno occlusive crises (acute chest syndrome, stroke and avascular necrosis). Median CD34 cell dose infused was 6.57x 10⁶ cells/kg. Median neutrophil and platelet engraftment was on day +12 and day +20 respectively. Of the 33 patients, 27 survived without sickle cell disease (with complete donor chimerism), with Karnofsky scores of 100. At median follow up of 711 days (range 33-1538) the SCAfree survival, overall survival and transplant- related mortality after transplant were 82%, 94%, and 6%, respectively. Ten patients developed CMV reactivation post transplant and one patient developed PRES. Six patients developed acute GvHD Grade 2-4. Chronic GVHD was seen in six patients including extensive chronic in 3 patients. Two patients expired and the cause of death was grade IV acute gut GVHD. All patients with full donor chimerism remained free of any SCA-related events after transplantation.

Conclusion: Outcome of HSCT in SCA has improved significantly. With better conditioning regimens, improved supportive care, the outcome of alternative donor transplant (matched unrelated donor, mismatched unrelated donor, haploidentical) and adult SCA has improved and matches matched sibling donor transplant. HSCT should be strongly considered as a curative modality for selected patients suffering from SCA.

Keywords: Sickle cell disease, HSCT, Outcome





Immunosuppressive therapy versus haploidentical transplantation in adults with acquired severe aplastic anaemia

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Abstract Content

Background: Immunosuppressive therapy (IST) has been recommended for acquired severe aplastic anaemia (SAA) patients without appropriate matched related donors, and transplantation from haploidentical donors (HID) for SAA have not become the generally suggested alternative. However, recent outcomes of haploidentical transplantation in SAA have greatly improved. Our study aimed to compare treatment outcomes between HID haematopoietic stem cell transplantation (HSCT) and IST in SAA adults.

Methods: We retrospectively reviewed the medical records of 113 SAA adults who received IST (N = 37) or HID HSCT (N = 76) within six months after diagnosis from 2009 to 2017. All patients were treated at the two of the largest and most experienced centres for aplastic anaemia in China.

Results: The estimated 8-year overall survival (OS) was comparable between the IST and HID HSCT groups (75.6% vs. 83.7% respectively, P = 0.328), but the failure free survival (FFS) was significantly lower in the former than the latter (38.5% vs. 83.7% respectively, P=0.001). Further, significant improvement in FFS with HSCT over IST was also true for patients under 40 years old. At the last follow-up, patients in HSCT group achieved better performance scale scoring than those in IST group (KPS of 100 [20-100] vs. 90 [20-100], P = 0.002). In terms of blood routine, 83.1% (54/65) of patients in the HSCT group showed complete recovery compared to only 38.2% (13/34) in the IST group (P < 0.001).

Conclusions: These data suggest that HID HSCT could be an effective alternative treatment option for SAA adults when matched sibling donors and matched unrelated donors are not available. Further prospective study is required to confirm our encouraging results.

Keywords: Immunosuppressive therapy, haploidentical transplantation, aplastic anaemia, adult





Peripheral Blood Stem Cell Transplantation in Aplastic Anemia Patients: Comparable Results versus Conventional Bone Marrow Transplantation

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Abstract Content

Background: Aplastic anemia is a rare disorder and is usually fatal if left untreated. Definitive therapies for aplastic anemia include hematopoietic stem cell transplantation (HSCT) and immunosuppressive therapy. The aim of this study was to compare the outcomes of allo-PBSCT with allo-BMT in patients with aplastic anemia.

Methods: This study included patients who received HSCT from a fully HLA-matched sibling donor between 1991 and 2013. Choices of stem cell sources included bone marrow (BM) or peripheral blood stem cells (PBSCs). The day of neutrophil and platelet engraftment, acute and chronic GVHD, disease-free survival and survival were compared overall assessed and between the two study groups. Results: In this study, the outcomes of 185 patients receiving allo-HSCT using PBSCT (n=145) and BM (n=45) were assessed and compared over a time period of 22 years. An absolute neutrophil count engraftment occurred in 90% and 93.8% of patients transplanted with bone marrow and peripheral blood stem cells, respectively (p-value=0.406). Platelet engraftment was 85% in the BMT group versus 93.1% in the PBSCT group (p-value=0.118). The 5-year disease-free survival was 52.3% and 73.5% in the BMT and PBSCT groups, respectively (p-value=0.007). The 5-year overall survival was 72.5% and 78.2% in the BMT and PBSCT groups, respectively (p-value=0.362). Twenty-four (60.0%) patients in the BMT group and 77 (53.1%) patients in the PBSCT group developed acute GVHD (p-value=0.438). The cumulative incidence of chronic GVHD was 25.7% (95% CI: 12.6%, 41.0%) and 52.2% (42.8% and 60.8%) in the BMT and PBSCT respectively years transplantation (p-value=0.014). groups, within two after Conclusion: The 5-year disease-free survival was significantly higher in peripheral blood recipients, showing the preference of peripheral blood stem cells over bone marrow to prevent disease relapse. The study demonstrated a decrease in the rate of disease relapse after PBSCT when compared to BMT. Furthermore, if chronic GVHD is adequately controlled, allo-PBSCT should definitely be considered the preferred graft source in these patients.

Keywords: Hematopoietic Stem Cell Transplantation; Aplastic anemia





Long-term outcome of allogeneic hematopoietic stem cell transplantation from HLA-matched sibling donor in young patients with severe acquired aplastic anemia.

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Abstract Content

INTRODUCTION: Severe aplastic anemia (SAA) is a rare multi-lineage bone marrow failure disorder and matched related hematopoietic stem cell transplantation (HSCT) is the treatment of choice especially in young patients (age < 40 years old). We retrospectively analyzed patients who received HLA-matched sibling allogeneic HSCT (MSD allo-HSCT) at our institution.

METHODS:

The clinical data of 15 acquired aplastic anemia (AA) patients received MSD allo-HSCT from 2008 to 2017 were analyzed retrospectively. Six patients were male and nine were female. Median age was 23.3 (4 – 40) years old. Eight patients had transfusion-dependent intermediate aplastic anemia (AA), six had SAA and one had very severe aplastic anemia (VSAA). Six (40%) patients received more than 20 units of transfusions (red blood cells and/or platelets) and two (13.3%) patients failed to respond to the previous immunosuppressive therapy. The median time from diagnosis to HSCT was 3 (range: 1.5 - 17) months. All patients received allogeneic peripheral blood stem cell (PBSC) transplantation (allo-PBSCT). Some various conditioning regimens were used such as cyclophosphamide (CY) + horse anti-thymocyte globulin (h-ATG) (10 patients), CY + h-ATG + Fludarabine (FLU) (3 patients), CY + FLU (1 patient), CY (only one patient). Fifteen patients received prophylaxis for graft-versus-host disease (GVHD) with cyclosporine (CSA) plus short-term methotrexate (MTX).

RESULTS:

The median number of infused CD34(+) cells and MNC were 7.31 (5.76 - 7.90)×10⁶/kg and 6.83 (4.50 - 9.70)×10⁸/kg in allo-PBSCT, respectively. Engraftment was observed in all patients. The median time to neutrophil (ANC) recovery and to platelet (PLT) recovery were 12 (range: 9 - 20) days and 12 (range: 8 - 28) days, respectively. Six (40%) patients developed acute GVHD (aGVHD) and all of them had grade I-II aGVHD. One patient suffered from chronic GVHD (cGVHD) which was well managed with corticoid. CMV reaction occurred in 5 (33.3%) patients and was controlled with Ganciclovir. Of two patients who had secondary graft rejection, one patient successfully received second stem cell transplantation and the other achieved partial response following with h-ATG + Cyclosporin. Median follow-up time was 27 (5.3 - 127) months. Three-year estimated overall survival (OS), disease free survival (DFS), GvHD-free relapse-free survival (GRFS) was 100%, 93% (95% CI: 79% – 100%) and 93% (95% CI: 79% - 100%) respectively. Early complications after transplantation included febrile neutropenia (11 patients), severe pneumonia (2 patients), platelet transfusion refractory (2 patients), multi-drug resistant sepsis (2 patients). Chronic renal failure, hypothyroidism, cataract, femoral head avascular necrosis were the most common late complications. At report time, 93.3% of patients were alive with normal hematologic parameters and most patients really did experience good levels of quality of life (QOL) during 5 years after transplantation.

CONCLUSION:

MSD allo-HSCT is an effective therapy for young patients with acquired AA. The outcome of allogeneic HSCT in patients with acquired AA at our institution was comparable to the results of the other previous studies



-Links an

Keywords: Stem cell transplantation, aplastic anemia





Myeloablative conditioning regimen and alternative donor hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria

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Abstract Content

Introduction: To evaluate the safety and effecacy of myeloablative conditioning regimen and alternative donor hematopoietic stem cell transplantation (HSCT) for the patient with paroxysmal nocturnal hemoglobinuria (PNH) who lack matched sibling donor (MSD). Methods: We retrospectively analyzed 11 patients with PNH who underwent alternative donor HSCT in our hospital between September 2012 to April 2018. Six cases received matched unrelated donor (MUD) HSCT, other five underwent haploidentical donor (HID) HSCT (one of them got the second HID-HSCT after secondary engraftment failure following first MUD-HSCT). All the patients were failed to be treated by cyclosporine, corticosteroids or androgens and dependent on blood transfusion or with intermittent hemolysis before HSCT. Three cases were classic PNH and the other eight were Aplastic Anemia-PNH syndrome. Male to female was five to six. The median age was 24 (range,13 to 41) years old. The median percentage of CD55- and CD59- deficiency on the granulocytes before HSCT were 91.13% (range, 10.64% to 97.46%) and 89.97% (range, 35.38% to 99.41%) respectively by flow cytometry. The median disease course before transplantation was 24 (range, 8 to 120)months. Myeloablative conditioning regimen was consistent with Busulfan (iv; 3.2 mg/kg per day) for 4 days, Cyclophosphamide (1.8g/ m²per day) for 2 days or Fludarabine (30 mg/m²per day) for 5 days, and Rabbit anti-human thymocyte immunoglobulin (Sanofi, France; 2.5 mg/kg per day) for 3 days. The sources of donor's cells were peripheral blood stem cells (PBSC) in MUD-HSCT and bone marrow stem cells combinating PBSC in HID-HSCT. Prophylaxis of GVHD included tacrolimus, mycophenolate mofetil, and short-term methotrexate. Results: All the patients achieved primary engraftment and survived till the last follow-up date, the median follow-up time was 22 (range, 3 to 70) months. The median myeloid and platelet engraftment time were 11 (range, 10 to 15) and 12 (range, 11 to 25) days respectively. All patients showed full donor chimerism (FDC) and PNH clones were not detected at the first evaluation post-HSCT. Five patients developed grade I to III acute GVHD within 100 days after transplantation. Two patients developed chronic GVHD, one was limited in skin and the other had lung involved. Three patients showed a decreased donor chimerism at the median post-transplantation 27(range,25 to 77) days. All of them returned to FDC after donor lymphocyte infusion (DLI). The median transfused mononuclear cell number was 0.2 (×108/kg) at the median 27(range, 26 to 77) days post-HSCT, they returned to FDC at the median 3(range, 2 to 4)weeks after DLI. Nine patients had GVHD free survival, eight of them lived without taking immunosuppressants, the other one was on three months post-transplantation. Two patients still took enough immunosuppressants on account of chronic GVHD. Eight patients experienced cytomegaloviremia at the median 35(range, 21 to 45) days post-HSCT. One patient developed hemorrhagic cystitis on 49 days post-HSCT. No one had Epstein-Barr virus infection or post-transplantation lymphoproliferative disorder. Conclusion: Our study suggested that myeloablative conditioning regimen is suitable for allo-HSCT in the treatment of PNH. Alternative donor HSCT may be an optimum option for patients with PNH who lack MSD.

Keywords: Myeloablative conditioning regimen; Alternative donor hematopoietic stem cell transplantation; paroxysmal nocturnal hemoglobinuria





Salvage Therapy With Dose-Escalating Ruxolitinib As A Bridge To Allogeneic Stem Cell Transplantation For Refractory Hemophagocytic Lymphohistiocytosis

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Abstract Content

Introduction: Hemophagocytic lymphohistiocyosis (HLH), a severe immune dysregulatory disorder, is manifested by clinical signs including the development of fever, splenomegaly, and cytopenias caused by genetic mutations affecting the cytotoxic function of T lymphocytes and natural killer (NK) cells while the curative option is allogeneic stem cell transplantation (allo-SCT). However, only a minority of patients could survive to allo-SCT. Ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, might be a salvage therapy for patients with refractory HLH based on preclinical study. Unfortunately, there are no clear data regarding the optimal timing and dose of ruxolitinib for HLH or its safety as a bridge to allo-SCT. Herein, we present one patient with refractory HLH, who were clinically deteriorating and experienced a dramatic improvement with ruxolitinib mono-therapy, and survived to allo-SCT.

Methods: We give the patients several examinations including inflammatory factor, EBV, NK cells functional analysis, T-cell receptor gene test, Next-generation genomic DNA sequencing, Sanger sequencing of genomic DNA, bone marrow biopsy and so on. For the sake of sustaining to allo-SCT, the patient was treated with a HLH-directed therapy (HLH-04): dexamethasone (10 mg/m2 per day), etoposide (15 mg/m2 twice a week), cyclosporin A and intrathecal methotrexate (15 mg dose). After the failure of first allo-SCT, the dosage of Ruxolitinib raised from 5 mg BID to 25 mg BID until the second allo-SCT.

Result: The 14-year-old girl was initially showed the elevated of peripheral blood and cerebral spinal fluid EBV-IgG (>1:10,420), EBV-EA (1:640) and EBV-DNA load of greater 106 copies/ml and EBV was presented in her NK-cell. According to the sorting-PCR result a NK-cell clone was detected. She suffered recurrent fever, pancytopenia, splenomegaly, continued rise in ferritin (>5000 ng/mL) and chronic hepatitis. Perforin expression of NK cells and CD8+ T cells decreased significantly (17.66% and 7.85%), NK cell cytotoxicity is also impaired (14.7%) and decreased CD107a expression. Next-generation genomic DNA sequencing from the patient and her father detected one heterozygous mutations in exon 7 of RAB27A at nucleotide 560 G>A, resulting in an Argnine to Glutamine change at amino acid 187 (p.Arg187Gln). Additionally, both her mother and brother showed a dysfunction of NK cell. She was diagnosed as a refractory HLH after the hemophagocytosis was detected in her bone marrow. After a short response of HLH-04, the disease deteriorated. As she remained in pancytopenia and STR was only 0.08%, she was suspected of graft failure. And the serum IFN-y and IL-10 elevated synchronously. The patient was processed Ruxolitinib as an alternative "salvage" agent to control the disease. However, the patient's body temperature was uncontrolled discontinuity which could be overcame by dose-escalation of ruxolitinib indicating resistance to ruxolitinib. After 2-month treatment of ruxolitinib, the platelet counts and fibrinogen level steadily increased, ferritin concentration decreased from a peak. Additionally, cytokines such as serum IFN-y and IL-10 levels decreased to normal ranges underwent second allo-SCT and all indicators became normal.

Conclusion: Thus, our study shows the possibility of ruxolitinib acting as a safely second line salvage therapy and also a bridge to allo-SCT to promote engraftment.

Keywords: Refractory Hemophagocytic Lymphohistiocytosis; Ruxolitinib; Allogeneic Stem Cell Transplantation





ESTABLISHMENT OF HAPLOIDENTICAL TRANSPLANT PROGRAM IN PAKISTAN; A REALISTIC SOLUTION TO OVERCOME DONOR SHORTAGE

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Abstract Content

Introduction: Donor shortage is a limiting factor in the availability of stem cell transplant. Despite of donor marrow registries and cord blood banks, 20-25% of the patients still do not find a suitable matched donor. In Pakistan, consanguinity is very common; 68% of all the wedlock occurs within the extended family or tribes. Therefore up to 69% of BMT patients find HLA matched donor. Haploidentical sibling/parental donors program is potentially workable solution in Pakistan to overcome the donor shortage. Aim of this study is to determine the outcome of HISCT in hematological disorders.

Methods:Patients with hematological disorders who underwent hematopoietic stem cell transplantation between October 2013 and May 2018 were included in study. Both bone marrow and peripheral blood stem cells were collected for transplantation (as per institutional policy for disease and donor age). Conditioning regimens used with respect to primary disease. Graft versus host disease (GVHD) prophylaxis regimen comprised of Cyclophosphamide on day +3 & +4 followed by Tacrolimus and Mycophenolate mofetil. Patients were observed for acute GVHD (<100days) and chronic GVHD (>100days) for skin, gut, lungs and liver.

Results:Over the period of 4.5years, 35 Haplo-identical transplants were done, among them more prevalent conditions were beta thalassemia (n=15, 87% survival) aplastic anemia (n=5, 60% survival), severe combined immunodeficiency disorder (n=3, 66.6% survival), acute myeloid leukemia (n=4, 50% survival) as shown in Figure 1. Mean age of patients was 11.7±14years. Across the gender and blood group transplants were done in 12(34%) and 9(26%) patients respectively. Neutrophil and platelet engraftment is shown in Figure 2. Episode of acute Graft versus host disease (III-IV) was observed in 5 (14%) patients. Mucositis (Grade I-III) and Hemorrhagic cystitis was observed in 8(23%) and 4(11.4%) patients respectively. Five (14%) patients had Cytomegalovirus (CMV) reactivation. Primary graft failure occurred in 3(14%) patients, while Secondary graft failure in 4(19%) patients. Overall survival was 54.3% (Figure 3)

Conclusion: Haploidentical BMT is a new ray of hope for patients lacking a full matched donor transplant in Pakistan. There is dire need to develop a donor registry at national level in our country, in order to implement haploidentical transplant strategy at large scale.

Keywords: Haploidentical transplant, hematological disorders, donor shortage,





Outcome of advanced myelofibrosis and myeloproliferative neoplasm treated with allogeneic hematopoietic cell transplantation following reduced-intensity conditioning regimens

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Abstract Content

Background : Allo-HCT is the only curative treatment for advanced MPN including MF, but substantial risk of TRM is a major obstacle.

Methods: We performed a reduced intensity conditioning allo-HCT for advanced MF patients (n=28) with intermediate-2 and high risk accompanying symptomatic splenomegaly, transfusion-dependent anemia, refractory thrombocytopenia, and significant constitutional symptoms. From 2011 to 2017, 30 patients in intermediate-2 (n=9) to high-risk (n=19) group based on DIPPS-plus were transplanted. Patients with MPN-unclassifiable (n=1) and essential thrombocythemia with leukemic transformation (n=1) were also included in this study. JAK2 was observed in 14 (V617F in 13, exon12 in 1), CALR mutation in 4, and all-negativity in 5 patients. We firstly searched matched sibling donor (MSD, n=12) followed by matched unrelated (n=10) or partially mismatched unrelated (n=4) donor and, then haploidentical familial donor (n=4). Graft sources were PBSC and we mainly applied RIC regimens consisting of intravenous fludarabine (30 mg/m² for 5 days) and busulfan (3.2 mg/kg for 2 days) with (n=25) or without (n=3) total body irradiation (TBI) of 400 or 800 cGy. Anti-thymocyte globulin (ATG) was administered at a dose of 2.5 to 10 mg/kg according to the donor type and short course methotrexate and calcineurin inhibitors were used for GVHD prophylaxis. In 2 patients with severe comorbidity, we used nonmyeloablative conditioning regimen consisting of alemtuzumab and TBI 400 cGy without ATG, and sirolimus was used for GVHD prophylaxis.

Results: Except for 1 early death in aplasia, all showed successful engraftment. Including 2 patients treated with nonmyeloablative regimen (recovered after an additional stem cell infusion from the same donor), total 4 patients (16.1%) showed delayed graft failure at a median 6 months post-HCT (range, 3.8-13.8). The rest 1 recovered after cessation of all immunosuppressive drugs, and 1 died after 2^{nd} allo-HCT. Among the 23 patients with at least 1 BM results after 1 month post-HCT, 19 (82.6%) showed significant improvement of BM fibrosis (range, 28-661 days). After median follow-up duration of 28.6 months (range, 6.1-116.0), 2-year OS was 65.3% (80% in triple-negative subgroup), 2-year NRM was 28.7%, and 2-year graft-and-relapse-free survival (GRFS) was 29.7%, which suggested there were fatal high-grade GVHD in this cohort. Acute GVHD was observed in 18 (5 grade II, 7 grade III, 4 grade IV) and a cumul;ative incidence of grade III-IV acute GVHD was 38.3%. Chronic GVHD was 27.1%. Among them, significant hepatic GVHD was observed in 9 patients (5 acute, 4 chronic). Among 9 dead patients, 7 died due to fatal hepatic GVHD and 2 died due to septic pneumonia. Multivariate analysis revealed 2-year OS was significant factor for fatal hepatic GVHD (HR=9.8, 95%CI 1.0-94.7, *p*=0.048) and the significant factor for fatal hepatic GVHD was unrelated or mismatched donor HCT.

Conclusion: RIC allo-HCT can be a valid choice for advanced MPN and MF providing a graft-versus-fibrosis effect, but fatal hepatic-GVHD was frequently observed in unrelated or mismatched donor transplants which should be overcome.

Keywords: Myeloproliferative neoplasm; Myelofibrosis; allogeneic hematopoietic cell transplantation; reduced intensity conditioning





Allogeneic bone marrow transplantation from unrelated donor for a patient with idiopathic CD4+ lymphocytopenia

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Abstract Content

Idiopathic CD4+ lymphocytopenia(ICL) is characterized by persistent low CD4+ T-cell count (<300 cell/µl or <20% of the total lymphocytes in peripheral blood) without evidence of HIV infection or any other cause, and the patient usually experienced severe opportunistic infection or malignancies. Because of its rarity, the clinical course, immunologic characteristics, CD4+ T-cell kinetics, long-term outcome, and prognosis of this syndrome remain poorly defined. There is no standard therapy, while cytokine therapies and allogeneic hematopoietic stem cell transplatation (allo-HSCT) are applied. Here, we present a case of severe ICL, successfully treated by allogeneic bone marrow transplantation (BMT).

A 39-year-old man with severe lymphocytopenia visited our hospital. While he had a past history of systemic lupus erythematosus and lupus nephiritis, the symptoms were ameliorated by low dose steroids. Two years before the visiting, he had experienced repeated opportunistic infections: lung and brain abscess with Rhodococcus equi, and invasive candidiasis. He had normal serum immunoglobulin levels, but had decreased CD4+ T-lymphocyte count in peripheral blood (less than 10 /ul) without evidence of HIV infections. Additionary, CD8+ T-lymphocyte, B-lymphocyte, and NK cell counts were also markedly decreased. While his sister also had a mild lymphocytopenia, exome-sequencing analysis using his and his families' specimens revealed no genetic alternations associated with previously reported congenital immunodeficiency. He was diagnosed as ICL, and received BMT from a HLA-mismatched unrelated donor. The conditioning regimen was based on intravenous fludarabine (30mg/m²) from day -8 to day -4, intravenous melphalan (70mg/m²) from day -3 to day -2, and a total body irradiation (2Gy) on day -1. The number of CD34+ cells in the transplantation was 2.08 x 106/kg. Tacrolimusm, short-term MTX, and rabbit ATG (1.25mg/kg) were used as graft-versus-host disease(GVHD) prophylaxis. The neutrophil and platelet engraftments were achieved on day +21 and day +33, respectively. He did not develop any acute GVHD nor documented- infection during follow-up period after BMT. Six months after BMT, chimerism analysis of T-lymphocyte and myeloid cells about 95% of donor type. However, the number of CD4+ T-lymphocyte in peripheral blood was about 50 cells/µl.

While allo-HSCT is the curative therapeutic option for patients with ICL, appropriate conditioning regimen has not been establishd. Myeloablative conditioning regimen may be accompanied by the increased risk of mortality and morbidities in patients with immunodeficiency disorders such as a common variable immunodeficiency. In this case, non-myeloablative conditioning regimen can induce stable donor chimerism with less toxicity. Allo-HSCT using non-myeloablative conditioning regimen could be a treatment option for patients with ICL.

Keywords: idiopathic CD4+ lymphocytopenia; Allogeneic bone marrow transplantation; non-myeloablative conditioning regimen





Feasible outcomes of hematopoietic stem cell transplantation with total nodal irradiation and ATG conditioning for adult patients with severe aplastic anemia despite severe comorbidity.

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Abstract Content

[Introduction]

Hematopoietic stem cell transplantation from HLA-matched sibling donor (MSD-HSCT) is curative treatment for severe aplastic anemia (SAA). Nevertheless, unmet needs for approach to minimize transplant related morbidity exist for patients with severe comorbidity.

[Methods]

We conducted retrospective study with 13 SAA patients who received MSD-HSCT despite severe comorbidity at the time of transplant. The conditioning regimen (TNI-750/ATG) consisted of a single dose of total nodal irradiation with 750 cGy and antithymocyte globulin (Thymoglobulin®, 1.25 mg/kg/day for 3 days or 2.5mg/kg/day for 2 days). Stem cell source were G-CSF mobilized peripheral blood for all patients.

[Results]

The median age of patients was 52 years (range, 29-64), 7 old patients (≥50 years) were included. Four and Five patients performed HSCT despite concurrent uncontrolled infection and life-threatening hemorrhagic episode. With median HCT-CI score was 2 (range, 0-5) points in all patients, five patients (38.5%) presented high HCT-CI score. Infused median CD34+ cell dose was 4.7x106/kg (2.3-11.9). Neutrophil and platelet engraftments were achieved in all patients, at a median of 11 days (range, 8–13) and 13 days (range, 4–64), respectively. Two patients with subsequent secondary graft failure achieved successful engraftment after a second HSCT. All patients are alive with median follow-up of 41.7 (1.7-62.4) months. There was no patients who developed ≥Grade III acute GVHD whereas ≥moderate acute GVHD occurred in one patient at 5.5 months after HSCT.

[Conclusion]

This study demonstrated that MSD HSCT with TNI-750/ATG could be feasible treatment option for SAA having severe comorbidity.

Keywords: Aplastic Anemia, Hematopoietic stem cell transplantation, Total Nodal Irradiation, ATG





Early outcome of matched unrelated donor haematopoietic stem cell transplants for thalassaemia major performed at a single centre in Sri Lanka

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Abstract Content

Introduction

Haematopoietic stem cell transplantation (HSCT) is the only recognized potential cure for thalassaemia. Only 30-35% of patients have a matched family donor. Matched unrelated donors (MUD) from marrow donor registries are a potential source of stem cells for those without a suitable family donor. Sri Lanka has over 2000 patients with transfusion dependent thalassaemia (TdT), however, lack a marrow donor registry. The first successful MUD HSCT in Sri Lanka for TdT was performed at Asiri Central hospital in July 2017. This abstract describes the early outcome data of MUD HSCT for TdT performed at a single centre in Sri Lanka

Method

Retrospective analysis of 5 consecutive MUD HSCTs performed for TdT at Asiri Central hospital from July 2017 to June 2018. Data was extracted from patients' clinical records.

Results

5 patients (female: male=3:2) with TdT. Age range 1.8 to 15 years. All had 10/10 HLA matched donorrecipient. All had peripheral blood stem cells from donors in the international donor registry, DATRI India. Four had conditioning regimen Thiotepa-Fludarabine-Treosulfan-ATG (T-F-T-ATG). One had Fludarabine-Busulfan-Cyclophosphamide-ATG (F-B-C-ATG). Graft vs host disease (GVHD) prophylaxis for both regimen were cyclosporine and methotrexate (15mg/m² on D+1 and 10mg/m² on D+3, D+6, D+11). One patient developed anaphylaxis to intravenous cyclosporine and changed to tacrolimus. Haematological recovery in all was on D+11 to D+12. All 5 had full donor chimerism on D+15, D+28 & D+56. None had complications at discharge from hospital. Two had mucositis (grades 2 &3) pre-engraftment. One (F-B-C-ATG) reactivated CMV which responded to gancyclovir. Three out of 4 (F-B-C-ATG) developed acute GVHD. Two had grades 1&2 skin and liver which responded to steroids, while one has persistent acute GVHD of the gut & liver. Overall survival and thalassaemia free survival was 100% at a median follow up period of about 6.4 months (56days - 365days).

Conclusions

MUD HSCT performed at a single centre in Sri Lanka for TdT appears to have an early outcome comparable to those reported from international centres of excellence. However, long term follow up data is required to substantiate this.

Keywords: Thalassaemia, MUD, transplant, Sri Lanka





Stem Cell Transplant for Severe Aplastic Anemia in Pakistan; Data from a developing country

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Abstract Content

Introduction:

The haematological entity, Idiopathic Aplastic Anaemia (AA), is characterized by bone marrow hypoplasia causing pancytopenia. The disease afflicts the Asian population two to three folds higher than the other regions and variant environmental exposures are accredited as the cause. In Pakistan, Approximately 400-500 new cases of aplastic anemia are diagnosed every year, only 20-25% of patients receive curative treatment. From the year 2001 onwards, efforts for developing allogenic stem cell transplant were started, but initially due limited health resources in our country, the average number of transplants was less than 50 per annum. Currently with the support of provincial government, around 75-100 patients of aplastic anemia are receiving allogenic stem cell transplant. To compare the differences in survival and the incidence of acute and chronic GVHD in peripheral blood versus bone marrow transplant in patients with AA.

Methods:

Study Design: It is a non-interventional prospective study, conducted at National Institute of Blood Diseases and Bone marrow transplant from 2011 to 2017. All patients diagnosed as Very Severe Aplastic Anaemia with ECOG score of not more than 2 were offered either Peripheral Blood Stem cell or Bone marrow harvest with full matched sibling donor.

Procedures: All healthy donor received injection GCSF 10mg/kg/day for four days followed either by a peripheral blood stem cell collection or a bone marrow harvest, aiming for the minimum HPC dose of $> 4x10^6$ cells/kg of recipient's body weight. The product was then infused to patients and their clinical course was closely followed for engraftment and its complications i.e Primary or secondary graft failure, and Acute and Chronic GVHD.

Results:

Ninety two patients of Very severe aplastic anaemia underwent haematopoietic stem cell transplant. Mean age of patients and donors were 15.3 and 15.9 years respectively. Peripheral blood stem cell transplant was carried out in 55(61%) of the patients and the rest of the patients 37(39%) received bone marrow harvest product. Overall survival at 6years was 53% and 65% for PBSC and Bone marrow harvest transplant respectively. Primary graft failure was documented in 24% of PBSC transplants and 9% of bone marrow harvest transplants. Rate of Secondary graft failure was 13.5% for PBSC and 16% for bone marrow transplant (p value=0.24).

Conclusion:

Overall survival and quality of life of patients suffering from aplastic anemia has drastically improved with the advent of stem cell transplant in Pakistan, transplant program needs further expansion in order to cater the needs of patients coming from different regions of country.

Keywords: Aplastic Anaemia, haematopoietic stem cell transplant



Topic: Clinical cellular therapy Abstract No: 8732

Successful treatment of refractory cytomegalovirus colitis after haploidentical hematopoietic stem cell transplantation using CD45RA+ depleted donor lymphocyte infusion.

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Abstract Content

Introduction: Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for highrisk acute leukemia, whereas there is a risk of severe infections and graft-versus-host disease (GVHD). Recently, HSCT with CD45RA+ naïve T cell-depleted stem cell grafts was reported to reduce the incidence of chronic GVHD, while preserving rapid T cell recovery and transfer of protective virus-specific immunity. Moreover, CD45RA+ depleted donor lymphocyte infusion (DLI) showed a promising result of an effective antiviral boost after haploidentical HSCT. Herein, we report on the successful treatment of refractory cytomegalovirus (CMV) colitis after haploidentical HSCT by CD45RA+ depleted DLI.

Case: A 21-year-old female patient with relapsed acute B lymphoblastic leukemia underwent a haploidentical HSCT using post-transplantation cyclophosphamide from mother. Diarrhea occurred on day 55, and methylprednisolone was administered under the impression of GVHD. Because watery diarrhea did not improved by GVHD treatments, colonoscopic biopsies were performed on day 68, which revealed CMV colitis. Ganciclovir induction and subsequent foscarnet induction treatment could not improve her colitis, and neutropenia occurred by drug-induced bone marrow suppression.

We planned CD45RA+ depleted DLI to treat the refractory CMV colitis and augment immune recovery on day 87. Using a closed bag system, whole blood from donor was separated by density centrifugation to obtain a leukocyte enriched cell fraction for further processing with the CliniMACS system. According to the manufacturer's protocol, CD45RA+ cells were depleted with CliniMACS CD45RA reagent. The log10 CD3+ CD45RA+ cell depletion was -1.57, and 0.5x10^6 CD3+ cclls, 4.5 x10^4 CD3+ CD45RA+ cells, 33.5 x10^4 CD3+ CD45RO+ cells per body weight (kg) of recipient weight were infused. The patient did not experience any acute complications, acute or chronic GVHD. Diffuse wall thickening involving entire colon was gradually improved, and CMV pp65-specific cytotoxic T lymphocyte was observed on ELISPOT assay after 4 weeks from DLI. The patient was discharged on day 138, and is on disease-free status for 11 months from HSCT.

Conclusion: We report a case with refractory CMV colitis after haploidentical HSCT, to whom CD45RA+ depleted DLI was safely administered. This approach can be an effective tool for the improvement of antiviral immunity, while not increasing the risk of GVHD after HSCT.

Keywords: CD45RA+ depletion; haploidentical hematopoietic stem cell transplantation; cytomegalovirus colitis





Clinical Outcomes Following LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassemia in the Northstar HGB-204 Study

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Abstract Content

BACKGROUND

Autologous hematopoietic stem cell (HSC) gene therapy holds promise as a potential treatment option for transfusion-dependent β -thalassemia (TDT). LentiGlobin Drug Product (DP) contains autologous CD34+ cells transduced ex vivo with the BB305 lentiviral vector encoding a β -globin gene with a T87Q mutation. Northstar (HGB-204; NCT01745120) is an international, multi-center, phase 1/2 clinical study evaluating the safety and efficacy of LentiGlobin in patients with TDT.

METHODS

CD34+ HSCs were collected via mobilization/apheresis and transduced with the LentiGlobin BB305 vector. After busulfan myeloablative conditioning, patients were infused with transduced cells and monitored for engraftment, vector copy number (VCN), vector derived hemoglobin (HbA^{T87Q}), red blood cell (RBC) transfusions, adverse events (AEs), vector integration site analysis, and replication competent lentivirus (RCL). Summary statistics were determined as median (min-max).

RESULTS

Eighteen patients with TDT (8 β^0/β^0 and 10 non- β^0/β^0 genotypes) aged 12-35 years received LentiGlobin DP with a median follow-up of 27.4 months as of 21 September 2017. Median DP VCN was 0.7 (0.3-1.5) copies/diploid genome, median cell dose was 8.1×10^6 (5.2-18.1 $\times 10^6$) CD34+ cells/kg, and proportion of transduced CD34+ cells was 17-58%. The toxicity profile observed to date has been typical of single-agent busulfan conditioning. No grade \geq 3 DP-related AEs and no evidence of clonal dominance or vector-mediated RCL were reported. Serious AEs after DP infusion were reported in 6/18 (33%) patients: veno-occlusive liver disease (n=2) and 1 event each of cellulitis, infectious diarrhea, gastroenteritis, Klebsiella infection, hyperglycemia, and cardiac and catheter-related thromboses.

Nine of 10 patients with non- β^0/β^0 genotypes have not received transfusions for a median of 29 (15-35) months and at last study visit, total Hb was 8.4-13.7 g/dL and HbA^{T87Q} was 3.6-9.3 g/dL. One patient with a non- β^0/β^0 genotype who continued transfusions had a 28% reduction in annual transfusion volume (DP VCN: 0.3).

Two patients with β^{0}/β^{0} genotypes have not received a transfusion in >1 year and at last study visit, total Hb levels were 10.2 and 10.3 g/dL and HbA^{T87Q} levels were 9.7 and 7.0 g/dL, respectively. Six patients with β^{0}/β^{0} genotypes continued transfusions with annual transfusion volumes decreased by a median of 60% (11%-76%) at last follow-up.



CONCLUSION

With up to 3 years of follow-up in the Northstar study, patients with TDT have demonstrated ongoing clinical benefit with an acceptable safety profile. Eleven patients (90% [9/10] non- β^0/β^0 ; 25% [2/8] β^0/β^0 genotypes) have discontinued transfusions while 7/18 patients had annual transfusion volume reductions of 11-76%. Results from completed study will be presented.

Keywords: gene therapy, beta-thalassemia, lentiviral vector







The Status of CAR-T Cells in vivo from the Perspective of PD-1 **Expression and Its Clinical Significance**

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Abstract Content

Introduction: PD-1 (programmed death 1) is an important immunosuppressive molecule expressed mainly on the surface of activated mature T lymphocytes. After CAR-T cell infusion. PD-1 expression increases as CAR-T cell proliferates. Tony activation of CAR-T cells leading to early exhaustion. Therefore, the faster the expansion of CAR-T cells, the higher the expression of PD-1. However, in some patients, CAR-T cells expand at a slow rate and are weak in the process of competing with tumor cells. In this case, we hope to prolong the survival time of CAR-T cells in vivo, which bring us to use PD-1 inhibitors to re-activate the immune response effect of CAR-T cells on tumor cells. In this study, we detect the expression of PD-1 in various T cell subsets after CAR-T cell therapy, and in combination with the expansion of CAR-T cells and the clinical manifestations, to investigate the indication role of PD-1 expression in CAR-T cell exhaustion and the clinical significance.

Methods: We collected the peripheral blood of 10 patients after CAR-T cell therapy at different time points. Flow cytometry was used to detect lymphocyte surface molecules, including CD3, CAR, CD4, CD8 and PD-1. T lymphocyte populations were isolated and the ratio of CAR+ and CAR- cells was labeled. The ratio of PD-1+ cells was labeled in CAR+, CAR-, CAR+CD4+, CAR+CD8+, CAR - CD4+ and CAR-CD8+ cells. Statistical analysis was performed using the R-Studio software package, and repeated measures of variance analysis were used between different time points.

Results: 10 patients with good clinical response and complete data were analyzed and summarized. At the initial of CRS (Cytokine release syndrome), the proportion of PD-1+ cells in CAR+, CAR+CD4+, CAR+CD8+ cell subpopulations were (42.4±26.8) %, (44.2±22.7) % and (38.1±25.8) %, respectively. Then, after reaching the peak level of CAR-T cell expansion, the proportion of PD-1+ cells in each cell subpopulation were (64.2±30.5) %, (68.2±26.5) % and (60.8±32.1) %. After that, PD-1 expression began to decline as CAR-T cells started to exhaust. The proportion of PD-1+ cells in CD4+ cells was always slightly higher than that in CD8+ cells. In CAR- cells, we saw the same change patterns as in CAR+ cells.

Conclusion: The above results indicated that PD-1 can not only serve as an indicator of the exhaustion of CAR-T cells, but also affect the immune function of normal T cells in vivo. For patients who are difficult to obtain complete remission, PD-1 inhibitors may be useful in prolonging CAR-T cell existence and re-gain the immune response effect on tumor cells.

Keywords: CAR-T cells, PD-1, exhaustion, flow cytometry



Topic: Clinical cellular therapy Abstract No: 8896

Gene therapy for hemophilia A using lentiviral vector-engineered CD34+ hematopoietic stem cells

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Abstract Content

It now has been well documented that genetic engineering of hematopoietic cells provides a potential cure for disorders ranging from monogenic heritable disorders to cancer. State of the art engineering of transplantable human hematopoietic stem cells (HSCs) employs the use of recombinant lentiviral vectors. In recent studies, these vectors have shown excellent safety profiles when used to transduce HSCs as well as immunocompetent cells. We have developed a lentiviral vector to treat hemophilia A caused by mutations in the F8 gene, leading to deficiency of FVIII protein and severe bleeding.Hemophilia A has been conventionally treated with recombinant or plasma derived FVIII requiring 3-4 intravenous injections every week to treat or prevent bleeds. Apart from compliance related issues, the incidence of neutralizing antibodies in nearly 30% of patients and its high annual cost, have restricted access to this therapy. Very recently, adeno associated virus (AAV) vector-based gene therapy has shown remarkable success in hemophilia. Unfortunately, over 50% of patients are ineligible for such therapy due to pre-existing neutralizing antibodies to the AAV vector. Lentivirus vector-based gene therapy has been shown to be effective as a one-time treatment in immune deficiency and hemoglobin disorders with long term stable protein expression.Our product candidate, designated CD68-ET3-LV-CD34, consists of autologous CD34+ cells transduced with amonocyte lineage-restricted transgene and self-inactivating lentiviral vector (LV), termed CD68-ET3-LV, encoding a bioengineered coagulation FVIII transgene. Proof of concept studies established efficient transduction of murine bone marrow with CD68-ET3-LV followed by successful transplantation into hemophilia A mice and resulted in high level, life-long production of FVIII with hemostatic correction. There were no signs of vector-related toxicity in these mice. We also tested FVIII expression in transduced human CD34+ cells. CD68-ET3-LV gene transfer into hCD34+ cells was used to obtain in vitro and in vivo pre-clinical pharmacology, pharmacokinetic and toxicology assessment of CD68-ET3-LV-CD34. We first showed that the clinical vector could be produced at levels necessary to support a clinical trial. We then demonstrated that CD68-ET3-LV could reproducibly and efficiently transfer the transgene into hCD34+ cells with vector copy number of about 1 per diploid genome equivalent. These transduction levels were achieved without affecting the transplantation potential of these hCD34 cells. Monocyte differentiation ex vivo of these hCD34⁺ cells showed increased FVIII expression, confirming the lineage restricted activity of the CD68 promoter. To assess in vivo pharmacology, normal human CD68-ET3-LV-CD34+ cell product was administered to immunodeficient mice. Sustained plasma FVIII levels were observed in CD68-ET3-LV-CD34⁺ administered mice. Similar to transplanted hemophilia A mice, no signs of product related toxicities were observed compared to mice receiving non-transduced hCD34⁺ cells. Collectively, using two mouse models, one being hemophilia A mice and the second being engraftment of human cells into immune compromised mice, these findings support the safety and efficacy of CD68-ET3-LV-CD34+. These data have encouraged us to propose a phase 1 clinical trial.

Keywords: gene therapy hemophilia stem cell lentivirus vector





Myeloid conditioning with c-kit-targeted CAR-T cells enables donor stem cell engraftment without high-dose chemotherapy or radiation

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Abstract Content

Background: There is considerable interest in finding less toxic and more focused approaches to achieve the conditioning before bone marrow (BM) transplantation. We explored a novel approach in which chimeric antigen receptor (CAR)-T cells targeting c-kit (c-kit CAR-T cells) were used for conditioning to achieve significant engraftment of hematopoietic stem cells (HSCs).

Methods: T cells were derived from C57BL/6 Thy1.1/CD45.2 mouse spleen and were co-transduced with c-kit CAR \pm CXCR4. The recipient mice (Thy1.2/CD45.2) were pretreated with low-dose cyclophosphamide (CY, 125 mg/kg), followed by the injection of 5x10⁶ CAR-T cells. These CAR-T cells were subsequently removed using anti-Thy1.1 antibody prior to HSC transplantation from congenic Thy1.2/CD45.1 mice (3x10⁶ cells/mouse).

Results: CAR-T cells efficiently depleted the BM c-kit* population (from 10.5% to 1.6%) in vitro and completely suppressed colony formation. In initial in vivo studies with no pre-treatment of mice, we observed poor expansion of CAR-T cells along with no trafficking to BM (<1% of cells). Pre-treatment with low-dose CY induced massive expansion of CAR-T cells in vivo, but most of the cells were located outside the BM and were mainly trapped in the spleen. In contrast, overexpression of CXCR4 on the CAR-T cell surface along with CY pre-treatment resulted in the sufficient CAR-T cell expansion and migration into the BM (11.9%). Furthermore, the BM c-kit+ population was significantly reduced (9.0% to 0.1%). Severe pancytopenia was confirmed in peripheral blood (hemoglobin level reduced from 13.0 to 2.2 g/dL) along with BM aplasia (Figure A). The subsequent single injection of anti-Thy1.1 antibody completely depleted the CAR-T cells. When donor BM cells were transplanted into mice conditioned in this manner (CY+CAR-T+Thy1.1 antibody), these mice completely recovered the hematopoiesis with significant engraftment of donor BM in all lineages in peripheral blood and long-term HSCs in BM (30 – 40% donor chimerism) (Figure B). Using these mice as donors, serial transplantation into sub-lethally radiated mice resulted in almost the same proportion of HSC repopulation (25 - 30% original donor chimerism). Finally, when mice with chronic granulomatous disease (CGD) were treated with this protocol (CY+CAR-T+Thy1.1 antibody followed by BMT), they displayed recovery of reactive oxygen species production by engrafted normal granulocytes, and reduced susceptibility to Aspergillus infection (Figure C).

Conclusions: Our findings provide proof-of-concept that c-kit CAR-T cells can be used to achieve sufficient conditioning without the use of high-dose chemotherapy or radiation. A key element was the co-transduction of CXCR4 that greatly increased trafficking to the BM, which might be generalizable to enhance targeting to designated organs or solid tumors. Our study adds to the list of tools for safer BM transplantation in non-malignant hematological disease or congenital immune deficiency.

Keywords: CAR-T; conditioning regimen; c-kit



Topic: Clinical cellular therapy Abstract No: 8924

Gene therapy for major haemoglobin disorders through lentiviral vector based gene transfer

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Abstract Content

Allogeneic hematopoietic stem cell transplantation (alloHSCT) has been available for >35 years for β thalassemia major and sickle cell disease. However, <10,000 alloHSCTs have been performed during this period due to various reasons. (Haematologica, 102:2-11, 2017). Several groups have reported successful lentiviral vector based gene replacement in autologous HSCs for these disorders in recent years. We have evaluated three 3rd generation self-inactivating lentiviral vectors (CMCEUv1, CMCEUv3 and CMCEUv4) with a transgene sequence for corrective gene transfer of the β -globin coding sequence. For erythroid-specific expression, a 3.1 kb fragment of locus control region of beta globin cluster containing the DNase hypersensitive sites, HS4, HS3, and HS2, were included. While CMCEUv1 has a 180bp β -promoter, CMCEUv3 has the same but with a co-transcriptional cleavage (CoTC) sequence and CMCEUv4 has a 266bp β-promoter with the same CoTC sequence. The T87Q mutation was also introduced in the coding sequence to provide a marker for the transgene protein due to differential HPLC mobility and introduce antisickling property. These vectors were systematically evaluated in two preclinical models: an ex-vivo human erythropoiesis model and the Townes mouse model of sickle cell disease (h α /h α : β^{S}/β^{S}). The former is a two-phase liquid culture system involving expansion and differentiation of HSCs. Briefly, in phase 1, CD34+ cells are cultured in the presence of SCF, Flt3, IL3, IL6 followed by a phase 2 culture with SCF, Epo, and IL3. The erythroid differentiation is then assessed by measuring surface expression of Glycophorin A and transferrin. cDNA from these cells is amplified for the β-globin exon2 using FAM labelled primers and subjected to Dralll restriction digestion. With this, we could demonstrate that about 16% of the β – globin transcripts derived from the transduced HSCs were from the transgene. (Figure 1) The transduced HSCs had 1-3 vector copy numbers (VCNs). In the in vivo sickle cell disease mouse model, transduced Sca1+ cells harvested from SCD mice were transplanted into lethally irradiated congenic C57BL/6 mice. Haemoglobin expression was measured along with complete blood counts and oxygen saturation. A gradual increase in the transgene haemoglobin was observed up to 17 weeks. (Figure 2) CMCEUv1 and CMCEUv4 showed better transgene expression than CMCEUv3. We also demonstrated an improvement in the pO2 levels from 32mM of Hg to 24 mm Hg in transplanted mice as well as a reduction in sickling index in the transplanted mice, and near normalization of the white blood counts. These data show that these two vectors are effective in transferring the β -globin transgene and expressing significant quantities of haemoglobin. The best among these would need to be tested in human HSCs transplanted in a suitable pre-clinical model. If successful, these studies will pave the way towards a clinical trial for the major Hb disorders in the Asia Pacific regions, where there is a very high prevalence of these disorders.

Keywords: Lentivirus vector hemoglobin disorders gene therapy



Topic: Clinical cellular therapy Abstract No: 8957

Safety and efficacy of autologous CD19/CD22 dual targeted CAR-T therapy for adult patients with relapsed/refractory B-cell malignancies

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Abstract Content

Introduction Patients with relapsed/refractory (R/R) B-cell malignancies experience poor outcomes under conventional available therapies. CAR-T cell therapy has emerged as a novel treatment option for R/R B-cell malignancies with complete remission (CR) rate of 50% and 90% in R/R lymphoma and acute lymphoblastic leukemia (ALL) patients, respectively. Further efforts will be directed towards improving efficacy of CAR-T cell therapy for R/R lymphoma. Herein we have developed a novel CAR that simultaneously targets both CD19 and CD22, which could prove more effective for patients with R/R B-cell malignancies.

Methods We designed a CD19/CD22 dual targeting CAR-T cells. The structure of our CAR has antigen recognition domain of both CD19 and CD22, with 4-1BB costimulatory and CD3z signal domains. Patients received 2-10x106 CAR-T cells/kg after FC (Flu 30mg/m2 day 1-3, CTX 500mg/m2 d2-3) pretreatment chemotherapy. The primary objective of this trial is to evaluate safety. Additional objectives include assessment of T cell engraftment and tumor response.

Results As of August 10, 2018, 15 heavily pretreated adult patients were included (12 with B-cell lymphoma and 3 with ALL). The average CAR-T cell infusion dosages were 5.9×10^6 /kg (ranged from $1.1 \cdot 10 \times 10^6$ /kg) (P>0.05). Average peak expansion of CAR-T cells post-infusion were 65.6% (6.9%-86.8% in CD3 positive T cells) at 8.9 ± 2.65 days after CAR-T cell infusion. Among patients with R/R ALL and R/R lymphoma, 3/3 (100%) and 7/11 (63.6%) patients achieved CR. For lymphoma patients, 3/11 (27.3%) patients achieved PR. 3/3 (100%) and 8/12 (66.7%) experienced cytokine release syndrome (CRS) in R/R ALL and R/R lymphoma patients, respectively. Grade 3-4 CRS developed in 1/3 (33.3%) and 1/12 (8.3%) of patients in ALL and lymphoma patients. Neurotoxicity was observed in 1 patient with lymphoma. No patient died of CAR-T associated complications.

Conclusion CD19/CD22 dual targeting CAR-T cells have prominent anti-tumor activity against relapsed/refractory B-cell malignancies. More patient enrollment will be required to confirm our results.

Keywords: Chimeric antigen receptor T cells, Cytokine release syndrome, lymphoma, acute lymphoblastic leukemia



Nursing care of 1 cases of capillary leak syndrome complicated with large herpes zoster after allogeneic hematopoietic stem cell transplantation

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Abstract Content

Objective: To summarize the nursing experience of 1 cases of capillary leak syndrome complicated with large herpes zoster after allogeneic hematopoietic stem cell transplantation. **Methods**: Using the improved helium neon laser to irradiate the times of rash and the distance of the radiation, closely monitoring the patient's condition, strictly controlling the infusion speed, accurately recording the entry and exit, strengthening the observation of the edema, the herpes neuropathic pain and the protection of the complications such as the pressure injury. **Results**: After 3 days of treatment, the scab began to scab and the eschar was removed after 5 days. After 10 days, the scab skin was all shedding and healing. The herpes pain was reduced to 3 points on the fifth day NRS 6 after the laser irradiation, and the pain was reduced to 1 at tenth days. There was no stressful injury in the whole body and no serious complications were discharged smoothly.**Conclusion**:Capillary leakage syndrome(CLS) is one of the rare early complications after allogeneic hematopoietic stem cell transplantation(allo-HSCT),Its clinical manifestations are complex and the skin of the whole body is fragile. By improving the frequency and distance of He-Ne laser to irradiate herpes, it can effectively relieve herpes neuropathic pain, accelerate the healing of herpes and reduce CLS skin. Complications, alleviated the sufferings of the patient

Keywords: Allogeneic transplantation; Capillary leakage syndrome; Zoster; Nursing





One Stop Service for Patients Receiving Autologous Haemopoietic Stem Cell Transplant

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Abstract Content

Introduction

Autologous Haemopoietic Stem Cell Transplant (AHSCT) is a common treatment option for patients with lumphoma or myeloma nowadays. Around 50% lymphoma patients can be cure and myeloma patients can prolong the life around two years after AHSCT.

The AHSCT service has been established in our hospital since August 2013 and around 12 cases to have the treatment every year. Aim for well preparation for the patients to receiving treatment and minimize the complications, the service model of "Case Manager" was established to provide holistic care to the patients who plan to proceed AHSCT.

Obective

Provide one stop service to the patient for better patient benefit and outcome.

Methodology

Case Manager Selection and Training

Two Advanced Practice Nurses (APNs) selected to be the case manager who completed the Post-Registration Certificate Course of Haematology & Bone Marrow Transplantation (BMT) Nursing and Apheresis training. Aims to well prepare the APNs to take up the role of case manager, they were seconded to Apheresis unit and Bone Marrow Transplant unit for knowledge and clinical skills enhancement in Queen Mary Hospital which the leading hospital of HSCT in Hong Kong. In addition, they joined four weeks overseas clinical attachment in Haematology & BMT unit in a hosptal of Australia to learn from their experience and enrich their exposure.

Collaboration with Multidisciplinary Team

The case managers are act as service coordinator to collabloration with multidisciplinary team to set up the guidelines and make the service arrangement, including infection control team, Haematology Laboratory, BMT Laboratory, Physiotherapist and Dietitian.

Furthermore, the case manager works with the Haematologist closely to facilitate the service smoothly and maxmize the patient's benefit.

Case Manager Model

When the new case diagnosed lymphoma or myeloma, the case manager will interview the patient and relatives to explain the diagnosis, treatment plan, complications and prognosis, as well as related health education. The case manager will follow the patient's treatment progress and arrangement of the AHSCT, as well as tranplantation schedule.

The case manager also set up the nurse clinic. It is aim to provide health assessment, workup and health education to patients and relatives before transplantation, as well as post-transplantation follow up and monitoring.

Result and Outcome



The AHSCT established in United Christian Hospital of Kowloon East Cluster (KEC) in Hong Kong since August 2013. Total 53 patients received the treatment till March 2018. Total 37 of them were suffering from Myeloma and 16 of them diagnosed lymphoma. All of them were well recovery after AHSCT without severe complications.

The patient satisfaction surveys are highly appreciated of the case manager service model in KEC and facilitate the patient to go through patient's journey smoothly during disease management.

Keywords: lymphoma; myeloma; autologus haemopoetic stem cell transplantation





Physical and strength exercise for fatigue management in hematopoietic stem cell transplantation recipients: A systematic review

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Abstract Content

Background: Patients with hematopoietic stem cell transplantation (HSCT) experienced fatigue before, during, and after transplantation, but they have different levels of fatigue depending on the type of disease, treatment, and measurement tools. Most cancer patients said that fatigue will reduce their physical activity and energy, reduce their interest in things, decrease executive power, increase psychological pressure, and sleep disturbances, which will affect quality of life. It can be seen that the effect of fatigue on the patient is enormous.

Objective: The main purpose of this article is to review the literature of the effects of aerobic and strength exercise interventions on the fatigue patients, and to provide clinical staff with reference to the treatment of exhaustion problems in patients undergoing hematopoietic stem cell transplantation and to carry out relevant research in the future.

Methods:We search database contains the EBSCO database, Pubmed, and EMBase. The inclusion and exclusion criteria were used to screen the literature for analysis and review.

Result: Four exercise interventions in five studies were effective in reducing fatigue. During the process, individual exercise plans will be designed based on the patient's condition to promote patient compliance and ensure patient safety. Examination of research design and intervention measures revealed that there are still gap for improvement in the number of samples, control of patient attrition, random and double-blind control, dose and integrity of intervention research, implementer factors, and look forward to the future under rigorous research and design.

Conclusions and practical application: Systematic literature verified that aerobic and strength exercise interventions have a positive effect on improving fatigue. It is recommended that aerobic exercise and strength training be added to the hematopoietic stem cell transplantation unit. The way of exercise which tailor-made to improve the exhaustion of the patient and promote the recovery of the patient's physical function.

Keywords: Hematopoietic stem cell transplantation, exercise, fatigue



Survival of patients with hematological malignancies receiving hematopoietic stem cell transplantation: Single center experience based on retrospective analysis from case management

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Abstract Content

Background / Purpose

We want to explore will different hematopoietic stem cell transplantation (HSCT) type influence the survival of patients with hematological malignancies post HSCT. What's the clinical survival status of patients with hematological malignancies receiving HSCT, based on cancer case management, in one medical center in Taiwan? We compared the death incidence density (death risk) among three types of HSCT which donors from Auto (ASCT), Sibling Donor SCT (SD-SCT), and Unrelated Donor (UR-SCT) for patients with hematological malignancies and hypothesized those with ASCT have the best survival.

Methods

This retrospective cohort study enrolled 315 patients with hematological malignancies receiving HSCT, including lymphoma, acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL), were managed by the cancer case manager, in a medical center in Taiwan, from 2010 to 2017. Data were analysed using SPSS version 20.0, and the hypothesis was tested by Cox regression model.

Results

The mean age was 45.9 years, 57.1% were male, 52.1% were lymphoma; AML with 27.6%, 42.2% had ASCT, 34.6% had UD-SCT, 136 patients died post HSCT. Among the 136 expired patients had mean age of 49.0 years, 55.9% were male, 57.4% were lymphoma (AML was next, 29.4%), UR-SCT were 44.1% (SD-SCT was next, 28.7%). The mean survival years of 315 patients were 2.56 years. ASCT had the best survival (3.32 years), followed by SD-SCT (2.07 years), and the last one is UR-SCT (1.95 years). It was found that the death incidence density (death risk) of UR-SCT is 4.25 times higher than ASCT (95% CI of HR: 2.58-6.99), and 4.50 times higher than SD-SCT (95% CI of HR: 2.89-7.00) after controlling for the confounders of age, sex and diagnosis of patients with hematological malignancies.

Conclusions

According to the hematological malignancies case manager's experience in Taiwan, from 2010 to 2017, can confirm the death incidence density (death risk) of UR-SCT is the highest indeed and HC patients receiving ASCT and SD-SCT survived one year more than those receiving UR-SCT. The study from one medical center show the clinical survival status of patients with hematological malignancies receiving HSCT.

Keywords: hematological cancer, hematopoietic stem cell transplantation, cancer case management, survival analysis



Fall risk assessment of adult inpatients with hematologic malignancies at Blood Transfusion Hematology Hospital – Hochiminh City – Vietnam in 2018.

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Abstract Content

Introduction: Falls and their related injuries have a significant impact on the physical, mental and social health of patients. In Vietnam, according to Patient Safety Committee, falls prevalence rate accounted for 4.6% per total of medical incidents. Assessing risk of falling in adult patients with hematologic malignancies is the most important when they are admitted to the hospital for blood transfusion, chemotherapy, stem cells transplantation... Falls is one of the causes of increasing the burden diseases, lengthening a patient's stay, reducing quality of life and enhancing healthcare costs. The Morse Fall Scale is used in several care settings for fall risk assessment and supports the implementation of preventing nursing intervention. Our works aims to assess risk of all adult inpatients at Blood Transfusion Hematology Hospital in 2018.

Method: Cross – sectional description study is developed at all clinical departments. The Morse Fall Scale is used as the main instrument. Data collection takes place from June to September, 2018.

Predict result: We are on data collection period so that results of the study are not available. Momentary, we display the predict outcomes. The results will be implemented as soon as the fulltext is submitted.

- Predict outcome 1: Estimating the prevalence of risk of the hospitalized adult patients.
- Predict outcome 2: Analyzing the Morse Fall Scale scores of hospitalized adult patients in association with their characteristics, diagnoses and stages of treatment.



Symptom Distress, Sense of Coherence and Quality of Life among Adult Survivors Received Peripheral Blood Stem Cell Transplatation-A pilot study

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Abstract Content

Peripheral blood stem cell transplantation can prolong survival rate in patients with specific cancers. It may notion the importance of quality of life during following survival years in the same time. Sense of coherence has been found significantly correlated with quality of life. Individual with a strong sense of coherence tend to perceive their situation as understandable, manageable and meaningful. This is the first study to evaluate the relationships among sense of coherence, symptom distress and quality of life of adult survivors received peripheral blood stem cell transplantation (PBSCT) in Taiwan. The purpose of this study were 1) to understand the frequency or distress level of symptom, sense of coherence and quality of life, and 2)to determine the relationship among symptom distress, sense of coherence and quality of life. A descriptive and cross-sectional study design was used. Purposive sample 39 patients received peripheral blood stem cell transplantation within 5 years were recruited by filling out three self-reported questionnaires (i.e., SCT, SOC, FACT). Using the SPSS 14.0, data was analyzed by descriptive statistics, t-test, ANOVA, Pearson's correlation coefficient. Results indicated that: 1)the most common symptoms was fatigue, follow by skin change, nausea, activity decrease and cough; 2)the most distressed symptom was fatigue, follow by vomiting, sleep disturbance, pain and cough; 3) the mean score of SOC for the participants was less than the healthy population; 4) the participants with old age, male and high school education had higher SOC scores. 5) none significant correlation between sense of coherence and symptom distress, nor between sense of coherence and quality of life; 6) a significant correlation between symptom distress and quality of life. The findings from this study would contribute to the literature for the sense of coherence, symptom distress and quality of life among specific cancer patients received PBSCT in Taiwan.

Keywords: symptom Distress, sense of coherence, quality of life, peripheral blood stem cell transplatation





HSCT Long Term Follow Up Clinic – The Singapore General Hospital Experience

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Abstract Content

The adult Haematopoietic Stem Cell Transplant Programme (HSCTP) at Singapore General Hospital (SGH) was established in 1985. SGH offers transplant types ranging from autologous, allogeneic, and mismatched cords. To date, more than 1500 transplants were performed. The combined 1 year and 5 years overall HSCT survival rates in SGH is 64% and 50% respectively.

In December 2017, the SGH HSCTP set up a dedicated Long Term Follow Up (LTFU) clinic to better monitor HSCT survivors for late complications of transplant. This LTFU clinic is co-run by a haematologist, Advanced Practice Nurse (APN), and a haematology pharmacist. Patients who were more than 1 year post allogeneic transplant with no active acute post transplant complications were referred to the LTFU clinic. At the clinic, detailed medical history and head to toe physical examination were performed. LTFU specific investigations were performed and results reviewed. Patients all received lifestyle and dietary advise and medication reconciliation, including the review of their prophylactic vaccination status. Referrals to relevant medical specialists were made for routine screening and continued medical surveillance.

Eighteen patients were reviewed in the LTFU clinic from January to end June 2018. The number of months post transplant for clinic attendees ranged from 12 to 286 months. Ten patients were transplanted for the indication of acute leukaemia, and 7 patients received myeloablative conditioning regimes. Ten patients had graft versus host disease (GvHD), of which 7 patients had chronic GvHD. Six patients were found to have undiagnosed hypertriglyceridemia (median 19 months post transplant; range 12 to 59 months post transplant). One patient was diagnosed with osteoporosis (66 months post transplant); and another patient diagnosed with iron deficiency anemia (286 months post transplant).

The LTFU clinic functioned to screen for late transplant related complications. In this small series, previously undiagnosed medical conditions were picked up in half of the patients. Catch up prophylactic vaccinations were administered for all patients according to departmental HSCTP guidelines. Moving forward, post autologous HSCT survivors will be referred to the LTFU clinic.

Keywords: allogeneic transplant; long term follow up; late effects of transplant;





Nutrition and Rehabilitation of Hematopoietic Stem Cell Transplantation Patients

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Abstract Content

[Background]

Decrease in oral dietary intake due to complications after hematopoietic stem cell transplantation (HSCT) is a major problem, resulting in a decline in activities of daily living due to malnutrition and malaise. It may hinder satisfactory recovery despite appropriate treatment and may sometimes cause serious problems such as prolongation of hospital stay and delay of rehabilitation into society. Therefore, at our hospital, we have been working on improving the quality of life (QOL) of patients who have undergone HSCT, in cooperation with the nutrition department and the rehabilitation department. Herein, we describe our efforts and the activities conducted in our hospital.

[Activities]

In the nutrition department, an expert round by the Nutrition Electrolyte and Endocrine Support Team is held once a week for HSCT patients, after initiation of the conditioning regimen. The Nutrition Electrolyte and Endocrine Support Team evaluates the patients' nutritional status, discusses the contents of diet and fluid therapy, and considers the requirement for enteral nutrition. In addition, the body composition of the HSCT patients is analyzed using the InBody S10 (InBody Japan Inc., Tokyo, Japan), and we provided nutritional guidance during the pre-transplant period, engraftment, and discharge, and then, annually until 5 years after HSCT.

In the rehabilitation department as well as the nutritional department mentioned above, physical fitness measurement and other tests (e.g., grip strength, isometric knee extensor muscle strength, one-leg standing time with eyes open, and 6-minute walk test) are routinely performed at regular intervals. We examine the patients and provide them with exercise guidance according to their results. Depending on the extent of bed rest prescribed to the patient, rehabilitation is performed daily in the patient's room or in the rehabilitation room, during hospitalization. Such information about the HSCT patients is shared with the medical staff at the weekly team conference. This helps the medical staff to understand their role in helping HSCT patients, which include giving them professional intervention as experts in the field. Therefore, these activities help us achieve our final goal i.e., patients' relief and satisfaction, and improvement of the patients' QOL.

[Conclusion]

Multidisciplinary evaluation with objective data and cooperation is very important for HSCT patients. Thus, it is expected that nurses, doctors, registered dietitians, rehabilitation therapists and other medical staffs keep caring for patients and their family in close contact with one another as the HSCT team.



Functional Assessment of Cancer Treatment-the Simplified Chinese Version Translation of the Bone Marrow Transplantation Scale and the Scale's Verification of Reliability and Validity

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Abstract Content

[Abstract **]** Objective: To translate FACT-BMT Version 4 to Simplified Chinese version, and test the reliability and validity in Chinese post-BMT patients. **Method**: To translate FACT-BMT Version 4 to Simplified Chinese version following Brislin's method and accomplish culture adaption in 137 post-BMT patients in Peking University People Hospital, and test the internal coherence and content validity. **Result: The Cronbach's coefficient is** 0.71~0.90, 0.83 in total. The S-CVI is 86.9%. 22 items' I-CVI is above 0.80. **Conclusion**: Generally, domestic BMT patients can understand FACT-BMT version 4 SCHI. This scale has high internal consistency and content validity, and is capable to measure the physical health, psychological emotion and social role of BMT patients in China.

Keywords: Scale translation; Reliability and validity testing; Bone marrow transplant; QOL



Assessment of the quality of life and its related predictors in acute leukemia patients early after hematopoietic stem cell transplantation

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Abstract Content

Objectives: In the past several decades, survival and complication problems in bone marrow transplantation have been significantly improved, leaving life quality problems to be a major concern for the patients. Studying the trajectory of QoL (quality of life) recovery after hematopoietic stem cell transplantation (HSCT) helps us to find out solutions to improve the life quality. However, the poor QoL score early after transplantation has not been well studied, especially in acute leukemia patients. In this research, we aim to clarify the short-term QoL of acute leukemia (AL) patients early after HSCT and related predictors to its recovery.

Materials and methods: Patients who had received bone marrow transplantation in 2013-2015 at the stem cell transplantation department, hematological disease hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS&PUMC), aged over 16 years, alive and without a life-threatening relapse or complication, with a minimum follow-up of one month after transplantation were enrolled. We grouped those patients according to the follow-up duration after transplantation. With the use of short-form 36 questionnaire (SF36), physical/functional and emotional/mental recovery were evaluated. Baseline equivalence testing was performed on QoL outcomes using t-tests for the continuous category. Univariate analysis was performed by two-way ANOVA analysis to evaluate the effect of those variables and the effect of follow-up group interaction. A linear regression model is used for the multivariate analysis.

Results: In our research, 326 AL patients responded to our QoL survey, making a response rate of 86.68%. 190 patients were within six months after transplantation, 63 patients were 6-12 months and 73 patients were more than one year after transplantation. The mean PCS (Physical Component Summary) score varies significantly differently at different stages post-transplantation (p=0.040), with a significantly lower score in patients within 6 months and a fantastic increase in patients over 12 months post-BMT. Inconsistency with PCS, there is a period of slightly decrease of MCS (Mental Component Summary) scores in groups 6-12 (p=0.008). In particular, clinically meaningful differences were observed for RP(Role-Physical) (p=0.002), SF (Social Functioning) (p=0.001) and RE (Role-Emotional) (p=0.039) scales. A multiple regression analysis was used to examine the association between the demographic variables and QoL). For clinical characteristics, despite follow-up duration, with a history of aGVHD and cGVHD impaired both physical and mental recoveries. There are several sociodemographic variables were related with QoL scales. It is interesting to note that patients who were taken care by their spouses showed worse recovery in QoL than those who were taken care by parents/kids (p=0.023, p=0.044), with a pronounced difference in the early period after transplantation. Additionally, bad financial status and no employment after transplantation were shown to impair clinical QoL recovery significantly.

Discussion and conclusions: In conclusion, those independent factors affecting patients' QoL recovery give us new insight about which patients we should provide more care and psychological counseling to, for their preparation of future life.

Keywords: Short-term post-transplantation; Quality of life; Informal caregiver; GVHD; acute leukemia.



Medical collaboration for long-term follow up of post-transplant patients at the Non-transplant center

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Abstract Content

[Introduction] The long-term physiologic effects after allo-HCT include nonmalignant organ or tissue dysfunction; changes in quality of life (QOL). In Japan, several transplant centers have set up a long-term follow up (LTFU) outpatient department, thereby contributing to improved patient QOL. In these facilities, medical remuneration points can be claimed towards counseling by a multi-professional team to patients who have received allo-HCT. However, transplant center are unevenly distributed in Japan, resulting in taking long hours to visit the outpatient department. Certified nurse for LTFU and medical doctor for allo-HCT belong to our institution (not transplantation center), therefore, we made attempt to provide LTFU in post-transplant patients, especially in patients who live near from our hospital. [Methods] This study enrolled four patients who were being followed up after being transferred to our institution following allo-HCT. Certified nursing administrators with experience in allogeneic transplantation was considered as meeting the requirements for making a claim. The flow of outpatient LTFU in our institution was as follows: 1) blood collection, 2) a nurse checked for complications and provided lifestyle guidance in a hospital ward consultation room. The nurse filled out the medical chart and informed an outpatient physician about the patient's condition in advance if necessary. 3) A pharmacist provided guidance on medication in the outpatient department. 4) The attending physician conducted the examination. 5) The nurse confirmed the next outpatient appointment. [Results] Patient 1: Acute lymphocytic leukemia (ALL), male in his 30s, HLAidentical sibling transplantation, moderate chronic graft-versus-host disease (cGVHD). We mainly assisted him with returning to work. Patient 2: Myelodysplastic syndrome (MDS), female in her 60s, HLA-matched unrelated donor bone marrow transplantation, severe bronchiolitis obliterans (BO) which requires home oxygen therapy (HOT). Support was focused on lifestyle guidance, infectious control and psychological support with the help of the family, on the basis of the symptoms. Patient 3: MDS, male in his 60s, HLAidentical sibling transplantation, moderate cGVHD, focused on improving self-care behavior against GVHD. Patient 4: AML, female in 30s, HLA-identical sibling transplantation, non-cGVHD, hormone replacement therapy due to early menopause. Focused on psychological support. [Conclusion] Our attempt enables four patients to receive LTFU in our institution near form their homes, resulting in shortening the time to visit outpatient department. We showed that medical collaboration for LTFU is possible at hospitals where transplantation was not performed. Issues that need to be addressed include introduction of check sheets in accordance with the long-term follow-up guidelines, securing a place within the outpatient department, and certified nurses who meet the requirements for making a claim. We aim to improve the QOL and promote rehabilitation into society in post-transplant patients by addressing the above-mentioned issues.

Keywords: Post-transplant, Long-term follow up, Quality of life, Medical collaboration, Non-transplant center,


The Experience of Integrating Hospital-Based Palliative Consultation service to a Young Adult Patient with Acute Lymphoblastic Leukemia during Terminal Stage

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Abstract Content

Terminal cancer patients suffer from physical, mental, and spiritual impacts because of side effects of treatment, uncertainty, and fear of death. Besides, those mental and spiritual sufferings also impact their family. This paper is a nursing-care experience of integrating hospital-based palliative consultation service to a young patient with acute lymphoblastic leukemia during terminal stage. The patients confronted the cancer prognosis with many aspect of sufferings after receiving peripheral blood stem cell transplantation (PBSCT). The nursing period was from May 25th, 2017 to June 24th, 2017. The author, as a role of hospice care nurse on a palliative consultation service team, observed patient, discussed issues with the patient and family, and communicated with the palliative consultation team to conduct a comprehensive evaluation on physical, mental, spiritual, and psychosocial aspects. The patient health problems included dyspnea, difficulty making medical end-of-life decisions, and anticipatory grief. The author applied physical assessment and pain management to assist in communicating, coordinating, and providing suggestions on medicine that relieved the patient's symptoms. Moreover, the author used complementary therapies to help with the conscious disturbance and fear of death caused by dyspnea; kept the patient company; guided the patient and family to express their feelings and needs by supporting and active listening, clarified the goal and directions on end-of-life care; and assisted them to overcome fear of death in reaching the mental and spiritual peace. During palliative consultation care period, the holistic healthcare is the greatest support to help patients and their families to face end-of-life care. Therefore, clinical healthcare providers should early start introduction and discussion about palliative care in cancer care. Palliative care is helpful to provide patient-centered holistic healthcare. In addition, it is essential to train volunteers of spiritual care to join the palliative care team to assist and comfort patients and their families during palliative care. Through this the nursing care experience of palliative consultation, authors hope to serve as a reference to the holistic care with medicine treatments and complementary therapies in order that patients and their family could walked through the dark times and achieved a state of peaceful mind during the last mile of life.

Keywords: Hospital-Based Palliative Consultation service; peripheral blood stem cell transplantation





REVIEW OF THE LITERATURE ON CARING FOR LONG TERM CENTRAL VENOUS CATHETERS (CVCS) Le thi Son, MSN

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Abstract Content

Abstract

Introduction: A long term central venous catheter (CVC) is a vital component in caring for the cancer patients (Hickman's/ Broviac or Portacath/ Port). The patients' veins may become damaged by frequent, needle insertions or chemotherapy. The long term CVCs make it easier a nd more comfortable for patients to receive treatments such as chemotherapy and parental nutrition, transfusion or to have blood samples taken. It's important in stem cell transplant. The presence of these catheters place patients at risk of complications of CVCs, especially catheter-related Blood stream Infections (CRBSI). Methods and techniques used during CVCs insertion by medical staff and CVC management by nurses are critically important to preventing complications of long term CVCs.

Methods: This review will focus on updating the guidelines of producers, results of some researches and new recommendations of CDC – 2017and APSIC -2016 (Association for Professional in Infection Control and Epidemiology).

Results: To provide the nurses with useful information about knowlegde and techniques to preventing complications of long term CVCs (Infection, air embolus, blocked catheters, rupture, leakage and slipping accident of CVCs).

Conclusion: Updating knowledge on caring for CVCs need to take place frequency and go on. Most complications of long term central venous catheters can be prevented by good nursing care.

Key words: Long term CVCs, caring and preventing complications





Prevention of perianal incontinence dermatitis in GVHD patients by cluster intervention measures

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Abstract Content

Objective: The perianal skin of patients with acute GVHD who suffer from massive diarrhea is easily damaged due to the stimulation of feces which results in the damage to the integrity of the perianal skin and the loss of natural barrier. Coupled with the use of immunosuppressants, patients are easily infected. In order to reduce the irritation of perianal skin of these patients, our center has adopted cluster intervention measures since 2016 including the education of nurses and caregivers, the correct assessment of the disease, the application of skin protectants and transparent dressing, and the use of artificial anal bags.

Methods: Eighteen patients with intestinal aGVHD after hematopoietic stem cell transplantation from January 2016 to October 2016 were enrolled. And the application and effect of cluster intervention measures were summarized. The specific scheme is as follows: 1. according to the number of diarrhea and the amount of diarrhea, different combinations of hydrocolloid dressing, 3M liquid skin protectant and artificial anal bags are respectively selected to reduce the irritation of perianal skin. 2. professional personnel nursing: The responsible nurses for nursing intestinal aGVHD are relatively fixed which is beneficial to the homogenization of nursing measures. 3. education and guidance: to guide the responsible nurses to learn the correct evaluation method of irritant dermatitis, the correct use method of hydrocolloid dressing, 3M liquid skin protectant and artificial anal bags; to guide the caregivers to learn the correct time and method of using 3M liquid skin protectant and to learn the method of correctly recording stool volume.

Results: Among 18 patients, the number of diarrhea was 5-10 times/day, 7 cases; 11-15 times/day, 5 cases; 16-20 times/day, 2 cases; 20 times or more, 2 cases; incontinence, 2 cases. The amount of diarrhea was 500-1000ml/day, 3 cases; 1000-1500ml/day, 5 cases; more than 1500ml/day, 10 cases. Diarrhea lasted less than 10 days, 3 cases; 10-20 days, 3 cases; 20-30 days, 5 cases; 30 days or more, 7 cases. The duration is up to 160 days. Through the application of cluster intervention measures, none of the 18 patients develops perianal incontinence dermatitis and the longest use time of artificial anal bags was up to 5 days. Compared with historical data, cluster intervention measures have reduced the incidence of anal incontinence dermatitis from 25 % to 0 % in patients with intestinal aGVHD after hematopoietic stem cell transplantation.

Conclusion: The cluster measures adopted by our center can effectively reduce the incidence of perianal incontinence dermatitis in patients with intestinal aGVHD after hematopoietic stem cell transplantation.



The program evaluation of education workshops for LTFU outpatient care nurse between 2012 and 2017 in Japan

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Abstract Content

Introduction: After hematopoietic stem cell transplantation, proactive monitoring for post-transplantation complications such as Graft Versus Host Disease (GVHD) and infectious diseases are desired by doctors and patients. Moreover, nurses have the critical role of long-term follow-up that improves patients' and their families' quality of life by enabling them to have a smooth return to their social lives such as work or school. In Japan, in 2012, medical service fee for the guidance and management after hematopoietic stem cell transplantation was set up, and HSCT implementation hospitals in Japan established specialized outpatient services (LTFU: Long-term Follow-up) for after HSCT patients. Since 2012, the Nursing Committee of the Japan Society for Hematopoietic Cell Transplantation has been planning workshops to train the LTFU outpatient care nurses and system maintenance including the creation of guidelines. In this study, we illustrate the current implementation state of the workshop, content evaluation, and future issues related to the LTFU system in the outpatient clinic setting.

Methods: Retrospective analysis was conducted for achievements related to program contents, participant achievements, and implementation evaluation of LTFU outpatient care nurse education program workshops held between 2012 and 2017.

Results: Workshop contents were determined by examining the LTFU guidelines of ASBMT/CIBMTR/EBMT and the publicly available information on LTFU of a US facility via doctor and nurse representatives who are the Directors and Board of Trustees of the Japan Society for Hematopoietic Cell Transplantation. The contents of the 3-day program are "Current status of allogeneic transplants," "Multidisciplinary team approach," "Post-transplant infection," "Post-transplant non-infectious late complications," "Chronic GVHD," "Rehabilitation," "Life guidance after discharge (infection prevention, daily life, social activities)," "Self-care support," "Practicality of LTFU Outpatient Administration," "Problems and issues of pediatric patients," "Ethical problem solving," and "Case study." The event was held seven times in Tokyo and Nagoya; 1,041 nurses (median age: 35; median nursing experience: 11 years; median transplantation nursing experience: 6 years) completed the training. The affiliated facilities had 0-150 annual transplants. A total of 333 participants were in Kanto, 181 in Kinki, 143 in Kyushu and Okinawa, 104 in Hokkaido and Tohoku, 95 in Chubu, 43 in Koshinetsu, and 25 in Hokuriku. The difference in the attendees' readiness was indicated by their responses during the course and by evaluating their planning and implementation. One task was to study the corresponding educational content. Since 2017, we have been creating opportunities for trainees to discuss their tasks and future goals together, and provided initiatives to encourage them to act out the practical aspects of the learning content.

Conclusion: Since numbers of LTFU outpatient care nurses have annually increased, the establishment and continuation of LTFU outpatient services is ongoing. Regardless of transplantation experience, the training content tasks will be the acquisition of chronic GVHD symptom assessment skills, survivorship support for transplantation patients with long-term follow-up of more than 5 years, acquisition and strengthening of communication skills for consultation support, and maintenance of a training method to allow more interested candidates to attend.

Keywords: LTFU; outpatient care; Nursing education; program evaluation;



The changes in knowledge before and immediately after education workshops for LTFU and current stage of behavior change in Japan

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Abstract Content

Introduction: A post-hematopoietic-stem-cell-transplantation (HSCT) patient guidance/management fee was newly established as a medical service fee in Japan in 2012. One of the requirements for claiming this fee is the placement of nurses who have received nurse training provided by the Japan Society for Hematopoietic Cell Transplantation. Education workshops for The Long-term Follow-up (LTFU) is a three-day consecutive program based on data from the literature and feedback from doctors and nurses who are experienced in transplantation. The participants' characteristics assessed" for clarity in this training program include a minimum of 6(Pediatrics 3) transplants performed at the hospital, experience as a nurse, experience in transplant nursing, and level of clinical ladder for HSCT nurses. However, the actual nurse readiness for participation in the program remains unknown. Therefore, the purpose of this study was to evaluate the readiness of the participants based on the changes in knowledge before and immediately after the training and current stage of behavior change in order to understand the problems of the training program.

Methods: A cross-sectional survey was conducted using self-administered questionnaires. Survey items included knowledge before and immediately after the seminar as assessed using the desired nursing practices for LTFU nurses created in 2016 (an either-or choice between "I know" and "I do not know") and stages of behavior change for each item (Stage 1: precontemplation, Stage 2: contemplation, Stage 3: preparation, Stage 4: action, and Stage 5: maintenance) and basic attributes. Items of desirable nursing practice comprise 59 items over seven domains of "long-term follow-up system," "actual support," "team medicine," "infection control," "self-care," "rehabilitation," and "problems specific to infants."

Result: The total number of participants was 133. The three-day program comprised 15 lectures (each for 45-90 minutes) and a case study (150 minutes). We collected the questionnaire from 132 participants (collection rate: 99%). Mean years of experience as a nurse was 12.1 (SD: 6.6), mean years of experience in transplant medicine was 5.6 (SD: 3.0), and the mean number of transplant cases in 2015 was 26.6 (SD: 22.3). Changes in the percentage of the response of "I know" in each domain after training were as follows. long-term follow-up system transplant: 58% to 93%, actual support: 82% to 95%, team medicine: 78% to 94%, self-care: 83% to 94%, infection control: 83% to 94%, rehabilitation: 54% to 93%, and problems specific to infants: 23% to 46%. In addition, 70% of the participants responded that they wanted to engage in these practices and 20% responded that they were already engaging in them. Of the participants who responded that they wanted to incorporate them into practice, 34% of them were in Stage 3 (preparation) and 59% of them in Stage 2 (contemplation).

Conclusion: In general, there was improvement in knowledge. It can also be said that the motivation to incorporate what has been learned into practice increased. In the future, we need to understand how they are actually used and discuss what learning programs are necessary.

Keywords: LTFU; Nursing education; readiness of nurses; Nursing of practice; Behavior change



Improving the Management Quality of Graft-versus-Host Disease and Infection for Hematopoietic Stem Cell Transplantation Survivors

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Abstract Content

Background

Hematopoietic stem cell transplantation (HSCT) survivors may encounter various forms of graft-versushost disease (GvHD) or infection after discharging from hospitals. Case managers can help physicians to manage these problems through phone calls, E-mail, or social media, such as Line. In order to improve the care quality, developing an efficient way to deal with the problems is mandatory.

Methods

The standard operation procedure of case managers in HSCT team was established in 2015. While receiving the incoming queries, the case managers will evaluate the symptoms according to-National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: IV. The 2014 Response Criteria Working Group Report-criteria and designated them to be either emergent, urgent, or not urgent. For patients with emergent problems, the case managers will suggest them to visit emergency rooms and inform primary care physicians. For patients with urgent problems, the case managers will arrange an earlier out-patient-clinic follow-up and inform primary care physician. For patients with not urgent problems, the case managers will give nursing education. All patients will be followed once one week later.

Results

Totally 414 patients have been handled by the case managers between July 2015 and March 2018. There were total 2,288 contacts for GvHD and infection related symptoms. The most common contact subjects were queries regarding skin lesions (21%), followed by gastrointestinal (GI)tract (12%), and oral mucosa (10%). The detail of symptoms were listed in Table. Case managers in HSCT team could have a standard coping strategy to evaluate the most common symptoms via phone calls. We have established an efficient duty shift system, so that the case managers can take over each others' work without compromising the care quality.

Conclusions

GvHD and infection are two major concerns for patients receiving HSCT. Unfortunately, the symptoms majorly present after patients discharged from hospitals. Here we showed that case managers can efficiently manage the symptoms in manner of a system-based practice and improve the communication between patients and primary care physicians.

Keywords: Hematopoietic Stem Cell Transplantation Survivors, Care Quality



A prospective audit of functional, cognitive, body composition, and nutritional changes during the first 3-months post-allogeneic haematopoietic stem cell transplant (HSCT).

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Abstract Content

Introduction

Currently there are limited studies looking at the relationship between nutrition, body composition, function, and cognition in patients undergoing allogenic haemopoietic stem cell transplant (HSCT). This prospective study aims to assess changes in nutritional status, body composition, functional, and cognitive status in patients for the first 3 months following allogeneic HSCT. Data gained from this study may provide valuable information for future studies and practice for Dietitians and Occupational Therapists (OT).

Methods

This prospective, single centre study was approved by the institute's human research ethics committee prior to commencement. Patients were recruited pre-transplant via the bone marrow transplant Clinical Nurse Consultant and during pre-transplant education sessions. Participation was voluntary and signed consent obtained.

Study parameters included body composition (fat mass, muscle mass, total body water), patient generated subjective global assessment (PG-SGA), grip strength, fine motor skills, and cognition assessed by the dietitian and OT. Baseline measures were taken pre or on admission. Post-transplant measures were taken on discharge and fortnightly post-discharge till 3 months post-transplant. Majority of the measurements were collected on the same day by the OT and dietitian. The planned sample size was 20.

Results

At time of submission, 16 patients were recruited, one active. The study population had a median age of 52.6 years, age range 22-70 years. There were 13 males and 3 females. Five received Reduced Intensity Conditioning (RIC) related allo-HSCT, 5 RIC Matched Unrelated Donor (MUD) transplants, 4 Haplo allo-HSCT, and 2 MUD allo-HSCT. Four patients were withdrawn due to acute illness within the first 30 days post-transplant. 26% of participants completed body composition measures from pre-admission to 30 days, 40% completed these measures to discharge and 33% have withdrawn or were incomplete. Body composition data shows average weight loss of 6.56kg in 60% of subjects, average muscle loss of 3.38kg in 53% of subjects and 4.3kg of fat loss in 60% of subjects. 42% of participants had complete set of measures for grip strength, fine motor skills and cognition. Analysis of results to-date shows grip strength measured by dynamometer decreased by average 10% in the dominant hand and 8% in non-dominant hand at 3months post-HSCT. Cognition scores measured by MOCA remain similar to pre-transplant level.

Conclusion

We observed decrease in weight, muscle mass, and grip strength in allo-HSCT patients in the early posttransplant period. We have also identified issues that may interfere with assessments especially during early peri-transplant period. These include: (1) repeated measures during the inpatient transplant stay were not always feasible due to acute illness post-transplant and time limitations; (2) consideration for more sensitive measures for cognition. This study will continue till 20 subjects are recruited and follow up assessments completed. Assessment data collected will be analysed at completion of recruitment. Information collected will be used to design future studies aiming to improve the care of transplant patients.



Acknowledgement: This study received a multidisciplinary grant from St Vincent's Clinic Foundation. We also acknowledge the support of all staff of the Department of Haematology, SVH Sydney and participants of this study.

Keywords: allo-HSCT; cognition; body composition; nutrition; post-transplant





Fall risk assessment of adult inpatients with hematologic malignancies at Blood Transfusion Hematology Hospital – Hochiminh City – Vietnam in 2018

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Abstract Content

Introduction: Falls and their related injuries have a significant impact on the physical, mental and social health of patients. In Vietnam, according to Patient Safety Committee, falls prevalence rate accounted for 4.6% per total of medical incidents. Assessing risk of falling in adult patients with hematologic malignancies is the most important when they are admitted to the hospital for blood transfusion, chemotherapy, stem cells transplantation... Falls is one of the causes of increasing the burden diseases, lengthening a patient's stay, reducing quality of life and enhancing healthcare costs. The Morse Fall Scale is used in several care settings for fall risk assessment and supports the implementation of preventing nursing intervention. Our works aims to assess risk of all adult inpatients at Blood Transfusion Hematology Hospital in 2018.

Method: Cross – sectional description study is developed at all clinical departments. The Morse Fall Scale is used as the main instrument. Data collection takes place from June to July, 2018.

Result:

The final included 99 inpatients with the length of stay was 10.73 ± 1.18 days. The mean of Morse Fall Scale score is 41.12 ± 2.27 . There were 40 (40,4%) hospitalized patients with high risk fall score, 2 (2.02%) patients having fallen down and 11 (11.1%) patients having got history of falling.

Regression analysis showed the following patient's characteristics to be independently associated with an increased risk of falling: age (R^2 = 0.64, 95% CI -0.002 – 0.018, p = 0.033), injection vein (R^2 = 0.125, 95% CI -0.211 – 0.838, p = 0.003), number of injection veins (R^2 = 0.125, 95% CI -0.106 – 0.442, p = 0.011), oxygen therapy (R^2 = 0.125, 95% CI -0.044 – 0.189, p = 0.031)

Conclusion:

The largest group of hospitalized patients was classified as at hight risk for falls according to the MFS. Adult inpatients with hematologic malignancies are more prone to fall and should be considered in fall protective measures. The results of this study allowed the identification of factors associated with the risk of fall in adults inpatients at BTH in the hospital stay. These findings may surpport the planning of nursing actionss aimed at preventing the risk in the postoperative period.



Implementation of a collection of blood stem cell medical and nursing care process

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Abstract Content

Background: Due to recent developments in the technology of bone marrow transplantation, peripheral blood stem cell transplantation is fast emerging as one of the major treatments for selected hematologic disorders and solid tumors. The collection process is complicated, which needs a cross-departmental cooperation to keep these operations well functioning and punctually on time, and make sure that improved the quality of care and patient safety.

Method:

1. Establishing a standardized protocol by Medical Technologist, Doctor and Nurse together.

2. Design and application of nursing instruction progress form for collection of peripheral blood stem cells.

- 3. Planning of multidimensional in-service education programs:
- (a) Holding related classes for collection of peripheral blood stem cells.
- (b) E-Learning.
- (c) Increasing the number of reference books for self-learning.

Result:

1. The correcting rate of nursing care for the collection of peripheral blood stem cells knowledge will be improved from 38% to 92.6%.

2. The completion rate of medical and nursing care for the collection of peripheral blood stem cells will be increased from 51.15% to 98.46%.

The target of this project will be achieved by issues above completely.

Conclusion: This project significantly improved the correct rate of knowledge and the completion rate of medical and nursing care in this ward, which is helpful to the care process fluently and patients safety.

Keywords: collection of blood stem cell,care process,patient safety





Improve patient quality of life by transplant nurse selection of venous access for autologous haemopoietic stem cell transplant

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Abstract Content

Introduction

Central venous access device (CVAD) is used to stem cell collection in mobilisation, administrating chemotherapy, stem cell reinfusion, injection of antibiotic, blood transfusion during autologous haemopoietic stem cell transplant (AHSCT). In 2013, United Christian Hospital starts to provide AHSCT service to lymphoma and myeloma patients. At the beginning, tunnelled central venous catheter was inserted to each patient for AHSCT and kept the catheter over 4 months. However, patient opinion showed that long term catheter affected their daily life. They needed self-performing catheter care daily, frequently attended clinic for catheter flushing and wound care. In addition, there was risk of developing catheter related blood stream infection for long term CVAD in evidence based practice.

Methodology

New era of treatment trend, subcutaneous target therapy and oral medication were standard treatments and instead of intravenous chemotherapy for myeloma patient in 2014. Their venous access condition was not worse as lymphoma patients who received many times of peripheral conventional chemotherapy.

Haematology team reviewed and discussed the necessary of central venous catheter based on patient opinion and the change of treatment. Our team redesigned the patient journey of AHSCT to improve service and reduce patient burden of long term CVAD. Transplant nurse interviewed patient and assessed venous access condition at nurse clinic to determine which venous access method should be used for AHSCT.

Result

From 2014 to 2017, 29 numbers of myeloma cases were successfully shifted from long term CVAD to short term CVAD or peripheral access for AHSCT after attended transplant nurse assessment. 70 % of AHSCT patients were without burden of long term CVAD.

Conclusion

It was successful that myeloma patients were free from long term CVAD. It also reduces the operation of long term CVAD and attendance of hospitalization. However, most of lymphoma patients were still required to insert long term CVAD for stem cell collection and complicated conditioning chemotherapy BEAM during AHSCT.

Keywords: CVAD; transplant nurse; patient journey; venous access





Reviewing the performance of bone marrow transplantation unit in Imam Reza hospital,Kermanshah,Iran

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Abstract Content

Reviewing the performance of bone marrow transplantation unit in Imam Reza hospital, Kermanshah, Iran

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One of the best and modern achievements of medical science is transplantation an organ that in a relatively short time in the world medical history has accepted as a new and inimitable way for currying many diseases. The hematopoietic stem cell transplantation (HSCT) is needed cell intravenous infusion for reestablishing bone marrow function in diseases that bone marrow destroyed or weakened. this approach is doing as a redeemer way after chemotherapy with high dosage for malign diseases. bone marrow transplantation is the main and final therapy for many of hematologic and malign diseases such as aplastic anemia kinds of thalassemia and leukemia and hereditary metabolic disorders.

During last 3 years in BMT ward at Imam Reza hospital of Kermanshah 66 successful case of bone marrow transplantation done. 72.73 % of patient done autoloug transplantation and 27.27% done alogen transplantation. From this cases 27.27% of patient are women and 72.73% are men 37.88% are uneducated and others are respectively 30.30% under diploma 15.15% diploma ,7.58% of patient were alliterated,7.58% were under the diploma and the rest of patient had college degrees. The average age of patient was 41-50 year old. MNC taken from patients in 25% of patients 3-5,in 45.31% of patients 6-8,23.44% of patients 9-11 and in the 6.25% of patients was more than11 .the blood group in the 40.91% of patients was A

In the 19.7% was B, in the 6.06% of patients was AB and 33.33% of patients was O . 89.39% of the patients was RH+ and the other was RH-. Chimerism hematopoietic in the 100% of patients was 90%.

From all of transplanted patient 54.55 % affected by multiple myeloma, 15.15% Hodgkin's lymphoma 4.55% nonhodgkins lymphoma ,16.67% AML, 6.06% ALL and 3.03 % myelofibrosis .

66.67 % of patients before transplantation have not recurred. In 95.31% of patient's, cell separation done just once. In 4.69 % of patient cell separation done twice.

Obtained MNC average of patients was 6-8 %.

79.37% of patient's engraftment is done between 6 to 10 days. The average received platelet of patients was 21 to 30 bags.



After transplantation 90.63 % of patients did not have complication. After dismission 9.37% of patients hospitalize again due to several causes. In pursuance of patients 95.83 % continue their life without any problem .pearson correlation between CD3-CD34 is 76% and between CD3-MNC is 238 % and maximum correlation between CD34-MNC was 330%.

Keywords: BMT transplant -cancer





Topic: Other transplant-related issues, e.g. late effects of transplant, palliative care Abstract No: 8523

Proposing a New Nursing Informatics Model to Manageming Complexity

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Abstract Content

Nowadays, Nursing informatics (NI) is a specialty that integrates nursing science, computer science, and information science to facilitate management and communication of data, information, knowledge, and wisdom in nursing practice. The key elements of nursing informatics implementation have been considered as healthcare promotion, advanced systems, internet and network. Nursing informatics (NI) Improves consumers, patients, nurses, and other providers in their decision-making in all roles and settings. This paper presents an overview of nursing informatics describing their characteristics, effects on quality factors, main building blocks. It then proposes an Autonomous Nursing Informatics model. Characteristics and autonomic elements as building blocks of the proposed model architecture have been explained. Finally, it discusses on challenges such as learning, competencies and the building blocks life cycle.





Efficacy and safety of biosimilar filgrastim on unrelated cord blood transplantation: a single-institutional retrospective analysis

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Abstract Content

Background: Filgrastim has been widely used for hematopoietic recovery after hematopoietic stem cell transplantation. Recently, domestically manufactured biosimilar filgrastim (Filgrastim BS Syringe for Injection "F", Fuji Pharmaceuticals, Japan, BF) has been approved for the same indications as for the originator filgrastim (Gran Syringe, Kyowa Hakko-Kirin, Japan, OF). However, evidence of the efficacy and safety of BF for unrelated cord blood transplantation (CBT) has not been reported. Therefore, we evaluated the efficacy and safety of BF and OF (historical control) for CBT.

Methods: Twenty-two consecutive patients with hematological malignancy between January 2012 and December 2014 were retrospectively assessed. All patients recieved single-unit CBT. Patients received BF (n=12) or OF (n=10) from day 1 after CBT for hematopoietic recovery. GVHD prophylaxis consisted of tacrolimus and a short course methotrexate. The time to hematopoietic recovery, total filgrastim dose, duration of filgrastim administration, total transfusion units, incidences of engraftment, documented infection, febrile neutropenia, acute and chronic graft-versus-host disease (GVHD), incidence and severity of adverse events, hospitalization duration, and 100-day and 1-year overall survival (OS) were evaluated.

Results: The median total dose of BF and OF used for hematopoietic recovery was 9.68 and 10.80 mg, respectively. The median duration of BF and OF administration was 22 days and 24 days, respectively. The median time to neutrophil recovery of BF and OF groups was 22 days and 25 days, respectively (figure 1). The engraftment ratio of BF and OF groups was 100% and 80%, respectively. The median total number of units of platelet and red blood cell transfused was 170 and 10, respectively, for BF group, and 220 and 12, respectively, for OF group. The median duration of hospitalization for BF and OF groups was 1.8 months and 2.9 months, respectively. The probability of OS at 100 days and 1 year was 82.5% and 82.5%, respectively, for BF group, and 90% and 70%, respectively, for OF group. There were no significant between-group differences in time to hematopoietic recovery, total filgrastim dose, duration of filgrastim administration, total transfusion units, incidences of engraftment, incidence of febrile neutropenia, documented infection including bacterial and invasive fungal infection, cytomegalovirus antigenemoia, acute and chronic GVHD, incidence and severity of adverse events, hospitalization duration, and OS. Multivariate analysis demonstrated that filgrastim type was not a significant factor for neutrophil recovery. Median total filgrastim cost per patient was 4,058 and 8,276 US dollars for BF and OF, respectively (Figure 2). The cost of filgrastim in BF group was significantly lower than that in OF group.

Conclusions: We revealed that BF is comparable to OF with regard to safety and efficacy when used for hematopoietic recovery after CBT. These findings, and the fact that BF is more cost-effective and therefore economically preferable in a national public health service, support the use of BF for hematopoietic recovery after CBT.

Keywords: biosimilar filgrastim, originator filgrastim, unrelated cord blood transplantation





Topic: Other transplant-related issues, e.g. late effects of transplant, palliative care Abstract No: 8548

Change of Supportive Care Needs and Related Factors in Patients Underwent Hematopoietic Stem Cell Transplantation

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Abstract Content

Background: The patients of hematology often receive hematopoietic stem cell transplantation to extend their life. However, there are no researches for the needs of patients from pre-transplant to post-discharge.

Purpose : To investigate the severity of symptoms, the changes of care needs and related factors in patients -- before, during, and after -- hematopoietic stem cell transplantation (HSCT).

Method: The longitudinal study design employed a sample of hospitalized patient underwent HSCT. The data were collected within 48 hours prior and after admission of the transplant ward (T0), 48 hours before transferring out of the transplant ward within one week after the transfer to general ward (T1) and discharged one month afterwards (T2). Instruments used include symptom severity scale, Enrichd social support inventory and supportive care needs survey short form 34 (SCNS-SF34) were used to collect data.

Results: A total of 98 patients were recruited and 79 patients completed the study. Dry mouth and pain were two of the top three symptoms at T0, T1, and T2. Skin rash was the most severe symptom within one month after discharging. "Health Care Systems and Information" was the top one care need at T0, T1, and T2. Age, marital status, presence or absence of chronic diseases, the types of disease, duration of illness, sources of hematopoietic stem cells, social support, severity of symptoms, and different stage of transplants were identified as significant factors of care needs by generalized estimating equation (GEE).

Conclusion/Implications for Practice: The severity of symptoms is a factor that affects the most domains of care needs. Clinical caregivers should provide continuous assessment of symptoms and cares to improve their quality of life.

Keywords: hematopoietic stem cell; transplantation; symptom distress; care needs





Clinical effect of Power peripherally inserted central catheter and central venous catheter in hematopoietic stem cell transplantation

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Abstract Content

Objective: An effective intravenous infusion pathway is important in the treatment of malignant hematopathy by hematopoietic stem cell transplantation. Central venous catheter (CVC) is the main vascular pathway in transplantation reported both by domestic and foreign literatures. To observe the clinical efficacy and safety of high pressure-resistang double lumen peripherally inserted central catheter (Power PICC) and central venous catheter(CVC) in patients with stem cell transplantation. Methods: This was a matched crosssectional study with 60 patients with leukemia who were treated with catheterization of central venous.Inclusion criteria: patients aged between 18 and 60 who have been diagnosed with leukemia, accepted up 4 times chemotherapy and CR. Exclusion criteria: patients with heart, liver or kidney dysfunction; Patients with perianal and oral diseases; Patients with significant focal infection. Indwelling time, success rate of catheterization, complication, velocity and stem cell engraftment time were recorded between the Power PICC group and CVCgroup. Statistical analysis was performed with SPSS 21.0. Continuous variables with normal distribution are presented with the mean and standard deviation (SD), or the median and interquartile range (IQR) when they do not conform to normal distribution. Comparisons of continuous variables between the two groups were performed with the Student's t-test or Mann-Whitney U test, and categorical variables were compared using the Chisquare test, P < 0.05 was statistically significant.Results: There were significant difference between the two groups on indwelling time [(18.47±4.44) min vs.

 (14.43 ± 1.72) min, t=3.719, P<0.001],complications[6.67% (2/30) vs.30% (9/30) , X2=48.445, P=0.002]andvelocity.However,no significant difference was found in success rate of catheterization and stem cell engraftmenttime(P>0.05). Conclusion: Power PICC performed beter than CVC with well tolerability and satisfactory efficacy, which is worthy of promotion and application in the future.

Keywords: Peripheally inserted central catheter;central venous catheter;Hematopoietic stem cell transplantation





Cardiac output response to exercise after allogenic hematopoietic stem cell transplantation: A case report with a 1-year follow-up

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Abstract Content

[Introduction] High-dose chemotherapy, total body irradiation (TBI), or graft versus host disease (GVHD) can cause cardiac complications. Our previous study revealed that cardiac output response to exercise in patients before hematopoietic stem cell transplantation (HSCT) were significantly lower than in age and sexmatched healthy controls. However, little is known about the long-term clinical course of this cardiac impairment. We here report the change in cardiac hemodynamic response during exercise after HSCT.

[Methods] A 46-year-old woman diagnosed with acute lymphoblastic leukemia underwent HSCT from 7/8 HLA-matched unrelated donor. She was treated with conditioning regimen consisted of etoposide (15 mg/kg for 2 days), cyclophosphamide (60 mg/kg for 2 days), and TBI (3 Gy for 4 days). She was administered, including remission induction therapy, a total dose of 150 mg/ m² of Daunorubicin and 4930mg/m² of cyclophosphamide. Skin GVHD was observed at day +49 and +90 from HSCT. She achieved engraftment of neutrophil on day +17 and discharged on day +116 from HSCT. The 6-minute walk test (6MWT) was performed at day -9 (pre-HSCT), day +112 (at discharge), and day +342 (1-year follow-up). Stroke volume (SV), heart rate (HR), cardiac output (CO), and cardiac index (CI) were continuously measured during the 6MWT using noninvasive thoracic impedance method (PhysioFlow Q-link, Manatec Biomedical). Echocardiography was performed only at before conditioning and 1-year follow-up. She received physical therapy throughout her hospitalization. The physical therapy program mainly consisted of resistance training, stretching exercise, and endurance training. A written informed consent was obtained from her for presentation of this case report.

[Results] The distance walked decreased at 4 months after HSCT compared to pre-HSCT and tended to improve at 1 year after HSCT (575, 380, and 445 m, respectively) although did not reach the distance of pre-HSCT. Hemodynamic cardiac parameters (SV, CO, HR, and Cl) at rest did not mostly change between three assessment times. Those parameters at the end of the 6MWT at pre-HSCT, 4 months, and 1 year after HSCT were as follows: SV: 75.6, 62.5, and 70.3 ml, CO: 11.0, 7.5, and 9.1 l/min, HR: 145, 120, and 133 beats/min, CI: 7.6, 5.1, and 6.0 l/min/m², respectively. No changes were seen in systolic cardiac function as evaluated left ventricular ejection fraction. Diastolic function as early peak flow velocity/atrial peak flow velocity ratio (E/A) and mitral early diastolic velocity/early diastolic annular velocity ratio (E/e') deteriorated at 1-year follow-up (E/A: 1.4 and 0.8, E/E': 6.1 and 11.1, respectively).

[Conclusion] These results suggest that exercise tolerance might be associated with cardiac output response to exercise and diastolic dysfunction.

Keywords: Cardiac output response; Impedance cardiography; 6-minute walk test





The efficiency of PBSC harvest from family donor, Analysis based on a National prospective Survey from 2000 to 2005.

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Abstract Content

Introduction. The Japan Society for Hematopoietic Cell Transplantation introduced mandatory registration system in 2000 for family donors who donated peripheral blood stem cell (PBSC). 3,188 healthy PBSC donors were registered and 3,264 PBSC harvest (PBSCH) were performed from 2000 to 2005. In this period, an additional prospective survey had conducted. With which the incidences of severe adverse events, late hematological malignancy and the poor mobilizer were analyzed, and these results were already reported. However, the analysis of factors on the efficiency of CD34⁺ cells harvest yield was not investigated sufficiently. Methods. We examined the following parameters for 2,872 PBSCH data according with the prospective plans with documented informed consent. 1) Day's number of G-CSF administration up to each PBSCH (#DaysG). 2) The number of collected CD34⁺ cells/kg/L (per donor's body weight and apheresis volume) (#CD34DWL) sorted by #DaysG in every PBSCH turn. 3) #CD34DWL and WBC counts with or without G-CSF administration on the day of PBSCH. Results. The number of donors. mean and standard error of mean (SEM) of #CD34DWL sorted by #DaysG are as follows. In the first turn of PBSCH (p<0.0001: ANOVA), #DaysG = 3: 11 donors, 0.151± 0.12 x10⁶/kg/L, #DaysG = 4: 1,974 donors, 0.280±0.009, #DaysG = 5: 769 donors, 0.387±0.01, #DaysG = 6: 32 donors, 0.393±0.07, #DaysG = 7: 1 donors, 0.385. #CD34DWL of the fifth day of G-CSF administration was significantly (p<0.0001) larger than that of the fourth day. In the second turn (p<0.005: ANOVA), #DaysG = 4: 10 donors, 0.300±0.10, #DaysG = 5: 1,580 donors, 0.308±0.08, #DaysG = 6: 453 donors, 0.250±0.015, #DaysG = 7: 15 donors, 0.151±0.012. In the third turn (N.S.: ANOVA), #DaysG = 5: 3 donors, 0.331±0.14 x10⁶/kg/L, #DaysG = 6: 403 donors, 0.197±0.012, #DaysG = 5: 49 donors, 0.112±0.03, #DaysG = 5: 5 donors, 0.078±0.11. In the fourth turn (N.S., t-Test), #DaysG = 6: 3 donors, 0.099x10⁶/kg/L, #DaysG = 7: 8 donors, 0.115. The means and SEMs of WBC counts and #CD34DWL for cases with or without G-CSF administration are as follows. The first turn of PBSCH with G-CSF: 40,916±203/µL (n=2,681), 0.307±0.008 x10⁶/kg/L (n=2,636), without G-CSF: 47,757±1,016/µL (n=107), 0.373±0.036 (n=115). WBC count is significantly (p<0.0001) larger in cases of PBSCH without G-CSF administration on the day of PBSCH than those with G-CSF, however #CD34DWL is not. The second turn with G-CSF administration: 39.788±263/µL (n=1,782), 0.290±0.008x10⁶/kg/L (n=1,754), without G-CSF: 45,063±748/µL (n=220) (p<0.0001), 0.331±0.02 (n=240) (N.S.). The third turn with G-CSF: 41,403±649/µL (n=327), 0.191±0.01 x10⁶/kg/L (n=320), without G-CSF: 45,057±1,139/µL (n=106) (p<0.01), 0.172±0.02 (n=108) (N.S.). Conclusion. When PBSC collection is performed with single turn of PBSCH, these presented results suggest that #CD34DWL might be sufficient to the target number (>2.0x10⁶/kg) in the PBSCH on both the fourth and fifth days of G-CSF administration, however that on the fifth day might be larger than the fourth day. When the WBC count on the day of PBSCH increase to around 45,000/µL, which suggest that #CD34DWL might be kept even without G-CSF administration on the day of PBSCH.





Nursing Leadership Challenges – Experiences of Patient Safety & Infection Control for a Bone Marrow Transplantation Ward Restoration

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Abstract Content

Background:

Restoration of bone marrow transplantation (BMT) wards may occasionally be encountered by medical centers. But relevant experiences and literature are lacking, leading to consultation difficulties. Here we provide the precious experiences during the BMT ward restoration from the biggest transplant center in Taiwan, and demonstrated the role and task of the head nurse as the central role during this process.

Methods:

- 1. Head nurse must first be familiar with the entire ward pipelines, air conditioning, temperature and humidity.
- 2. Repetitive conferences >15 times with relevant departments to discuss the construction project, remodeling impact, and to plan a thorough schedule for patient transplant timing, nurse shifts, ward cleaning, infection surveillance, and material supply.
- 3. Prior to ward closure, instruments functioning were ensured and with detailed ward inspection patrol.
- High-efficiency particulate air (HEPA) was kept operating for >15 times/hour ventilation rate during the ward closure, and was renewed after restoration with microorganism culture taken 48 hours after.
- 5. Caring the nurse staff's working complaints and mental pressure in different unit during the ward closure shift.
- Upon restoration, the ward environment and medical instrument surface was cleaned with 1000 ppm hypochlorite solution by well-trained janitors, and with additional two weeks reserved for microorganism culture.
- 7. Reverse osmosis (RO) water supply pipelines was sterilized with >200 ppm acetic acid to prevent biofilm, with the ward temperature, humidity and pressure calibrated to the reference.

Results

To ensure a safe environment, high standard of environmental cleaning and monitoring are required. By the above strategies, the BMT ward was restarted successfully, and passed the infection control detection: water micro-bacteria <5 CFU/mI, as well as zero microorganism growth of environment and air conditioning. No unexpected infection or adverse event of the patients was recorded after the restoration. It minimized the impact of the ward closure on staffs and provided gapless services for the patients.

Conclusion

With the head nurse vigorous managements, BMT ward restoration could be succeed with patient safety preserved. Our experiences may set up a guide or standard of operation (SOP) in aiding other institutes in the future.



Keywords: bone marrow transplantation, ward restoration, patient safety, infection control, nursing leadership





Twenty years of haematopoietic stem cell donation in the Asian Pacific region; an overview from the World Marrow Donor Association

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Abstract Content

Introduction

A key project of the World Marrow Donor Association (WMDA) is the annual global trends report, which has become an established instrument to describe the current status of haematopoietic stem cell (HSC) donation worldwide. They are used to observe trends and changes in number and stem cell source of HSC donations as well as the global exchange of these products.

Method

Organisations worldwide are asked to report data on the number of unrelated volunteer donors and cord blood products listed in their database since 1997. As well as the number and cell source of HSC donations provided and to which countries. Since 4 years the data collection has been done through an online questionnaire and the data is automatically stored in an online database, before that the data collection was done through an excel sheet by email. The data from before 2014 has been transferred to this online database as well and all data is readily available for exports for WMDA as well as all participating organisations. Quality control measures include data validation checks within the reporting system as well as manual data checks between years by the WMDA staff. For this abstract we have looked specifically at the HSC donations in the Asian-Pacific region over a period of 20 years.

Results

One third of the organisations participating nowadays in the WMDA annual global trends report are Asian Pacific. Their combined contribution to the global donor and CBU registry has increased significantly over the past 20 years. A quarter of the CBU available are banked in the Asian Pacific region as well as 18% of the volunteer unrelated donors registered. Together they provide 29% of HSC-marrow donations, 20% of HSC-Apheresis donations and 51% of HSC-Cord donations worldwide. The majority of these donations are national.

Conclusion

A remarkable observation is that the percentage of HSC-Cord donations has increased significantly from 0% in 1997 to 51% in 2017. This increase can mainly be contributed to the high use of cord blood in Japan. Also a significant growth is observed in the use of HSC-Apheresis from 6 donations (1997) to 2,823 donations in 2017. The increase is partly because Asian countries (e.g. India and China) significantly increased their number of unrelated transplants in general, and as is observed worldwide the use of HSC-Apheresis is the preferred choice of stem cell source compared to HSC-Marrow. This is why we observe a minor decrease in the number of HSC-Marrow donations in the last decade from 1,211 to 1,194.

Keywords: haematopoietic stem cell donation; global trends;





Treosulfan based conditioning in patients who are ineligible for standard myeloablative conditioning

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Abstract Content

Background/Aims: In the field of hematopoietic stem cell transplantation (SCT), there have been continuous searches for novel conditioning regimens that will reduce stem cell transplantation-related toxicity while retaining maximal anti-malignancy effect. Treosulfan has potent immunosuppressive characteristics, more prominent than its related chemotherapy agent BU, which makes it an attractive candidate for the use in conditioning regimens before allogeneic SCT. The combination of treosulfan and fludarabine is increasingly used for adults and children before HSCT due to its potent immunosuppressive and cytotoxic effects combined with low organ toxicity.

Methods: We described seven cases receiving treosulfan as a part of the conditioning regimen before allogeneic SCT. They were refractory disease state or complicated with serious co-morbidity and not eligible for standard myeloablative conditioning.

Results: The median follow-up was 20 months. Early regimen-related toxicities were usually mild and did not need additional treatment. All patients achieved a successful engraftment of donor cells. Four patients developed acute GVHD including grade II acute GVHD in two patients. The acute GVHD was manageable with local or systemic steroids. Non-relapse mortality within 100 day after SCT was absent. Viral reactivations including cytomegalovirus and/or Ebstein-Barr virus were identified in 4 patients. Two patients relapsed and one patient was dead due to disease progression. Others have been alive without disease relapse during follow-up.

Conclusions: Treosulfan based conditioning might be safe in patients who not eligible for standard conditioning. Randomized prospective studies will be needed to better define the role of treosulfan-based regimens in allogeneic transplantation.

Keywords: Treosulfan, Conditioning, allogeneic hematopoietic stem cell transplantation



Topic: Other transplant-related issues, e.g. late effects of transplant, palliative care Abstract No: 8813

STEM CELLS TRANSPORTATION FOR THE FIRST UNRELATED TRANSPLANTATION IN VIETNAM

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Abstract Content

INTRODUCTION

Hematopoietic stem cells transplantation from unrelated volunteer donors is an appropriate option for patients in need of a transplant when a sibling donor is not available. it has been growing steadily over the past decades. In 2017, the first unrelated donor stem cell transplantation was performed at Blood Transfusion Hematology Hospital (BTH), Vietnam. Outcomes with unrelated stem cells transplantation have improved significantly over the last decade due to factors such as the use of molecular HLA typing, improvements in donor searches, reduced toxicity in conditioning regimens, advances in prevention, and progress in treating transplant complications such as graft-vs-host disease (GVHD). Improvements in supportive care and tools for detection of minimal residual disease have also contributed to better results. However, the preparations, looking for matched donor, medications, transportation are still the essential problems effect to the transplantation.

METHOD

Case report: Restrospective medical record and first step statistic time to look for matched donor, transportation time, stem cells temperature when transport, fee of searching, CD34 result of stem cells after back to transplant center. From that, we evaluate the searching donor, preparation and transportation stem cells.

RESULT

This is the fastest case which had gotten the matched donor after over 43 days looking for. 20 meetings were organized with combination of 10 Departments. There were over 200 consecutive emails contact between BTH and Tzu-Chi Stem Cells Center. Fee for looking for matched donor is 15550 USD. Transportation cost is over 4000 USD. Inside stem cells box, temperature was maintained from 4.5°C to 6°C at the contact point. Duration time of transportation is 16 hours by car, train, airplane and ambulance. Total of admitted time after collecting is over 26 hrs. CD34 viability is over 97.89%.

CONCLUSION

Preparation for a hematopoietic cell transplantation from unrelated volunteer donors is lost a lot of time, money and effort. The strict cooperation of all departments in transplantation center and consecutive combination with Stem Cells Center are necessary. Transportation plan and modern equipment are the most important thing to preserve stem cells on standards conditions. The supports and sharing experiences from stem cell bank centers and experts on stem cell transplantation in the world are very necessary for our next unrelated transplant plan in future.



Note:

We know that the numbers in our result is not enough impressive but we hope that out abstract can be accepted and so great if it is oral presentation . We want to share and have questions for experts when we present. From that, we can have good preparations for the next stem cells transportation in future.





A Case Study on Efficacy of episil[®] Oral Liquid on Reduction of Pain from Oral Mucositis in Patients Received Hematopoietic Stem Cell Transplantation

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Abstract Content

Introduction:

episil[®] Oral Liquid (Camurus AB, Lund, Sweden) is a novel medical device, recently approved in Japan for treatment of oral mucositis. Following administered by metered dose pump, episil[®] spreads in the oral cavity and forms a strongly bioadhesive and protective lining of sore tissue in the oral cavity, resulting in a rapid and sustained pain relief of pain from oral mucositis. episil[®] was approved by the Food and Drug Administration and CE-marked within the European Union as a medical device for the management of oral pain including pain caused by oral mucositis/stomatitis. In Japan, episil[®] was approved as a medical device in July 2017 and listed on national reimbursement pricing list on April 2018. episil[®] contains no active pharmaceutical ingredient and has been demonstrated to be safe and locally tolerable with no known systemic side effects, and it is a medical device characterized by its simple mechanism of strong adhesion to the mucosa and coating of the wound. Although episil[®] was approved in several countries and regions, including Europe and the US, only a few clinical trials have so far evaluated the efficacy of episil[®] in patients received hematopoietic stem cell transplantation (HSCT). The aim of this study was to evaluate the efficacy of episil[®] in patients who received HSCT.

Methods:

This study targeted patients who received HSCT at our hospital during the period from December 2017 to March 2018 and were suffering from oral mucositis with pain score of at least 5 on the Wong-Baker FACES[®] Pain Rating Scale. For 2 hours after a single application of episil[®], the degree of oral pain and feeling of use were evaluated. The application of episil[®] was permitted to repeat in a subject who wished to continue the use of episil[®] on condition that the research staff judged it is possible and necessary in the subject. This study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Approval No. Rin 1711-001), and a written informed consent was obtained from all of participants.

Results:

A total of four subjects in total participated in this study. At 5 minutes after an application of episil[®], the oral pain scores were markedly decreased in 3 out of 4 subjects, and the pain scores remained suppressed 30 minutes to 120 minutes post dosing. A quite slight change in taste and sensation of irritation were reported by 2 subjects, and a slight feeling of discomfort was reported by 1 subject. All of subjects requested to continue use of episil[®] after completing the pain assessment 2 hour after dosing. No subject experienced adverse event and device deficiencies.

Conclusion:

In patients receiving HSCT, it has been suggested that episil[®] effectively relieved discomfort such as oral pain caused by oral mucositis. The use of episil[®] represents and interesting new strategy for the management of intraoral pain caused by e.g., oral mucositis in patients received HSCT.

Keywords: Pain; Oral Mucositis; Hematopoietic Stem Cell Transplantation; Medical device





Quality Improvement Initiatives: Characteristics and Outcomes of Haematopoietic Stem Cell Transplantation in Hong Kong

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Abstract Content

Introduction

Haematopoietic stem cell transplantation (HSCT) is an important, and potentially curative treatment modality for various serious haematological diseases. However, it carries treatment-related mortality and morbidity, and is associated with high costs. Regular outcome analysis is required to assess and monitor efficacy and safety, and to identify areas for improvement and further study. In Hong Kong, the HSCT Centre of Queen Mary Hospital (QMH) is the only facility that performs allogeneic HSCT in adults. As part of quality improvement initiatives, a set of quality indicators were developed for internal benchmarking and comparison with international experience. Evaluation results of the programme performance were reported in this study.

Methods

HSCT data of QMH from 2012 to 2016 were collected and analysed. Overall HSCT activity was reviewed; basic demographics and clinico-pathologic characteristics were examined. Quality indicators measured included survival rates, length of stay (LOS), and readmission rate. The data cut-off date was 28th February, 2018. Survival statistics followed the definitions of the American Society for Blood and Marrow Transplantation (ASBMT) and actual survival at 30 days, 100 days and one year after HSCT were calculated; causes of death were also assessed. LOS referred to the length of stay of the index hospitalisation episode for HSCT ("index episode"). Readmission rate was defined as the rate of unplanned readmission of HSCT recipients to any public hospital within 30 days of discharge from the index episode for any reason. Day admission for ambulatory procedures and emergency department visits without hospitalisation were excluded.

Results

In the five-year period from 2012 to 2016, 571 haematopoietic stem cell transplants were performed (Table 1). 531 transplants were counted towards the survival and LOS data, 427 of which being allogeneic. For autologous HSCT, the 1-year survival consistently met the target of \geq 90% from 2013 onwards. For allogeneic HSCT, the Centre's 1-year survival for patients who had their first transplant was also well above the target of 65% over the five-year period, being fairly stable at 78-79% (Table 2). Average LOS of index episode for autologous HSCT was 29 days in recent years (standard deviation = 8 days), while that of allogeneic HSCT was around 46-48 days (standard deviation = 20-21 days). Both were considerably longer than international figures. Readmission rates of patients undergoing their first HSCT were also monitored (n = 480, allogeneic 80%, autologous 20%). Readmission rate for autologous HSCT patients was improving over the years, from more than 30% in 2013 to 12% in 2016. Readmission rate for allogeneic HSCT patients was around 40%.

Conclusion

The QMH HSCT Centre fared reasonably well in general. Key survival statistics were reassuring and consistently outperformed the expected rate and international standard. Regular monitoring is required to detect trends. Meanwhile, published data on LOS and readmission rate were heterogeneous. Thus it was important to define internal benchmarks for these performance measures to take into consideration variations in local HSCT practice, health care system, and even social determinants of health. Periodic audits of outcome measures are valuable to recognise problems and identify improvement opportunities.

Keywords: quality improvement; outcome measures





Activity of the team SKiP (Supporting Kids Parents with Cancer)

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Abstract Content

Introduction: According to the finding by National Cancer Center Japan, there were 56,143 patients who were initially diagnosed as cancer and who have kids under 18 years old, and there were 87,017 children who have cancer parents in 2015. The parents who have cancer not only face and try to cure the disease itself, but also face the difficulties to interact with their kids, especially how to inform them the disease. In such condition, the parents are unable to inform it to their children. On the other hand, those children are sensitive enough to feel the change by the act of their parents. Moreover, the children often imagine the worst scenario when they sense such acts although their parents do not inform anything about disease directly, and they eventually face stressful situation. Also, for medical staff, there are difficulties to support those children due to the lack of plentiful such experience of situation. It is very valuable for medical staff to support how patients who have cancer decide to inform their children about the disease, and how the children feel and react themselves by hearing about cancer. We report the result of the current status.

Methods: In November 2013, the team Supporting Kids Parents with Cancer (SKiP) was launched by volunteers consisting of physicians, nurses, medical social workers, and nursing faculty staff for the purpose of enlightenment and education to medical professionals in order to support cancer families. Specific activities of the team SKiP are that medical professionals understand a significance of informing disease from parents who have cancer to their children, and we host a seminar for medical professionals regarding a support of cancer parents' decision-making. Additionally, we directly intervene the matters in between the cancer parents and their children. One of the examples is that we run a CLIMB® program (Children's Lives Include Moments of Bravery) for 1st to 6th graders. The purpose of this program is provided psychosocial intervention developed specifically to support the emotional needs of children with a parent who has cancer.

Result: The participants of the CLIMB®, 18 cancer patients/their families and 20 kids, evaluated that this program was very effective. Also, support request to us is increasing from physicians and nurses, and we recognize that it has been understanding by a lot of medical professionals about an activity of the team SKiP.

Conclusion: We are eager to continue those activities positively as a team for parents who have cancer and their children.

Keywords: Supporting Kids Parents with Cancer; Support for cancer families; CLIME program;





Topic: Other transplant-related issues, e.g. late effects of transplant, palliative care Abstract No: 8905

BPDCN— a rare and agressive hematologic malignancy: 3 case reports

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Abstract Content

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy with aggressive clinical course. It is derived from precursors of plasmacytoid dendritic cells. The tumor cells are characterized by blast-like morphology with pleomorphic cell size (Fig 1). On flow cytometry, they express CD4, CD45RA, CD56 and CD123 while other lineage-specific markers, such as MPO, CD3, CD19 are usually negative.

While the best treatment of BPDNC remains unclear, we present 3 patients with BPDCN receiving hematopoietic stem cell transplantation (HSCT) in our institute.

Case 1.

A 30-year-old male without underlying disease presented with multiple enlarging erythematous-based plaques over left zygomatic area for 1 year. No symptom was noted but the lesions enlarged gradually. Biopsy of the skin lesion revealed BPDCN. The patient received 6 cycles of CHOP (cyclophosphamide, hydroxydoxorubicin, oncovin, and prednisolone) chemotherapy and achieved first complete remission. Fifteen months later, the disease relapsed as multiple skin lesions over whole body (Fig 2) with bone marrow involvement. The patient received re-induction chemotherapy L-ESHAP (L-asparaginase, etoposide, methylprednisolone, cytarabine and cisplatin) and achieved second complete remission. Allogenic hematopoietic stem cell transplantation (allo-HSCT) was arranged for further consolidation.

Case 2.

A 46-year old male without underlying disease presented with hyperpigmented skin lesions over face and bilateral arms. Skin biopsy at other institute revealed BPDCN. He received 8 cycles of CHOP chemotherapy and achieved complete remission. One year later, the disease relapsed as hyperpigmented lesions over bilateral arms, and trunk. BM involvement was also confirmed. The patient achieved second complete remission after rescue ESHAP chemotherapy. Myeloablative conditioning with Bu 4 + Cy 4 (busulfan, cyclophosphamide) regimen followed by autologous hematopoietic stem cell transplantation (auto-HSCT) was done but second relapsed occurred 4 months later. The tumor was refractory to rescue ESHAP chemotherapy. The patient died of disease progression 2 years after auto-HSCT.

Case 3.

A 67-year-old male patient with hypertension, benign prostate hyperplasia presented with multiple erythematous skin patch and nodules over his back for 4 months. The skin lesions were non-painful, non-scaling, and movable with variable size and wax and wane pattern. The skin biopsy also confirmed the diagnosis of BPDCN. Staging PET scan showed hypermetabolic skin lesions at left neck, back, left gluteal and bilateral forearms. Bone marrow was negative for tumor involvement. After 3 cycles of CHOP chemotherapy, he achieved first complete remission. One cycle of ESHAP chemotherapy was administered for stem cell mobilization and auto-HSCT with BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning was administered. Eight months following auto-HSCT, several erythematous nodules over hand and flank area developed. Skin biopsy confirmed BPDCN relapse. After 3 cycles of AspaMetDex (L-asparaginase, methotrexate, dexamethasone) chemotherapy, PET scan revealed second complete remission. Four months after relapse, he received allo-HSCT with reduced intensity conditioning FI 5 + Bu 2 + Cy 1 (fludarabine, busulfan, and cyclophosphamide) regimen. The patient remained disease free 17 months after the allo-HSCT.



In conclusion, BPDNC is a rare and aggressive hematologic cancer. Disease relapse is common following conventional chemotherapy. Allo-HSCT at first complete remission seems to prolong life of these patients.

Keywords: Blastic plasmacytoid dendritic cell neoplasm, Allogenic transplantation





TEN YEAR ACTIVITY AND OUTCOME DATA OF TRANSPLANTS FROM A TERTIARY CANCER CENTRE IN INDIA

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Abstract Content

Abstract No: 8907

Background: Haematopoietic stem cell transplantation (HSCT) is potentially curative in the management of various benign and malignant conditions. The HSCT program at our centre began with the first stem cell transplant at Tata Memorial Hospital in March 1983 and continued till date.

Aims: To review the 10 year activity and patient outcomes of HSCT from the period - 1st November 2007 to 30th November 2017. Methods: All consecutive patients who underwent HSCT during the period November 2007-November 2017 were included in this analysis. The patient characteristics and transplant details were recorded. Disease Risk Index (DRI) and EBMT score were calculated for each patient.

Results: A total of 593 patients (169 female and 424 male) underwent HSCT during the above period. The median age of the patients was 31 years. A total of 132 (22%) patients were below the age of 18 years at the time of transplant. Autologous transplant was performed in 317 (53%) patients while 276 underwent allogeneic transplant. The median follow up was 4 years. The 5 year OS and RFS for the entire cohort were 62.3 % and 53.2 % respectively, while the 5 year OS, RFS for autologous and allogeneic transplants were 67.5 %, 56.2 % and 55.1 %, 50.9 % respectively. Disease wise 5 year OS and RFS were AML - 47.1 % and 44.1%;ALL- 51.5 % and 47.1%;HL- 72.9% and 62.7 %;NHL- 61.0% and 54.2 %;MM – 76.2 % and 57.1 %; CML - 69% and 59.5 %; Aplastic Anemia - 80 % and 65 %; MDS - 50 % and 46.7 %; Neuroblastoma - 36.8 % and 26.3 %; others (CMML, JMML, Thalassemia) - 42.9 % and 40 % respectively. The total number of deaths were 215 (38%), of which deaths due to relapse occurred in 144 (67%) and nonrelapse deaths in 63 (30%) patients (52 allogeneic and 11 autologous). The overall transplant related mortality was 11%. All patients were stratified according to DRI into Low , Intermediate, High and Very high risk groups. The 5 year OS and RFS for Low risk were - 64.5% and 64 %; Intermediate - 68.2 % and 58.1 %; High – 48.7 % and 41.7 %; Very high – 30.8 % and 23.1 % respectively. There was a statistically significant difference in the 5 year survival (both OS and RFS) between the low- intermediate and high very high risk groups in ALL (p = 0.02 and p = 0.05), MDS (p = 0.003 and p = 0.004) and MM (p = 0.003and p = 0.01), while in AML, CML, HL and NHL it did not attain statistical significance.

Summary/Conclusion: These outcomes are comparable to those from western countries and also show that stratification according to DRI and EBMT scores help in over all prognostication as well as in comparing outcomes amongst various diseases.

Keywords: HSCT : DRI :EBMT





Donor with hypoplasia bone marrow meanwhile full blood count and other examinations are normal can be used for patients receiving allogeneic hematopoietic stem cell transplantation

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Abstract Content

Introduction: Bone marrow aspirates are performed routinely as part of the pre transplant assessment on all potential donors in some centers. However, little is known of whether donor with hypoplasia bone marrow meanwhile full blood count and other examinations are normal can be used for allogeneic hematopoietic stem cell transplantation (allo-HSCT) when patients have no other suitable donorto replace.

Methods: Twelve patients using donors demonstrating hypoplasia BM received allo-HSCT at the Peking University Institute of Hematology between January 2010 and December 2017.Forty-eight patients using donors demonstrating hyperplasiaBMwere selected using the case-pair(1:4) method.We compared the clinical outcomes between two groups.

Results:The days harvesting stem cells(P=0.189), the median infused nuclear cells(P=0.784)and CD34+ cells (P=0.097) was comparable between two groups.Among hypoplasia BM group and hyperplasia BM group, the cumulative incidence (CI) of neutrophil engraftment at day 28(91.7% vs. 93.8%, P = 0.75)and platelet engraftment at day 150(83.3% vs. 93.8%, P = 0.48) and the median time to myeloid engraftment (13.5 daysvs. 14 days, P = 0.85) and platelet engraftment (14 daysvs. 14 days, P = 0.85) were not significantly different, respectively.The 3-year progression-free survival rate were67.8% VS. 71.7%(P = 0.98), respectively; the overall survival rate were69.8% VS.77.8%(P = 0.69), respectively;CI of non-relapse mortality were 18.5% VS. 13.6%(P = 0.66), respectively; CI of relapse were 10.2% VS.10.4%(P = 0.82), respectively. In multivariate analysis, donor with hypoplasia BMdid not show inferior clinical outcomes of patients after allo-HSCT.

Conclusion: If patients had no other suitable donorto replace, donor with hypoplasia BM can be used for patients receiving allo-HSCT as long as donor's full blood count and other examinations are normal.

Keywords: bone marrow aspirate; hypoplasia; normal donor; allogeneic hematopoietic stem cell transplantation





Evidence summary of management of nutrition support for adult patients with hematopoietic stem cell transplantation

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Abstract Content

Objective

In patients with hematopoietic stem cell transplantation (HSCT), malnutrition was found to be associated with poor outcome, increased complications and lower overall survival. There are, however, few interventional trials proving the benefits of nutritional therapy in this population compared with no nutritional treatment. Optimal management of nutritional support to improve outcomes of HSCT remains controversial. As a result, our aim was to retrieve, appraise and summarize the available evidences on management of nutritional support in adult patients with HSCT.

Method

We searched the National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines Network, (SIGN), National Institute for Health and Clinical Excellence (NICE), BMJ best practice, Clinicalkey, The American Society for Blood and Marrow Transplantation (ASBMT), The European Society for Blood and Marrow Transplantation (ASBMT), The European Society for Blood and Marrow Transplantation (ASBMT), The European Society for Blood and Marrow Transplantation (ASBMT), The European Society for Blood and Marrow Transplantation (ASBMT), The American Society of Hematology (ASH), Asia Oncology Nursing Society (AONS), Oncology Nursing Society (ONS), The Cochrane library, PubMed, Medline, CINAHL, EMbase, CNKI and CBM to collect literatures including guidelines, evidence summary, best practice information sheet, recommended practice, systematic review and consensus in the last ten years.

Result

Nine references including four guidelines, four systematic reviews, and one evidence summary were included. A total of eighteen items of best evidences were summarized with regard to six aspects, thas is, nutritional risk screening and assessment, nutritional Interventions (dietary counseling, enteral nutrition, and parenteral nutrition), chose of immunonutrition, nutritional support treatment for patients with graft-versus-host disease (GVHD), efficacy evaluation and follow-up of nutritional interventions. **Summary**

Specialized nutritional care for both before and after HSCT are necessary. Medical institutions should establish optimal management pathway or practice guidelines of nutritional interventions to prevent or treat malnutrition for these patients.

Keywords: Hematopoietic stem cell transplantation; Nutritional support; Evidence based medical





Outcome and Risk Factors of Transplantation-associated Active Tuberculosis in Allogeneic Haematopoietic Stem Cell Transplantation: A Nested Case Control Study

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Abstract Content

Introduction: Active tuberculosis (TB) is an uncommon but life-threatening complication of haematopoietic stem cell transplantation (HSCT). HSCT recipients are at significant high risk due to their immunocompromised state either because of delayed immune reconstitution or use of immunosuppressive medication for treatment of GVHD. Early recognition and prompt treatment are the key to good outcomes in this patient population.

Methods: From January 2012 to December 2017, a nested case control study was carried out in our centre to examine active tuberculosis incidence and study relative risk factors. A total of 730 consecutive patients who underwent allogeneic HSCT were studied. Fourteen (1.92%) patients matched the established diagnostic criteria of active tuberculosis. Fifty-six allo-HSCT recipients were set as control. No significant difference was found between the two groups on age, gender, underlying disease, donor type and ATG given as well as conditioning intensity.

Results: Twelve of the fourteen cases were pulmonary TB (85.7%), including four patients with miliary TB, while the other two were extrapulmonary TB (14.3%). The median time to onset of active TB was the 6.9 (range 1.5 to 32.5) months post-HSCT. The positive rate of T-SPOT in patients with TB is higher than those without TB, the difference was statistically significant.(HR =6.286, 95% CI,3.093-12.774; P =0.000). We also found Grades 2 to 4 aGVHD (HR = 3.975, 95% CI, 1.331-11.876; P =0.013), moderate-severe cGVHD (HR = 3.952, 95% CI, 1.113-14.027; P =0.033), Epstein Barr virus viremia (HR = 9.210, 95% CI, 1.204-70.452; P =0.032), the application of etanercept (HR=3.928, 95% CI,1.375-11.220; P =0.011), invasive fungal disease (HR = 3.909, 95% CI,1.351-11.316; P =0.012), relatively large dose of prednisone (HR=17.831, 95% CI, 2.330-136.476; P =0.006), and tacrolimus (HR=4.340, 95% CI, 4.340-4.340; P =0.009) were risk factors for active tuberculosis occurrence, but only the latter three remained significant after multivariate analysis. Each of the prognostic factors was assigned points based on their HR: invasive fungal disease (1 point); the use of FK 506(1 points); or presence of relatively large dose of prednisone (2 points). This total score stratified the cohort into 3 groups with very different risk of occurrence of TB: low risk group (0 to 1 point), the intermediate risk group (2 to3 points), and the high risk group (4 points). The 5-year cumulative incidences of active TB were 0, 30.7%, and 77.8% for each risk groups (p=0.001). With a median follow-up of 15.9 (range 3.8-80.6) months for patients with TB and 43.1 (range 3.4-80.3) months for control group without TB, the 3-year OS were 68.1% and 70.0%, respectively. Subjects with TB had significantly higher 3-year none relapse mortality than subjects without (24.76%±13.37% vs 5.66%±3.22%, P=0.0076). The causes of death in TB group were engraftment failure/multi-organ failure (n = 1), and respiratory failure(n = 3).

Conclusions: Our study provides an excellent foundation for predicting of active TB occurrence in allo-HSCT recipients, and helps target high-risk patients for early diagnosis and timely management decision making.





Topic: Other transplant-related issues, e.g. late effects of transplant, palliative care Abstract No: 8914

Relationships between the Resilience and Quality of Life of Hematopoietic Stem Cell Transplantation (HSCT) Survivors after discharge ~a pilot study

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Abstract Content

Introduction

In recent years, the success rate of hematopoietic stem cell transplantation (HSCT) has increased, and the long-term survival rate has also increased. According to the Taiwan Blood and Bone Marrow Transplant Society, there were 5,588 HSCT survivors from 1983 to 2015. The five-year survival rate of HSCT was about 50% from 2009 to 2015(Taiwan Society of Blood and Bone Marrow Transplantation, 2016). These survivors may face long-term physiological and psychosocial change. Compared to other cancer survivors, HSCT survivors had more long-term symptoms and had lower quality of life (Rosenberg et al, 2015). Resilience is the ability of humans to recover from changing states (Garcia-Dia et al., 2013). The resilience of survivors of HSCT is highly correlated with their health status and quality of life (Rosenberg et al., 2015). At present, there are few researches in Taiwan about this topic. Therefore, the purpose of this study is to explore the relationships between resilience and quality of life in patients with HSCT.

Methods

This is an ongoing cross-sectional correlation study. 36 survivors of HSCT were recruited after discharge at a medical center in southern Taiwan. After the instructions and fill out the consent form, the HSCT survivors were asked to fill out four self-reported structured questionnaires, including the demographic data and medical characteristics form, the Modified Chinese Short-Form Cancer Survivor's Unmet Needs, the Chinese Version of the Resilience Scale and Functional Assessment of Cancer Therapy–Bone Marrow Transplantation Scale, version4 (FACT-BMT). The data were statistically analyzed with SPSS version 22, by using independent sample t-test, analysis of variance, and Pearson's correlation coefficient.

Results

The HSCT survivors were about half male and female, with an average age of 47.6±13.5 years. Survival after transplantation was from 1.5 to 213 months, with an average of 39.8±46.3 months. The HSCT survivors' resilience score was moderate level (mean score: 141.6). The FACT-G average score was 87.75, the FACT-BMT average score was 117.64, and the FACT treatment index was 75.89. These average scores of quality of life of HSCT survivors in this study were superior to those patients with 100days after HSCT in United States(McQuellon et al., 1997; McQuellon et al., 1998). Resilience was positively correlated with FACT-BMT, FACT-G and treatment index (P<0.005). Further, the resilience also positively correlated with the domains of FACT-BMT, such as social/family health status, emotional health status, functional health status and transplant additional concerns (P<0.01). However, resilience was not significantly related to the physiological health domain of the FACT-BMT.

Conclusion & Implication

Resilience is highly correlated to the quality of life. If the patient has higher resilience, the quality of life of HSCT survivors will be higher, especially for social/family health, emotional health, functional health and transplant additional concerns domains. This results provide a preliminary knowledge base on the relationship between resilience and quality of life of HSCT survivors in Taiwan.

Keywords: resilience;hematopoietic stem cell transplantation;quality of life;cancer survivor;HSCT





Implementation of a State Wide Network for Quality Management and Accreditation in Haemopoetic Progenitor Cell Transplant Laboratories and Collection Centres.

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Abstract Content

Background: Haemopoetic Progenitor Cell (HPC) Transplants, with an expanding range of related cellular therapies, are an essential part of the management in Haematology & Oncology, and non-malignant diseases. As living tissues there are a wide range of quality management (QM) processes that need to be implemented with regard to patient, donor and workforce to ensure best practice, minimize costs and maintain efficient processes across the multiple stakeholders. We describe the implementation of a State Wide Network for Quality Management and Accreditation in HPC Collection Centres and Processing Laboratories.

Methods: NSW is a large state in Australia with an area of 810 thousand square km. It had a population in 2016 of 7.5 million, and that year a combined total of 589 autologous and allogeneic HPC transplants were performed (an increase by 22% over the previous 5 years). In addition, there is increasing use of other cellular therapies including donor lymphocyte infusions, pathogen specific T-cell infusions, and the emerging role of CAR-T cells. These therapies are performed at adult and paediatric clinical units over a large geographical area.

In the early 2000s there were rapidly increasing requirements of regulatory agencies both national and international (FACT, NATA and TGA). In response, a state-wide Quality Management (QM) service was established as a joint initiative by HPC transplant clinical / laboratory staff and the NSW State Ministry of Health to provide services to the 15 clinical units and 7 laboratories.

Objectives that needed to be achieved were: a.) creation of oversight committees; b.) hiring the QM team; c.) providing centralised offices and transportation facilities for the QM team; d.) selection of QM software to be utilized across all the sites; e.) obtaining memorandums of understanding (MOU) from Chief Executive Officers of geographic health services, Directors of Clinical Units, Directors of Laboratory Services and others; f.) configuration and implementation of an efficient service to harmonize documentation and processes across the units.

Results: This statewide initiative has been successful in:

- Sharing of highly specialised clinical and laboratory expertise
- Standardisation of practices, procedures and forms
- Independent auditing and collaborative implementation of quality improvements
- Benchmarking programs e.g. inter-laboratory frozen CD34 comparison
- Multicentre validations of quality indicators (cell yield, engraftment, survival) using extensive transplant data.
- Comprehensive education program including webinars, forums and training resources
- Patient experience systems


 Patient resources – autologous, allogeneic patient guides, with long term follow-up resources in development

Conclusion: Although a daunting task initially to achieve a harmonized QM program across 15 clinical HSCT units and 7 laboratories, patience and good will achieved a functional and efficient team and processes. The initiative has facilitated continued accreditation with additional benefits of sharing and comparing data, addressing opportunities for improvement across sites and developing education resources. There were also financial gains by increasing purchasing power of equipment and consumables over a network rather than as individual units, and rotating and sharing consumables prior to expiration dates. Patients are the primary focus with improvements and resources development aimed at maximising product quality whilst improving quality of life.

Keywords: Quality Management, Laboratory, Accreditaion





Secondary Solid Cancers after Allogeneic Hematopoietic Stem Cell Transplantation: Impact of stem cell source

Yuki Asano-mori^{*1}; Michiho Ebihara¹; Mitsuhiro Yuasa¹; Kosei Kageyama¹; Daisuke Kaji¹; Aya Nishida¹; Shinsuke Takagi¹; Hisashi Yamamoto¹; Go Yamamoto¹; Naoyuki Uchida¹; Shuichi Taniguchi¹ ¹Department of Hematology/ Toranomon Hospital/ Japan (日本)

Abstract Content

Background: Secondary solid cancer (SSC) is one of the most important late complications among long-term survivors after allogeneic hematopoietic stem cell transplantation (HSCT).

Patients and Methods: To evaluate the incidence, risk factors and outcomes of SSC after allogeneic HSCT, we reviewed the medical records of Japanese patients with hematological diseases who underwent allogeneic HSCT for the first time at the Toranomon Hospital between 1993 and 2015.

Results: A total of 1373 patients were included, with the median age of 54 (16-82) years old. Approximately two-thirds of the patients were male, and about 60% were diagnosed with myeloid neoplasm. Eight-hundred twelve patients underwent cord blood transplantation (CBT), 313 underwent unrelated bone marrow transplantation (uBMT) and the remaining 248 underwent transplantation from a related donor. Half of the patients received reduced-intensity conditioning. Cumulative incidence of grade II-IV acute GVHD and extensive chronic GVHD (cGVHD) were 47.9% and 25.6%.

A total of 48 patients developed SSC at a median of 4.8 years, with cumulative incidences of 2.9% at 5 years, 5.8% at 10 years, and 12.0% at 15 years after HSCT. More than two SSC in different organs occurred in 5 patients, and a total of 55 SSC were identified. The most common site was esophagus (13), followed by stomach (10), oral (9), colon (5) and lung (5). In univariate analysis, age>=50 and extensive cGVHD were identified as significant risk factors for SSC (HR 2.46, P=0.01 and HR 3.85, P<0.01). The risk of SSC after CBT was not different from that after related HSCT (HR 1.44, P=0.32), but was significantly lower than that after uBMT (HR 2.37, P<0.01). Multivariate analysis revealed that age>=50 years and extensive cGVHD were identified as significant risk factors for SSC (HR 2.85 and HR 4.24, both P<0.01). Thirteen patients died of infections (5), SCC (3) relapse (2), non-infectious pulmonary complications (2) and ischemic heart disease (1). The development of SSC significantly increased overall mortality (HR 3.45, P<0.01).

To focus on the impact of stem cell source on SSC, we compared the incidence and risk factors between CBT and uBMT after 2002, when CBT was introduced at our hospital. The median age was higher and the cumulative incidence of extensive cGVHD was lower after CBT compared to uBMT. (57 years vs. 51.5 years, P<0.01 and 16.9% vs. 44.2%, P<0.01). Cumulative incidence of SSC after CBT was significantly lower than that after uBMT (7.2% vs. 15.7%, P<0.01). In multivariate analysis, CBT was identified as an independent factor which decreased the risk of SSC (HR 0.50, P=0.047), in addition to the significant impact of age>=50 years and extensive cGVHD on the increased risk (HR 3.43 and HR 3.51, both P<0.01).

Conclusions: Endscopic screening is important as part of lifelong follow-up, especially for patients age>=50 or who have extensive cGVHD. Despite the limitations of differences in patient background, CBT may have potential for reducing the risk of SSC.



Speech Summary





Opening Ceremony: ASBMT/EBMT/WBMT/APBMT Joint Symposium Past, Now and Future of Hematopoietic Stem Transplantation

Date/Time: November 2nd / 09:30-11:45

Venue: Room 201

Speech Title:

Hematopoietic Stem Cell Transplantation Where we have come from and where do we go?

Speaker: James Gajewski, MD, MACP Affiliation: American Society for Blood and Marrow Transplantation

Speech Summary

Hematopoietic cell transplantation was developed initially as rescue following administration of high dose chemotherapy- radiation therapy treating cancer and marrow failure diseases. Originally donors were syngeneic, then HLA matched relatives and autologous. The advent of unrelated donor registries in the 1980's, enabled unrelated transplantation -thus allowing option of allogeneic transplantation to many more patients. The rarity of donor haplotypes still meant having donor for all individuals was problematic. The late 1990's new techniques of transplant allowed routine use of haploidentical donor, enabling almost all recipients to have a donor option. Transplant research now focuses on prevention of treatment toxicities, improved treatment of GVHD and targeted antileukemia cellular therapy. For haploidentical transplants, reduction of gvhd risk entails either the effector t cells are either removed in vivo or ex vivo, or having proliferation stunted with cytotoxic therapy. Treatment of ghvd is now moving towards targeting T cell and B cell intracellular signaling, t cell trafficking modulators, epigenetic modulation. The ability to expand t lymphocytes and NK cells, plus genetically engineer the expanded cells to target cell surface antigens have enabled the separation of gvhd from gvl and antiviral therapy. International collaboration enabled HCT to evolve from being a rare procedure to being done commonly. The IBMTR-CIBMTR, was created as an outcomes registry because single center data was not sufficient to understand the science of outcomes. This registry has provided >1000 peer-reviewed papers since 1972 with authorship from around the globe. Early in establishment of donor registries, the genetically linkages and disequilibrium within HLA necessitation necessitated world-wide unrelated donor search and harvesting. Now with cellular therapies happening around the globe, international collaboration is expanding to establishing international quality control and quality assurance inspections so that we can continue to learn from every patient treated and ensure all patients receive this therapy responsibly.





Past, now and future of hematopoietic stem cell transplantation (EBMT Perspectives)

Speaker: Nicolaus Kröger , MD Affiliation: University Medical Center Hamburg-Eppendorf

Speech Summary

For now 60 years ago, the first patients were transplanted with acute leukemia from a syngeneic graft after high dose total body irradiation. Since then, the transplant procedure has been continuously improved by better supportive care, such as infectious prophylaxis and treatment, but also improvement of HLA-typing and donor selection. Furthermore, alternative donors have become more available by establishing large unrelated donor registries around the world as well as using more umbilical cord blood and also more recently haplo-identical donors as stem cell source. Further improvement has been achieved by introducing GvHD prophylaxis with mono- or polyclonal antibodies or T-cell depletion strategies. Donor lymphocyte infusion are effective to treat or prevent relapse and use of reduced intensity conditioning has markedly decreased early transplant related mortality. All these achievements have led to a significant reduction of non-relapse mortality and a broader use of this treatment procedure is to be expected. Despite these achievements and improvement in reducing non- relapse mortality a substantial number of patients still will experience relapse. Thus, the current and future clinical efforts lie in the prevention of relapse which has become the most frequent cause of treatment failure after allogeneic stem cell transplantation. Here, novel less toxic agents, small molecules, monoclonal or bispecific antibodies and more recently also genetic modified T-cells such as CAR-T-cells offer new possibilities within the transplant concept to reduce the risk of relapse and enhance the rate of cure.





How does the past predict the future of allogeneic transplantation: lessons for the field?

Speaker: Daniel Weisdorf, MD Affiliation: University of Minnesota

Speech Summary

Allogeneic transplantation began many years ago as replacement therapy for patients with inherited immunodeficiency disorders or marrow injury induced by radiation. While early murine experiments had demonstrated that cellular transfer could restore hematopoiesis and immunocompetence, only beginning in the late 1950s and finally in the late 1960s were successful human allogeneic transplants performed. While the original concept involved cellular transfer to restore defective hematopoiesis or immunity, it was soon extended as supportive therapy for advanced hematologic malignancies. Myeloablative conditioning transplantation for advanced acute leukemia and other disorders allowed a fraction of patients to survive in remission for some time.

Improved understanding of the immunologic components of transplantation recognized that the adoptive transfer of new, donor-derived immunocompetent cells could induce a potent antineoplastic graft versus tumor effect which was linked to, but not exclusively related, to graft-versus- host disease (GVHD). This potent immunological based graft versus tumor affect allowed extension of the curative potential of myeloablative transplantation to patients with high-risk malignancy and by the early 1980s, even to those with asymptomatic early phase chronic myelogenous leukemia.

Substantial advances in supportive care including GVHD prophylaxis, transfusion practices, plus diagnostic and therapeutic approaches to viral and fungal infections greatly facilitated expansion of the field. This allowed transplantation for many more patients in an expanding group of centers. By the late 1980s, establishment of the National Marrow Donor Program in the US and other international registries allowed many more patients who lacked matched HLA matched family donors a chance for successful transplantation. Further options, beginning in the late 1980s allowed cryopreserved umbilical cord blood (UCB) units to be used for transplantation based on their highly proliferative and immunologically naïve capacity to engraft children and smaller adults, even if not fully HLA matched. More recent recognition of novel approaches to haploidentical transplantation, particularly using post-transplant cyclophosphamide or combined multicomponent regimens with intensive GVHD prophylaxis now offer suitable allogeneic donors for nearly every patient from amongst their relatives, volunteer adult unrelated donors or UCB units.

In the mid to late 1990s, recognition of the immunologic potency of allografts to limit relapse facilitated extension of allotransplantation to older or more frail patients through the use of reduced intensity or non-myeloablative conditioning regimens. Observed experience with the hierarchy of GVL sensitive diseases facilitated transplantation for numerous hematologic malignancies in remission and recognized particular sensitivity of certain lymphoid malignancies to this powerful GVL effect.

Notably, relapse remains as the biggest challenge and the most frequent cause of posttransplant failure. Novel approaches to improve the antineoplastic potency of transplantation are the next wave of advances we can expect. These advances may come through post-transplant maintenance therapy,



through antitumor vaccines or targeted therapy directed towards the tumor or even through supplemental cellular therapy. Cell therapies may include donor lymphocyte infusions, adaptively transferred natural killer (NK) cells, antigenically directed T cells (chimeric antigen or other) and other advances yet to be contemplated.

Limitations of GVHD morbidity and mortality may come through techniques to enhance regulatory T-cell (Treg) development post-transplant and techniques to induce stable tolerance without ablating the antitumor effects may make allografting even safer and more broadly available to those most needing it; particularly older adults affected by comorbid conditions.

Modern, much less morbid transplants can permit this enhanced antitumor impact and prevent relapse.

These stepwise advances in the field have developed over many years, yet are accelerating as understanding of immunologic and genetic biology accelerates in parallel. Most excitingly, more patients will be helped and more patients will be cured.





Present and future of hematopoietic stem cell transplantation -How the APBMT is facing the challenge-

Speaker: Shinichiro Okamoto, MD, PhD Affiliation: Asia-Pacific Blood and Marrow Transplantation Group (APBMT)

Speech Summary

APBMT has kept growing in terms of the numbers of participating countries/regions, their clinical activities, the level of science, and the strength of our collaboration. However, our group consists of countries where the disease for which transplantation are indicated, the infrastructure for supporting transplantation, financial background, and endemic of infectious diseases vary significantly. Thus, the challenges in HSCT vary significantly among our region.

One of our most important challenges is to increase the sites to perform HSCT and the access to it. The reasons contributing to this huge supply and need discrepancies include the lack of trained personnel and the ability of the healthcare system to cover the cost of HSCT. The APBMT vision for the forthcoming years encompasses this important issue by providing emerging countries with training opportunities in HSCT and ensuring the quality of HSCT among Asia-pacific area. APBMT will start HCT center accreditation project while harmonizing our approaches with the materials and recommendations of International Accreditation. The current FACT JACIE standards are beyond scope for 90% of centers in Asia-Pacific region, thus we are planning to commence our accreditation by step-up approach to finally reach the FACT –JACIE standards. In order to increase the opportunity of clinical studies among our regions, we need to foster the activity of APBMT transplant outcome registry. However, limited resources such as trained data managers and financial support impede the growth of our registry. To overcome this obstacle, we simplifying the report forms to and introduce EDC systems for promoting capturing of data.

These are the big challenges of APBMT, however, I remain optimistic and I believe great enthusiasm for hematopoietic stem cell transplantation and the passion of Asian peoples have undoubtedly contribute significantly to achieve this goal in the very near future.





Nursing (Keynote Lecture)

- Date/Time: November 2nd / 10:45-11:45
- Venue: Room 103

Speech Title:

Palliative care in acute healthcare settings

Speaker: Margaret O'Connor Affiliation: Monash University

Speech Summary

The traditional model of palliative care, has emphasized care for people facing the end of their life, mainly from cancer. Models have subsequently developed to address the needs of people dying from chronic illnesses, like heart failure; and multi-drug resistant non-communicable diseases, like tuberculosis.

The connection of palliative care expertise for people dying from acute illnesses like the failure of bone marrow transplant, has been slow to develop. There are many reasons for this, including that the clinical goal for acute illnesses like bone marrow transplant is focused on seeking a cure, right up to death.

This paper addresses the worldwide development of palliative care, highlighting the above emphases. Then the issues, challenges and ethical considerations in implementing palliative care alongside acute care are discussed, in order to promote the best care possible for those for whom treatment is ineffective.





Lunch Symposium 1~4

- Date/Time: November 2nd / 12:00-13:00
- Venue: 3F, 4F

Speech Title:

Update in advanced HL treatment post ISHL

Speaker: Dr Craig H. Moskowitz

Affiliation: Sylvester Comprehensive Cancer Center, University of Miami Health System, Florida, US

Speech Summary

The 11th International Symposium on Hodgkin Lymphoma just took place in Cologne, Germany in October. A number of clinical trials with HL patients were reported. Many of these studies combined conventional chemotherapy and targeted drugs such as the antibody-drug conjugate brentuximab vedotin (BV).

We are honored to have Dr. Craig H. Moskowitz, one of the world's leading experts on lymphoma and physician-in-chief for the Oncology Service Line at Sylvester Comprehensive Cancer Center, as our guest speaker to present the updates post ISHL.

One highlight we especially would like to present is the 5-year follow-up of the AETHERA phase III trial: **Study overview**

- Eligible cHL patients needed to be BV-naïve, must have received auto- HSCT before randomization and have been at high risk of relapse after auto-HSCT
- N = 329 patients randomized to receive BV (n = 165) or placebo (n=164)
- Intravenous BV (1.8 mg/kg) or placebo was administered once every three weeks for up to 16 cycles (start date 30–45 days post auto- HSCT)
- In the initial AETHERA trial, PFS by independent review was significantly improved in BV than placebo patients (HR = 0.57; 95%, CI 0.40-0.81; P = 0.0013).

Key findings

- · Median 5-year PFS: BV: not reached versus placebo: 15.8 months
- Five-year PFS rate: BV: 59% (95% CI, 51-66) versus 41% (95% CI, 33-49) [HR =0.521; 95% CI, 0.379-0.717]
- At the three-, four- and five-year follow-up, patients receiving BV presented with a reduction in PFS events of 30%, 28% and 30%, respectively, when compared to the placebo group
- In general, significantly fewer patients in the BV arm received further anti-cancer therapy (32%, n = 53) than those in the placebo arm (54%, n = 89; P < 0.0001).





Busulfan-containing conditioning regimen for autologous stem cell transplantation in patients with multiple myeloma

Speaker: Je-Jung Lee Affiliation: Chonnam National University Hwasun Hospital, Korea

Speech Summary

High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is recommended as standard consolidative therapy for transplant- eligible multiple myeloma (MM) patients. The most commonly used conditioning regimen for patients with MM is high-dose melphalan (200 mg/m2; MEL200). There are ongoing efforts to find a more effective conditioning regimen. Intravenous busulfan (BU) has been developed in 2003 and has characterized by low first pass-effect to the liver. It is expected to avoid fatal hepatotoxicity such as VOD. Korean multiple myeloma working party (KMMWP) has conducted a prospective, multicenter, phase 2 study evaluating the efficacy and toxicity of intravenous BU-MEL as a conditioning regimen for ASCT in patients with MM. A total of 99 patients with MM, enrolled between January 2013 and March 2016, received intravenous BU (9.62mg/kg) and MEL (140 mg/m) prior to ASCT. The overall response rate after ASCT was 94.0%, including 43.5% with a sCR/CR, 27.3% with VGPR, and 23.2% with PR. The frequent severe non-hematologic toxicity (grade 3-4) was infection (26.3%) and stomatitis (15.2%). Three patients (3.2%) developed VOD. No treatmentrelated mortality was observed. After median follow-up of 26.1 months, the median PFS was 27.2 months (range: 13.0-41.4) and median OS was not reached. In this study, conditioning regimen of intravenous BU-MEL was effective and tolerable. At this meeting, I will provide the Korean data of intravenous BU-MEL and BU-Thiotepa conditioning regimens for ASCT in patients with MM.





Cytomegalovirus infection in allogeneic hematopoietic stem cell transplantation

Speaker: Chieh-Lin Jerry Teng

Affiliation: Division of Hematology/Medical Oncology, Taichung Veterans General Hospital, Taiwan

Speech Summary

Invasive fungal infection is one of most severe complications in patients with hematological diseases. Acute leukemia, allogeneic hematopoietic stem cell transplantation (allo-HSCT), graft versus host disease (GVHD), steroid are risk factors for invasive fungal infection. Among all the pathogens of invasive fungal infection, aspergillosis is the most common one. The diagnosis of invasive aspergillosis (IA) infection is challenging. According to the evidence of IA infection, the diagnosis could be stratified into possible, probable, and proven diagnosis. Regarding the treatment, the best way to treat IA infection is to prevent it. Which patients need IA prophylaxis is debatable. Currently, patients with GVHD or previous history of IA could benefit from IA prophylaxis. When the IA infection occurs, the treatment should be diagnostic-driven. For patients with biological infection only, pre-emptive therapy should be considered. For patients who are not completely responsive to medical treatment, surgical intervention is mandatory.





Keynote Lecture 1: Microbiota in HSCT

- Date/Time: November 2nd / 13:00-13:50
- Venue: Room 201

Speech Title:

Gut microbiota injury in allogeneic hematopoietic stem cell transplantation

Speaker: Yusuke SHONO Affiliation: Memorial Sloan Kettering Cancer Center

Speech Summary

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered to be the strongest curative immunotherapy for various malignancies (primarily, but not limited to, hematologic malignancies). However, application of allo-HSCT is limited owing to its life-threatening major complications, such as graft-versus-host disease (GVHD), relapse and infections. Recent advances in large-scale DNA sequencing technology have facilitated rapid identification of the microorganisms that make up the microbiota and evaluation of their interactions with host immunity in various diseases, including cancer. This has resulted in renewed interest regarding the role of the intestinal flora in patients with hematopoietic malignancies who have received an allo-HSCT and in whether the microbiota affects clinical outcomes, including GVHD, relapse, infections and transplant-related mortality. In this presentation, we discuss the potential role of intestinal microbiota in these major complications after allo-HSCT, summarize clinical trials evaluating the microbiota in patients who have received allo-HSCT and discuss how further studies of the microbiota could inform the development of strategies that improve outcomes of allo-HSCT.





Nursing Symposium of GVHD issue

- Date/Time: November 2nd / 13:00-15:40
- Venue: Room 103

Speech Title:

Extracorporeal Photopheresis – Singapore General Hospital Experience

Speaker: Jessica Teo Mei Ling Affiliation: Singapore General Hospital

Speech Summary

Extracorporeal Photopheresis (ECP) consist of separation of Peripheral Blood Mononuclear cells(MNCs) by apheresis followed by exposing MNCs extracorporeal in a collection bag to UVA light with psoralen added into it and then reinfused to the patient.

ECP has been used to treat patients with cutaneous T cell lymphoma; graft vs host disease and a variety of immune-mediated inflammatory diseases.

Particular adverse event to look out for during ECP will be hypotension. Hence patient will be monitored closely during procedure for signs of hypotension. Hypotensive episodes are managed by temporarily stopping the procedure and administration of fluids. Transient fever has been noticed in some patients within 6 to 8 hours of reinfusion of the photoactivated MNCs. Post ECP patients are advise to avoid direct or indirect sunlight for 24hours following exposure to psoralen. If sunlight is inevitable, patients should shield their eyes and skin by concealing exposed skin or using sunscreen. Monitoring of temperature for the next 24hours are encouraged.

In Singapore General Hospital (SGH), ECP was started since 2008. Till date,

22 patients have been treated with ECP. Each patient will receive 12 sessions. For the first two weeks it will be twice a week. Thereafter it will be once weekly till patient's condition makes progress. Subsequently, physician will evaluate if there is a necessity to continue. In SGH we started ECP treatment using Cellex machine since the beginning and in May 2018 we started using UVA Pit system. Now both the systems are available for use. Physician will decide which system to use base on patient's diagnosis. In SGH, ECP has been vastly use for patient with GVHD skin; guts and liver. Only 1 patient with GVHD lung, eye and cutaneous T cell lymphoma each. Result of ECP is very affirmative.





The Nursing for Bone Marrow Transplantation Patients with Graftversus-host Disease

Speaker: Shujia Liu Affiliation: Peking University People's Hospital

Speech Summary

Graft-vs-host disease (GVHD) is a multisystem disease that arises as a complication of allogeneic hematopoietic stem cell transplant. It is due to recognition of the recipient's tissues by immune cells from the donor. Acute GVHD typically presents with the triad of rash, diarrhea, and hyperbilirubinemia. I will introduce the nursing for skin, intestines and liver respectively.





Graft-versus-Host Disease in Children after Hematopoietic Stem Cell Transplant: A Single-Center Experience in Taiwan

Speaker: Ying-Mei Liu Affiliation: Chang Gung University of Science and Technology and Linkou Chang Gung Memorial Hospital

Speech Summary

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many life-threatening cancers and non-malignant disorders. Each year, more than 1600 pediatric patients undergo allogeneic HSCT worldwide. Graft-versus-host disease (GvHD) is a significant cause of morbidity and mortality in pediatric patients who have undergone allogeneic HSCT. The emergence of more effective approaches for preventing and treating acute and chronic GvHD has resulted in reduced transplant mortality and relatively favorable long-term outcomes among pediatric HSCT recipients. Despite improved the survival rate for many life-threatening hematological and oncological diseases, pediatric HSCT remains a risky procedure. We conducted a single-center study of pediatric HSCT recipients and examined the outcomes related to chronic GvHD and quality of life. These outcomes were assessed after patients had received allogeneic HSCT for 1 year. Chronic GvHD was found to be the primary factor associated with poor posttransplant overall quality of life and emotional and social functioning. Understanding the symptom experiences of chronic GvHD in children is essential to guiding assessments and interventions for limiting symptom occurrence and distress.





Multidisciplinary approach to GVHD patients in Korea and nurses' challenges.

Speaker: Jin Young JUNG Affiliation: Seoul National University Hospital

Speech Summary

Despite improvements in prevention and treatment strategies, graft versus host disease (GVHD) remains a major concern to patients undergoing hematopoietic stem cell transplantation (HSCT) and caregivers.

GVHD has complex properties; (1) It is predictable but is difficult to distinguish from other conditions. (2) High grade of GVHD leads to high mortality. (3) There is no single solution for all situations. (4) It can last a life time.

Because of its properties, GVHD needs careful assessment, diagnosis and multidisciplinary intervention. I'll introduce some cases of multidisciplinary approaches to GVHD patients in Korea, and talk about challenges in GVHD nursing.





Prevention and care of Graft-versus-host disease in haploidentical stem cell transplantations for hematological malignancies in Taiwan

Speaker: Chang, Chiao-Fang Affiliation: National Taiwan University Hospital

Speech Summary

Since 1983, over 7000 HSCT were performed in Taiwan, and the number increased year by year. There are eighteen HSCT centers now in Taiwan, and 400 to 500 patients received HSCT every year. Anyway, to find a suitable donor is still a time-consuming work with only 60% successful rate, so that we are devoted to haploidentical stem cell transplantation (haplo-SCT) as in other parts of the world. There are two most noteworthy strategies of haplo- SCT, i.e. the Baltimore post-transplantation cyclophosphamide (PTCy) and the Beijing G-CSF primed bone marrow plus peripheral blood stem cells (GIAC-like, G-BM/PBSC). We aimed to compare these two approaches for hematological malignancies based on the Taiwan Blood and Marrow Transplantation Registry (TBMTR). From July to December 2017, 148 patients underwent haplo-SCT, either by PTCy (n = 61) or G-BM/PBSC (n = 87), were registered. All the PTCy-based grafts were PBSCs, while all the G- BM/PBSC received both BM and PBSC. Overall, 66% of PTCy-based group still received anti-thymoglobulin (ATG) for graft-versus-host-disease (GVHD) prophylaxis, and all recipients in the G-BM/PBSC-based group received ATG. Strategies to reduce the risk of developing GVHD are important, including nursing care from donor preparation to conditioning and GVHD prophylaxis. We share our results: Patients in the G-BM/PBSC group had a significantly higher 2-year survival rate (53% vs 35%, P=0.002) and a lower 1-year non- relapse mortality rate (17% vs 42%, P=0.020). Patients in the G-BM/PBSC group had a significantly higher incidence of grade II/IV acute GvHD (56% vs 25%, P<0.001), but the rates of grade III/IV acute GvHD (16% for the G-BM/PBSC and 13% for the PTCy, P=0.560) or extensive chronic GvHD (42% vs 21%, P=0.208) were similar.

Nursing care plays important roles in the care of HSCT patient and their family; especially in allo-HSCT, the donors need to be well prepared and cared. In addition, our responsibilities still include monitoring and evaluating GVHD and related complication, as well as safely and effectively administering a multidrug regimen to prevent or treat GVHD. Furthermore, providing patient and their family with education ensuring treatment adherence and effective self-management for expected side effects is essential, and some of them even require preparation for coping with worse quality of life resulting from GVHD and subsequent complications.

Key words:

haploidentical stem cell transplantation (haplo-SCT), Bone marrow (BM), Peripheral blood (PB), Post-transplant cyclophosphamide (PTCy), Graft- versus-host-disease (GVHD)





Nursing for GVHD patients after HCT in JAPAN

Speaker: Chika Yoshida, RN Affiliation: National Cancer Center Hospital

Speech Summary

More than 3,500 allogeneic hematopoietic cell transplantations are carried out annually in Japan. Approximately 1000 patients undergo transplantation from related donors, 1000 from unrelated bone marrow donors, and 1300 from cord blood donors, with an increasing number of haploidentical donors and unrelated peripheral blood stem cell donors. With the recent expanding application of allogeneic transplantation, appropriate cares to prevent complications and transplant-related mortality is important. Nurses play a major role in managing symptoms, supporting self-care and solving psychosocial problems in patients with GVHD.

Regarding symptom management, nurses should explain general ideas of prevention and treatment of GVHD before starting treatment, and should make efforts to share "common language" with patients and their families. In addition, efforts should be made to alleviate physical symptoms associated with damages from conditioning regimens so that patients can prepare for upcoming GVHD symptoms. Patient GVHD symptoms should be monitored carefully and necessary care should be provided based on the appropriate risk assessment of symptom appearance in individual patients. Every time the patient have a new or worsening symptom, the care method should be discussed among the multidisciplinary team and continuous care should be provided.

Regarding self-care support, nurses should explain self-care items necessary for transplantation treatment in advance of treatment, together with their importance and actual methods. Nurses should make sure that patients are routinely compliant with appropriate self-cares. Regarding psychosocial problems, early consultation with specialists such as psychiatrists and social workers is important. In the presentation, I will discuss several examples of GVHD nursing cares at all treatment stages.



Graft versus Host Disease

Speaker: Deepa Karmegam Affiliation: Apollo Cancer Centre, Chennai, India

Speech Summary

Graft-versus-host disease (GVHD) is an immune condition that occurs after transplant procedures when immune cells from the donor attack the recipient patient host's tissues; the disease is a side effect that is common after allogeneic bone marrow transplantation. In addition to bone marrow transplant procedures, GVHD can also occur after transplantation of solid organs that may contain immune system cells such as white blood cells or from a simple blood transfusion.

Tissues from healthy donors are checked prior to bone marrow transplant to see how closely matched they are to the host's own cells using HLA typing. When there is a close match in certain genetic markers, the risk of the disease is lower. The disease can range from mild to life-threatening in severity. There are two types of GVHD: acute GVHD and chronic GVHD.

The chance of developing GVHD is around 30%-40% when the donor and recipient are related and around 60%-80% when the donor and recipient are not related. The disease can affect many different organs in the body.

Graft versus host disease can affect the skin, gut and liver and needs to be treated with immunosuppressive medications like steroids and cytokine inhibitors. Patients need intensive nursing care and nutritional support. Numerous advances like post transplant cyclophosphamide and extracorporeal photopheresis have helped reduce the mortality due to GVHD. Graft versus host disease can be beneficial and provide immunotherapy against cancer cells in leukaemia and lymphoma patients.





Plenary Session 1: Topioc:Post-HSCT complications

- Date/Time: November 2nd / 15:30-16:40
- Venue: Room 201

Speech Title:

Cytomegalovirus infection in allogeneic hematopoietic stem cell transplantation

Speaker: Chieh-Lin Jerry Teng Affiliation: Division of Hematology/Medical Oncology, Taichung Veterans General Hospital, Taiwan

Speech Summary

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) not only improves survival times in patients with acute myeloid leukemia and acute lymphoid leukemia, but may also be the only curative therapy for very severe aplastic anemia. Nonetheless, the morbidity and mortality that are associated with allo-HSCT limit its clinical application and efficacy. Among all the complications by the allo-HSCT, Cytomegalovirus (CMV) reactivation is the major infectious complication between 30 and 100 days after transplantation. The clinical entity of CMV infection is unique. Reactivation of CMV appears in 60% of seropositive allo-HSCT recipients. Without appropriate treatment, asymptomatic CMV reactivation eventually progresses to symptomatic CMV diseases, which can result in death. Although the incidence of symptomatic CMV diseases has decreased significantly because of preemptive therapy, this life-threatening complication still develops in 30% of all allo-HSCT recipients. Use of antithymoglobulin, graft versus host disease, age, and haploidentical allo-HSCT are risks for CMV viremia in allo-HSCT recipients with certain risk factors. The most optimal prophylactic schedule for CMV viremia needs further investigation.





SOS and TMA after transplantation: Korean Reports

Speaker: Hee-Je Kim

Affiliation: Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Speech Summary

There have been numerous studies of patients complicated with vascular endothelial injury after allogeneic blood and marrow transplantation (Allo- BMT). Allo-BMT-associated non-infectious, vascular complications, including sinusoidal obstruction syndrome (SOS), thrombotic microangiopathy (TMA), are the major life-threatening issues associated with many related factors which leads to critical multi-organ failure and high rates of transplant-related mortality.

In real clinic, SOS and TMA after BMT were major contributing causes of death, which suggests that they should be prevented and/or treated at an early stage before it develops. We investigated our experiences using the available treatment options in efforts to find a successful therapeutic protocol that can enhance our understanding for the specific group patients. Further, we have tried to point out the reliable prediction factors for TMA in adult AML patients.



Fungal infection

Speaker: Artit Ungkanont, M.D. Affiliation: Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok Thailand

Speech Summary

Fungal infection remains one of the most important causes of morbidity and mortality during hematopoietic stem cell transplantation (HSCT), with reported mortality rate ranged from 29-90%. The most important risk factor of fungal infection is prolonged neutropenia while on broad spectrum antibiotics. HSCT patients have particular risk factors, namely acute graft versus host disease requiring medium to long term use of corticosteroids, and transplantation from alternate donor. Certain genetic predisposition, such as loss of function of polymorphism in dectin-1, leads to impaired immune response to Candida infection. Transplant centers in the tropical area, where weather is more suitable for fungus growth, certainly have more burden of fungal infection comparing to those in the colder weather. Clinical courses of fungal infection depend on the fungal classes which consist of yeasts, molds or dimorphic fungi. Candida spp are the most common yeast infection, usually involve gastrointestinal tract but can disseminate through mucosal barrier breakage. Invasive aspergillosis is usually found in patients with acute leukemia during induction and may have impact on transplantation later on. The practice of prophylactic antifungal therapy varies among places. Oral fluconazole has been routinely practiced. Posaconazole, found to demonstrate a survival advantage in AML patients, may have further role in HSCT in certain group of patients. However, timing of antifungal treatment must be planned to avoid interaction with drugs used during transplantation. Treatment of suspected fungal infection have shifted from empiric anti-fungal therapy to diagnostic-driven antifungal therapy. The benefit of empiric treatment has been marginal, since its initiation depended just on unresolved fever after broad spectrum antibiotic and may lead to over-treatment. Combination of diagnostic methods, such as high resolution CT scan, biomarkers such as glucan and galactomannan, together with nucleic acid testing has leaded to new decision model of treatment initiation.





- Date/Time: November 2nd / 15:30-16:40
- Venue: Room 102

Development of cellular therapy to enhance early hematopoietic/ immunological recovery after CBT

Speaker: Satoshi Takahashi Affiliation: Institute of Medical Science, University of Tokyo

Speech Summary

While overall survival after CBT is comparable to matched related or unrelated donor transplantation and quality of life of CB recipients are quite high because of low risk of chronic graft-versus-host disease, higher transplant related mortality especially during early phase after transplant is still observed. Delayed hematopoietic and immunological recovery, because of low cell dose and naive T cells in CB unit, are major reasons of early complications after CBT. In order to overcome the limitation of small cell dose, several techniques have been developed to expand CB-derived HSPCs ex vivo including HSPC-differentiation blockers, such as nicotinamide analog, copper chelator, inducing constitutive Notch signaling, or an aryl hydrocarbon receptor antagonist. However, all those techniques need CB cells cultivation at least 2 weeks which is potentially risk for induced transcriptional and epigenetic abnormalities, and takes higher cost. These facts led us to seek for a new strategy to overcome the cell dose barrier by using multiple CB units. In our series of mouse transplantation models utilizing a variety of mouse strains, we have tested whether multiple allogeneic HSPCs in combination can enhance hematopoietic recovery. Furthermore, using clinically relevant procedures, we successfully isolated a mixture of CD34+ HSPCs from multiple frozen CB units at one time regardless of HLA type disparities. These cells were transplantable into immune-deficient mice and contributed in a mixture to human hematopoiesis. We here show a proof that multiple allogeneic HSPCs in combination exhibit bridging effects, enabling their use not only in wider application of CBT. We believe those efforts contribute CBT as effective, safe and steady stem cell source for all patients who need allogeneic stem cell transplantation.





Emerging uses of cord blood in regenerative therapies of the brain

Speaker: Dr. Joanne Kurtzberg Affiliation: Duke University Medical Center

Speech Summary

Studies in children with selective inborn errors of metabolism have shown that cord blood cells, administered intravenously after myeloablative therapy, engraft in the brain. DUOC-01, a cord blood derived cellular therapy that promotes myelination, is undergoing testing to augment standard umbilical cord blood treatment in children with leukodystrophies. These observations led us to hypothesize that cord blood cells might also have efficacy treating patients with acquired brain injuries. Clinical studies to date have been performed to demonstrate safety and efficacy of intravenous infusions of autologous cord blood in babies with hypoxic ischemic encephalopathy, young children with cerebral palsy, congenital hydrocephalus and autism, and adults with acute ischemic stroke. Further development of these therapies using allogeneic cord blood products can provide access to these therapies for all.



MARCHAR

Speech Title:

Strategic umbilical cord blood cryopreservation for clinical therapeutic applications

Speaker: Kuo-Liang Yang Affiliation: Hualien Tzu Chi Hospital

Speech Summary

Hematopoietic stem cell transplantation has been widely employed for the treatment of malignant and nonmalignant blood disorders for some time. Attempts on using hematopoietic stem cell to treat neurological diseases or solid tumors have been tried occasionally in recent years. While autologous, related or unrelated bone marrow stem cells are considered as the first prioritized source of hematopoietic therapeutic stem cells, umbilical cord blood (UCB) is also accepted as an alternative cell source for patients needing bone marrow stem cell transplantation.

The advantages of UCB for hematopoietic stem cell transplantations are generally recognized as its speedy and timely availability and its less stringent requirement as far as histocompatibility between donor units and their respective recipients is the concern. Nevertheless, a number of disadvantages for UCB in stem cell transplantation are being reported, e.g., tardy in engraftment and delay course in platelet and neutrophil reconstitutions. While several factors may contribute to the above-mentioned weakness of UBC in hematopoietic stem cell transplantation, adequate total nucleated cell (TNC) count for a given recipient's body weight is probably one of the major criteria should be addressed in terms of UCB processing and preservation.

The aim of this presentation is to focus on how to bank UCB in order to increase qualified UCB for clinical application in hematopoietic stem cell transplantation.





Satellite Symposium 1 (Sponsored by Amgen)

- Date/Time: November 2nd / 16:40-17:30
- Venue: Room 201

Speech Title:

Optimal treatment for post-transplantation relapse in multiple myeloma

Speaker: Jin Seok Kim

Affiliation: Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital, 50-1 Yonsei-ro, Seodaemun-gu, Seoul

Speech Summary

Although overall survival (OS) has been markedly improved in transplantation eligible younger multiple myeloma (MM) patients after the introduction of bortezomib-based induction therapy and autologous stem cell transplantation (ASCT), most patients eventually experience a relapse after ASCT. Indeed, with the widely use of novel agents for patients with relapse or refractory MM, including proteasome inhibitors (PIs) such as bortezomib, ixazomib and carfilzomib, the immunomodulatory drugs (IMIDs), such as thalidomide, lenalidomide and pomalidomide, and the monoclonal antibodies, such as elotuzumab and daratumumab, OS has been markedly improved.

For the selecting an appropriate regimen for relapsed MM patients after ASCT, we have to consider many factors related with patients (including patient access and socioeconomics/healthcare coverage), underlying disease and previous treatment related factors. Patients who relapse less than 12 months after ASCT are considered as high-risk group even if evaluation by FISH previously classified their disease as standard risk. Patients with aggressive relapse and patients with high risk features may need multi-agent combination therapies (triplet therapy). Because bortezomib-based regimens are usually used for induction therapy in transplantation eligible MM patients, lenalidomide-based regimens such as carfilzomib+lenalidomide-dexamethasone (Rd), ixazomib-Rd, elotuzumab- Rd or daratumumab-Rd are commonly recommended in relapsed MM patients after ASCT. Lenalidomide maintenance therapy after ASCT has been approved in many countries according to the OS benefit from phase 3 clinical trials. Therefore, different strategies should be applied for the relapsed patients on lenalidomide maintenance after ASCT are usually treated with pomalidomide-based regimens or PI (bortezomib or carfilzomib) ± daratumumab-based regimens.

Although three drug regimens including PI and IMIDs should be considered as a second line therapy after ASCT, two drug regimens also can be considered especially in the low risk patients with significant comorbidities.





- Date/Time: November 2nd / 16:40-17:30
- Venue: Room 102

Update 2018 on Treatment Strategy for Indolent Lymphoma

Speaker: Mathias J. Rummel

Affiliation: Department of Haematology and Oncology, Hospital of the Justus-Liebig University, Giessen, Germany

Speech Summary

The StiL conducted several trials to optimize treatment strategies for patients (pts) with follicular/indolent lymphomas (FL, iNHL). The StiL NHL1-2003, multicenter, randomized, phase III compared Bendamustine plus Rituximab (B-R) and CHOP-R as first-line treatment in pts with indolent or mantle cell lymphoma. The study demonstrated a significantly prolonged progression- free survival (PFS) in the B-R group compared to the CHOP-R group, with a median PFS of 69 vs. 31 months, respectively. Median TTNT was significantly prolonged with B-R compared with CHOP-R (HR 0.52, p < 0.001).

In another randomized multicenter phase 3 study in first-line FL, StiL NHL7- 2008 MAINTAIN, the role of Rituximab maintenance (R-maintenance) following B-R was investigated: 4 versus 2 years of R-maintenance following B-R. Rationale: R-maintenance for 2 years is part of a standard treatment approach for previously untreated FL. In this study efficacy and safety of 4 versus 2 years of R-maintenance following treatment with B-R was evaluated. Results: A total of 612 pts with FL were enrolled. 555 pts were evaluable for response, and 497 responded to B-R induction. 350 pts were randomized to 2-years of R-maintenance. Median PFS appeared superior with 4- years versus 2-years of R-maintenance (HR 0.64). There was no difference in OS between groups. A historical comparison for PFS between responding patients given 2 years of R-maintenance in this MAINTAIN trial and subjects from the former StiL NHL1-2003 study (B-R versus CHOP-R) who received B-R only appeared to favor R-maintenance (HR 0.78).

Conclusions: The observed HR appear to favor 2 years of R-maintenance versus observation only following induction treatment with B-R. At the time of this analysis no definitive evidence supporting the benefit of a prolonged R- maintenance for 4 years was demonstrated. Updated analysis will be presented at the APBMT meeting.

Within this presentation a review of treatment strategies will be provided including recent results of international randomized studies such as an update of the PRIMA trial, the StiL trials, the GALLIUM trial (Obinutuzumab versus Rituximab combinations) and the RELEVANCE trial (Rsquare, Lenalidomide plus Rituximab versus Rituximab-chemotherapy).





- Date/Time: November 2nd / 16:40-17:30
- Venue: Room 103

Acute Myeloid Leukemia: Expectations in the Near Future

Speaker: Prof Noriko Usui Affiliation: The Jikei University School of Medicine

Speech Summary

The AML treatment landscape has changed considerably in the past few years with the introduction of novel agents such as midostaurin and gemtuzumab ozogamicin that has significantly improved patient outcomes in the front line setting. However these improvements were mainly seen in combination with chemotherapy for patients that were eligible for intensive chemotherapy and furthermore within a select group of patients that exhibit certain biomarkers. The same cannot be said for elderly patients or patients with co morbidities that are not eligible for the traditional 7+3 chemo induction therapy. This patients have been traditionally treated using lesser intensity agents such as HMAs and low dose cytarabine with an estimated median survival of anywhere between 4-10 months. These groups of patients are also deemed not suitable for transplant due to the high mortality rates encountered during such procedures. The introduction of other newer targeted molecular drugs (etc quizartinib, gilteritinib, enasidenib, venetoclax) has brought about much needed improvement in outcomes for both the chemo eligible and ineligible patients across therapy lines. These targeted drugs work via different pathways such as the JAK-Stat, MEK/MAPK, PI3K, mutated isocitrate dehydrogenase enzymes and the BCL-2 family. They are currently being studied as either monotherapy and in combination with other drugs. In summary, we expect further changes to the current treatment paradigm as more and more therapies are being sent through clinical trials and into the clinics.





- Date/Time: November 3rd / 08:10-09:00
- Venue: Room 201

Cooperation of Novel therapy and transplantation in treating hematological malignancies

Speaker: Ali Bazarbachi, MD, PhD Affiliation: American University of Beirut

Speech Summary

Disease relapse remains the first cause of mortality of hematological malignancies after allogeneic hematopoietic stem cell transplantation (allo- HCT). The risk of recurrence is elevated in acute myeloid leukemia (AML) patients with high-risk cytogenetic or molecular abnormalities, as well as when allo-HCT is performed in patients with refractory hematological malignancies or with persistent molecular or radiological (PET-CT scan) residual disease. For high risk AML and myelodysplasia (MDS), a post transplant maintenance strategy is possible, using hypomethylating agents or tyrosine kinase inhibitors (TKI) anti-FLT3 when the target is present. For Philadelphia positive acute lymphoblastic leukemia (ALL), there is a consensus for the use of TKI anti BCR-ABL as post transplant maintenance. In multiple myeloma, maintenance lenalidomide after autologous HCT prolongs survival. In lymphoma patients, maintenance rituximab after autologous transplant is promising in follicular and mantle cell lymphoma.





- Date/Time: November 3rd / 09:00-10:10
- Venue: Room 201

Graft-versus-Host Disease: biological insights from preclinical and clinical studies

Speaker: He Huang

Affiliation: 1.Bone Marrow Transplantation Center, the First Affiliated Hospital, Zhejiang University School of Medicine; 2.Institute of Hematology, Zhejiang University;3. Laboratory Of Stem Cell and Immunotherapy Engineering, Zhejiang Province

Speech Summary

Graft versus host disease (GVHD) remains frequent and a significant obstacle to allo-HSCT. Intestinal stem cells (ISCs) and their niche Paneth cells could be primary targets in Gastrointestinal (GI) aGVHD. Innate lymphoid cells (ILCs) play key roles in the biology of GI aGVHD. Recently, multiple populations of ILCs that generate IFN- γ , IL-5 and IL-13, and IL-17 and/or IL-22 have been described. We found that IL-22+ $\gamma\delta$ T17 was the core of cellular crosstalk networks in intestinal aGVHD. Intestinal $\gamma\delta$ T cells, which had a higher expression of IL-17 family and tight-junction genes in aGVHD, reduced at early phase and then increased at later stage of murine aGVHD. Intestinal IL-22+ $\gamma\delta$ T17 cells kept reducing at both early and later stage in aGVHD compared with non-aGVHD group. After improving the ratio of IL-22 group compared with normal aGVHD group. IL- 22+ $\gamma\delta$ T17 could also secret GM-CSF to recruit MDSCs, which could suppress Immune activation and attenuate aGVHD. MDSCs changed in consistent with IL-22+ $\gamma\delta$ T17 cells and ILC3 decreased during aGVHD

To date, no consensus has been reached regarding the optimal salvage treatment for SR-aGVHD. We performed a novel approach to treat severe SR-aGVHD with the combination of basiliximab and etanercept. At day 28, ORR (CR+PR) to treatment was 90.8% including 75.4% CRs. The incidences of CR per organ were 100%, 73.8%, and 79.7% for skin, liver, and gut involvement, respectively. Our data suggest that the combination of basiliximab and etanercept may constitute a promising new treatment option for SR-aGVHD,

Efficacy of histone deacetylate (HDAC) inhibitors and kinase inhibitiors (SYK

and JAK1/2 inhibitiors) in GVHD was proved by multiple publications of independent groups. Further studies in larger multicenter cohorts of patients are needed to identify the most effective and least toxic regimens.





- Date/Time: November 3rd / 09:00-10:10
- Venue: Room 102

Immunotherapy in Hodgkin lymphoma

Speaker: Alex F. Herrera, MD Affiliation: City of Hope National Medical Center

Speech Summary

Genetic alterations of the PD-L1/PD-L2 locus on chromosome 9p24.1 are a defining biological feature of classical Hodgkin lymphoma (HL). The resulting PD-L1 expression on Hodgkin Reed-Sternberg cells as well as the PD-L1 expressed in the HL microenvironment result in an ineffective host anti-tumor immune response and make HL a ripe target for PD-1 blockade. Anti-PD-1 antibody monotherapy has been effective and well-tolerated in patients with relapsed or refractory (rel/ref) HL, with the majority of patients experiencing an objective response (about 2/3 of patients) and a median duration of response of 16.6 months in the study with the longest follow-up. Based on these data, nivolumab and pembrolizumab were FDA-approved for the treatment of advanced rel/ref HL. Evidence has emerged that patients with HL benefit from continued PD-1 blockade beyond disease progression according to traditionally-defined response criteria and that the addition of or switch to chemotherapy after anti-PD-1 antibody failure can potentially re- induce clinical response. Subsequent studies have evaluated novel anti-PD-1 based combination regimens as well as the use of anti-PD-1 antibody therapy earlier in the course of a HL patient's therapy, including first salvage therapy for rel/ref disease (e.g. nivolumab plus brentuximab vedotin) and even first line treatment (e.g. nivolumab added to AVD chemotherapy). The current role of PD-1 blockade in HL is as monotherapy in patients with advanced rel/ref disease, but the results of ongoing studies and the evolving treatment landscape in HL will determine the role of PD-1 blockade in the future.

Other novel immunotherapies (e.g. bispecific antibodies, CAR T-cells) that are currently under study in HL will also be discussed.





Non-gene modified cellular immunotherapy in multiple myeloma

Speaker: Je-Jung Lee Affiliation: Chonnam National University Hwasun Hospital, Korea

Speech Summary

Multiple myeloma (MM) is characterized by generalized immune dysregulation, such as functional hypogammaglobulinemia and defects in T cell immunity, natural killer (NK) cell function, and antigenpresenting capacities of dendritic cells (DCs), resulting in susceptibility to infection as well as tumor progression. Additionally, there is a rise in immune suppressor cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), in the bone marrow microenvironment. The impairment in the function of several immune cells favors the tumor escape from immune surveillance and contributes to induce myeloma cell growth and survival. Recently, immunotherapy has emerged as a promising treatment for MM, and monoclonal antibodies, vaccines, and genetically engineered T cells may represent a new era for the treatment of myeloma. DC vaccination and NK cell therapy are very safe strategies that have shown some efficacy in a subset of MM patients and may become a crucial part of MM treatment when combined with immunomodulatory drugs, immune check-point blockades, or proteasome inhibitors. Genetically engineered T cells, such as chimeric antigen receptor (CAR) T cells or T cell receptor (TCR)-engineered T cells, have also shown encouraging results, despite of worries in terms of toxicities, in recent clinical studies of patients with MM. In this presentation, I will discuss the recent progresses of cellular immunotherapeutic approaches with vaccine using DCs and NK cells in management of MM.





Autologous Haematopoietic Stem Cell Transplant as Immunotherapy for Severe Autoimmune Diseases

Speaker: David D Ma

Affiliation : Department of Haematology and BM Transplant, St Vincent's Hospital Sydney and St Vincent Clinical School, Faculty of Medical, UNSW Sydney, Australia

Speech Summary

Severe autoimmune diseases (AID) remain debilitating and potentially fatal conditions in spite of recent development of biological therapies. As the safety of haematopoietic stem cell transplant (HSCT) continues to improve, it potentially offers a single treatment that may provide sustained disease control resulting in improved quality of life and survival by elimination of the autoreactive immune cell clones and the recovery of homeostatic immunity. Modern biological therapies can cause significant side-effects and can be more costly in the long term compared to the upfront, one off cost of HSCT. Our transplant centre has consistently contributed over the last two decades to the international effort in the research field. Data from transplant registries and clinical trials has provided mounting evidence on the type of AIDs likely to benefit from HSCT and the preferred transplant conditioning regimens. Establishment of centres of excellence with well-trained staff, collaboration among medical specialties, benchmarking by independent regulatory bodies and government support are the key elements for maintainable success. As countries become more familiar with the requirements and process of HSCT, AHSCT for AID will have a place in the treatment of patients with severe and selected type of AIDs. Supporting evidence for these issues will be presented.





TACT Joint Symposium 1: Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities

- Date/Time: November 3rd / 09:00-10:00
- Venue: Room 103

Speech Title:

Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities.

Speaker: Jacques Galipeau, MD Affiliation: University of Wisconsin in Madison

Speech Summary

Mesenchymal stromal cells (MSCs) have been the subject of clinical trials for more than a generation, and the outcomes of advanced clinical trials have fallen short of expectations raised by encouraging preclinical animal data in a wide array of disease models. In this presentation, important biological and pharmacological disparities in murine pre-clinical research and human translational studies are highlighted, and analyses of clinical trial failures and recent successes provide a rational pathway to MSC regulatory approval and deployment for disorders with unmet medical needs.





Plenary Session 5: Immunotherapy and Cell therapy_gene-modified

- Date/Time: November 3rd / 10:30-11:50
- Venue: Room 201

Speech Title:

CAR-T TREATMENT FOR REFRACTORY RELAPSED B-CELL ALL IN CHINA

Speaker: Pei-hua Lu, M.D. Affiliation: Lu Daopei Hospital in China

Speech Summary

Introduction:

After a long journey of development, the technology of CAR-T immunotherapy is becoming more and more mature. Up to August 2018, the registered CAR-T clinical trials worldwide indicated that USA and China are so far leading in this field. Sixteen CAR-T companies have filed IND for clinical trials in China. Since 2015 we, Lu Daopei Hospital, have collaborated with several CAR-T companies and have been doing CD19 CAR-T clinical trials for refractory and relapsed B cell ALL patients. So far we have completed more than 400 cases in our single institute with excellent results. Here we mainly select two CAR-T clinical trials to report.

Methods:

Patients' T cells were transduced with a lentivirus vector encoding anti-CD19- CD3ζ either with a CD28 or a 4-1BB co-stimulatory domain. All patients received a conditioning regimen of IV fludarabine (25 mg/m2/day) and cyclophosphamide (250 mg/m2/day) for 3 days before a single infusion of CAR-T cells with a median dose of 1x105 (0.1-10x105) cells/kg (CAR-T cells were provided from Beijing Immunochina Medical Science & Technology Co., Ltd; Hebei Senlang Biotechnology Co., Ltd).

Results:

On day 30 evaluation after CAR-T treatment , 91.6% patients achieved complete remission (CR) or CR with incomplete count recovery (CRi), and >85% achieved minimal residual disease (MRD)-negative CR. One-year overall survival (OS) was 76.5% and relapse-free survival (RFS) was 62.6%. Grade 0-II cytokine release syndrome (CRS) incidence was 82%, and grade III-IV, 16%. Patients with high-risk features such as CNS leukemia, high leukemia burden , CML transformed, or relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT) also were benefited from CAR-T treatment. After CAR-T treatment, majority patients underwent subsequent allo-HSCT in a median time of 2 months. The 1-year OS/RFS of the CAR-T bridged to allo-HSCT group was better than that of the non- transplant group (OS 87.5% vs. 63.4%, p=0.013; RFS 87.4% vs. 7.5%, p=0.001). While the OS of CR patients was significantly better than that of CRi pts (100% vs. 73.4%, p=0.038), the RFS was not yet statistically significant (75% vs. 56.4%, p=0.25). The median recurrence time in the group without additional allo-HCST was 100 days. Our two year data indicated that the RFS in the MRD (-) CR group was much better the MRD (+) CR group.

Conclusion:


High CR rate was achieved from CAR-T treatment for R/R B-ALL patients even in post allo-HSCT relapsed group. CRS was manageable. Overall, RFS was superior for patients bridging to allo-HSCT after CAR-T treatment than for those receiving CAR-T- treatment only.

Speech Title:

Hematopoietic stem cell based gene therapy for blood diseases.

Speaker: Alok Srivastava Affiliation: Christian Medical College & Centre for Stem Cell Research, Vellore, India

Speech Summary

Gene corrected autologous hematopoietic stem cell transplantation (HSCT) has been used to successfully treat patients with immune deficiency disorders for nearly two decades. A lentiviral vector based gene replacement product has recently been licensed in Europe. In recent years, through a similar approach, there has been remarkable success in the treatment of major hemoglobin disorders a major public health problem in the Asia Pacific region. Successful gene transfer through lenti or retro viral vectors by ex-vivo transduction of autologous HSCs resulting in expression of 4-8 G/dl transgene hemoglobin have been achieved in the treatment of patients with thalassemia major and sickle cell disease. These early successes have led to the initiation of Phase 3 studies which, if successful, can lead to the registration of the candidate product. Another major genetic disorder that is a challenge to manage in developing countries is hemophilia. Adeno associated vector (AAV) based gene therapy has now been shown to be successful for this condition in Phase 1/2 trials leading to initiation of Phase 3 trials. AAV based gene therapy can be limited by pre-existing immunity in >50% of patients and may not suitable for very young children. These gene therapies are likely to be extremely expensive given early indications of costs from currently approved products. It is important therefore that similar products be developed in an alternative model to allow access at much lower costs. We are developing a lentiviral vector mediated gene transfer to hematopoietic stem cells approach for the major hemoglobin disorders as well hemophilia A. Details are provided in abstracts of two presentations at this meeting. Pre-clinical data show significant expression of the relevant protein. The challenge is production of high quality GMP vectors for the clinical trial which is being addressed by appropriate collaborations and development of local expertise.





TACT Joint Symposium 2: Allogeneic Mesenchymal Stem Cells Therapy: feasibility using HLA-matched donor

- Date/Time: November 3rd / 10:15-10:50
- Venue: Room 103

Speech Title:

Allogeneic Mesenchymal Stem Cells Therapy: feasibility using HLA-matched donor?

Speaker: Yao-Chang Chen M.D. Affiliation: National Taiwan University Hospital

Speech Summary

Mesenchymal Stem Cells (MSCs) are considered immunoprivileged because they express HLA-Class I but not Class II antigens. Consequently, HLA- matching is considered unnecessarily in clinical applications using allogeneic MSCs, although there have been very few studies to compare the results of matched vs mismatched major histocompatibility complex (MHC) expression. However, recent human clinical studies often showed that results using allogeneic MSCs seemed not as well as using autologous MSCs. Meanwhile, substantial evidence now exist to prove with multiple studies documenting specific cellular & humoral immunoresponse against donor follow administration of these cells. Industrial allo-MSC product failure analysis also suggested that the role of immunogenesity cannot be neglected.

We propose that the immunoprivilege property of MSCs should be re- evaluated, while the feasibility using HLA-matched allogeneic MSCs should be considered.





TACT Joint Symposium 3: Experience of clinical trial of cell therapy

- Date/Time: November 3rd / 10:50-11:25
- Venue: Room 103

Speech Title:

Current Role of Endothelial Progenitor Cells for Patients with End-Stage Ischemic Cardiovascular Disease

Speaker: Fan-Yen Lee

Affiliation: Kaohsiung Chang Gung Memorial Hospital, Chang Gung University, Kaohsiung, Taiwan

Speech Summary

The population of patients with symptomatic chronic ischemic cardiac and vascular diseases is on the rise. Many of those patients remain severely symptomatic despite exhausting all conventional medical therapies. Mounting evidences suggest that microvascular insufficiency plays a noticeable role in the pathophysiology of ischemia. The science of therapeutic angiogenesis has been making much progress, and continuously evolving for over two decades.

Pre-clinical studies have provided evidence for safety and the potential therapeutic benefit of freshly isolated CD34+ cells. Clinical trials involving over several hundreds of patients have been completed providing data supporting the feasibility, safety and efficacy of CD34+ cell therapy for the treatment of refractory advanced cardiovascular disease. We will also share our experience with a prospective randomized double-blinded phase I clinical trial, using circulation-derived autologous CD 34 + cells in treating patients with end-stage diffuse coronary artery disease. We define end-stage diffuse coronary artery disease as diffusely obstructive coronary artery disease, which is poorly responsive to optimal medication and also unsuitable for either percutaneous coronary artery intervention or coronary artery bypass grafting.

The goal of ischemic tissue repair appears within reach and is entering a pivotal point of clinical trial for patients with critical ischemic cardiovascular diseases.

In order to take the full advantage of this novel therapeutic strategy, the advancement of CD34+ cell based treatment for ischemic tissue repair will require an ongoing collaboration among clinicians, scientists, regulators, industries, payors and patients. This will be a new hope for patients who are disabled with their condition and have exhausted all conventional medical and surgical therapies





Lunch Symposium 5~8

- Date/Time: November 3rd/ 12:00-13:00
- Venue: 3F, 4F

Speech Title:

Treatment Considerations in Relapsed and Refractory Myeloma

Speaker: Graham Jackson Affiliation: Freeman Hospital, The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Speech Summary

In this lecture we will demonstrate that treatments for multiple myeloma are improving all of the time and also discuss several important trends that are emerging.

Firstly, continuous therapy is important and prolongs PFS and OS. Secondly the duration of therapy in the real world setting can differ from trial data and this will undoubtedly impact on the outcomes of therapy. Thirdly triplet therapies are superior to doublets and some triplets can overcome the adverse impact of high risk cytogenetics. Finally differing treatments can have differing side effect profiles and myeloma physicians need to be aware of the impact of treatment on their patients.





Deferasirox for the treatment of iron overload after allogeneic hematopoietic cell transplantation

Speaker: Tachibana Takayoshi, M.D., Ph.D Affiliation: Kanagawa Cancer Center

Speech Summary

The aim of this study was to assess the safety and optimal dose of deferasirox for the treatment of iron overload after allogeneic hematopoietic cell transplantation (HCT). The primary endpoint was the maximum tolerated dose of deferasirox that was determined by the intrapatient dose escalation methods. A total of 16 patients with post-HCT iron overload were enrolled in the study. After excluding one case of early relapse, 15 remained evaluable. Their median age was 42 years (range 22-68). Median time from HCT to deferasirox administration was 9 months (range 6-84). Deferasirox was started at a dose of 5 mg/kg, and the dose was increased to 7.5 and 10 mg/kg every 4 weeks unless there were no grade \geq 2 of adverse events. Achievement rates of planned medication were 80% in 5 mg/kg (12 of 15), 73% in 7.5 mg/kg (11 of 15), and 60% in 10 mg/kg (9 of 15), respectively. The reasons for discontinuation of the drug were grade 2 of adverse events (n = 4), late relapse (n = 1), and selfcessation (n = 1). None of the patients developed grade \geq 3 of adverse events or exacerbation of GVHD. Among 11 evaluable cases, mean value of ferritin decreased from 1560 ng/ml pre-treatment to 1285 ng/ml post-treatment. These data suggested that 10 mg/kg of deferasirox may be maximum tolerated dose when given after HCT. Our dose escalating method of deferasirox is useful to identify the optimal dosage of the drug in each patient.





How do novel agents impact patient outcomes in mantle cell lymphoma?

Speaker: KWONG, Yok-Lam Affiliation: Chief of the Division of Haematology, Oncology and Bone Marrow Transplantation, Department of Medicine, University of Hong Kong

Speech Summary

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma with typically aggressive behavior. The genetic signature is the chromosomal translocation t(11;14)(q13;q32) resulting in overexpression of cyclin D1. While there is no standard of care for MCL, aggressive chemo-immunotherapy regimens containing rituximab and cytarabine followed by consolidation with autologous stem cell transplantation is the most utilized approach in young, fit patients and chemo-immunotherapy is most commonly used in older patients. Despite the improvement in response durations with currently available therapies, patients will inevitably relapse. In addition to improvements in immunochemotherapy, a succession of new molecular targets and corresponding drugs has revolutionized MCL therapy. The discovery of a novel agent which disrupts external signaling pathways through inhibition of Bruton's tyrosine kinase has been a particularly exciting breakthrough. The best way to sequence and combine these agents with existing regimens and how to overcome the problem of drug resistance represent new challenges in this rapidly developing field.





- Date/Time: November 3rd/ 13:00-15:30
- Venue: Room 102

Importance of Outcome Data Sharing in Asia-Pacific Region, WBMT 5th Work Shop Report

Speaker: Yoshiko Atsuta Affiliation: Japanese Data Center for Hematopoietic Cell Transplantation Registry Committee, APBMT

Speech Summary

Collection and analysis of information on diseases and post-transplant courses of hematopoietic cell transplant (HCT) recipients have played important roles to the improvement of therapeutic outcome of HCT globally. The speech summarizes the discussion at the Fifth Work Shop of the Worldwide Network for Blood and Marrow Transplantation held in September 2018, in Beijing.

In 2006, the Asia-Pacific Blood and Marrow Transplantation Group (APBMT) established its registry and launched transplant activity survey from 2007. Since then, the APBMT collected data annually and 138,165 HSCT data from 624 transplant teams in 18 countries/regions were accumulated from 2007 to 2017. The data is delivered in different way from each country/region: via 1) national registry, 2) contact person from a major transplant center, or 3) each hospital/center individually. APBMT data center gathers all data and analyze it.

Regarding HCT outcome data collection, the APBMT introduced Least Minimum Data (LMD) for participating countries/regions. Data collection status in recent years will be reported.

Characteristics of countries/regions which participate the APBMT are diverse in many aspects including activities of HCT, regulatory issues for medicine and medical research, economy and social infrastructure. In some countries/regions, national HCT outcome registries are active and perform important roles. The APBMT Outcome Registry basically encourage establishment of national registry in each of participating countries/regions.

In this regard, the APBMT Outcome Registry perform in part as data sharing style registry. The APBMT Data Center is currently building an electric data capture system for the LMD items based on the results of a survey in participating countries/regions. Development of this system will benefit the APBMT and some countries/regions directly by being able to provide their national data.



Transplant Programs in Indonesia: Report from dr. Kariadi Hospital Semarang

Speaker : Damai Santosa Affiliation : Dr. Kariadi Hospital/ Diponegoro University

Speech Summary

There are 3 transplant center in Indonesia, incluce: Dharmais National Cancer Center, Dr. Kariadi Hospital, Dr. Sutomo Hospital.

There are new 10 protective room at dr. Kariadi Hospitall. We have 30 nurses, which trained for bone marrow transplant services. The numbers of HSCT at dr. Kariadi Hospital in 2016- 2017 are nine patients. Type of HSCT are autologous and allogeneic transplant, donor source from sibling, disease indication such as AML, MM, Lymphoma. There is not all conditioning regiment available. BMT was covered by National Health Insurance.





Transplant Programs in Emerging Countries: Report from MYANMAR

Speaker: Aye Aye Gyi MBBS MMedSc DrMedSc FRCP Professor & Head, Department of Clinical Haematology Affiliation: North Okkalapa General and Teaching Hospital University of Medicine 2, Yangon, MYANMAR

Speech Summary

Under minimal resources, Myanmar started the first autologous HSCT for myeloma in 2014 at the North Okkalapa General and Teaching Hospital (NOGTH), which is currently the main center while the second center is under development at the Yangon General Hospital. The government is committed to support transplant program and capacity building although health budget is insufficient to cover all the requirements. Lack of health insurance system and limited funding are the major barrier for transplant activities. In 2016, only 5 transplant cases performed, all were autologous transplant for multiple myeloma. In 2017, allogeneic transplantation was started and clean room facilities were installed. Having only a few cases, all activities could be reported under the National Registry. There are no National Marrow Donor Program in Myanmar yet. National Blood Center of Myanmar has been trying to establish the program in near future and has started initiatives for HLA typing. Any support for the national marrow donor program would be most welcomed.

There are many limitations in promoting HSCT in Myanmar, in particular, shortage of trained person, large gap in capacity building, inadequate drug supply especially for resistant bacteria, fungi and CMV, lack of advanced laboratory facilities like HLA typing, Chimerism studies, diagnosis and monitoring of fungal and viral infections, MRD studies, etc.

However, National Collaboration was established with the centers like Singapore International Foundation and Health Authority of Singapore for transfusion workshops and transplant initiatives as well as with other centres like Siriraj Hospital, Thailand, St. Vincent's Hospital, Sydney, Australia, Christian Medical College, Vellore and Tata Memorial Centre, Mumbai, India, etc. The poster describing these collaborative activities in Myanmar with help from neighboring regions was awarded for the "Global Capacity Building Showcase" session at the 59th Annual Meeting of American Society of Hematology in 2017 indicating that limitations could be partly overcome by helping hands from the centers in the Asia-Pacific region despite many constraints still exist.



Transplant Program in Malaysia

Speaker: Bee ping Chong Affiliation: University of Malaya

Speech Summary

Malaysia started its bone marrow/haematopoietic stem cell transplant (HSCT) program in 1987 in University of Malaya Medical Centre by the paediatric department. The first adult HSCT was done in 1993 at the same centre. There are currently 13 hospitals doing HSCT and a total of 3626 transplantation (1978 allogeneic and 1648 autologous) done. The survival has improved over the years with patients underwent transplantation from 2010 to 2015 had the best survival compared to cases done before this period. The main issues of HSCT in Malaysia are: lack of donors, inefficient laboratory supports and financial constraint. Matched unrelated donors can overcome the shortage of suitable donors, but it is limited by small local registry and expensive procurement from foreign registries. Haploidentical family donors has huge potential but collaboration with centers in the other countries is needed for skill and knowledge transfer.





- Date/Time: November 3rd/ 15:35-16:25
- Venue: Room 201

CAR T-cell Therapy for Lymphoma

Speaker: Jeremy S. Abramson, MD, MMSc Affiliation: Massachusetts General Hospital, Harvard Medical School

Speech Summary

CAR T-cells promise to transform the management of B-cell NHL. Essential components of chimeric antigen receptors (CAR) include a single chain variable region (scFv) targeting tumor antigen, a costimulation domain, and an intracellular signaling domain. The CAR is inserted into the patient's T-cell, most commonly using a lentiviral or retroviral vector. Currently three major CAR T-cells are in advanced development for B-cell NHL: axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. All three products have an identical scFv targeting CD19, and intracellular signaling via CD3ζ. They differ, however, in their co-stimulation domains with axicabtagene employing CD28 and the other two using 4-1BB. This difference contributes to distinctions in expansion kinetics as well as timing and severity of toxicities. The products also differ in manufacturing process and dose. All three CAR T- cell products have shown remarkable clinical activity in chemotherapy- refractory DLBCL. Response rates have ranged from 52-82%, with durable remissions beyond 6 months observed in approximately 40% of subjects who have previously constituted an unmet medical need. Toxicities of these products include cytopenias, which may be prolonged, and hypogammaglobulinemia, which may require IVIG replacement. Unique toxicities of this cellular immunotherapy include a cytokine release syndrome (CRS), which may be severe and life threatening, as well as a neurologic toxicity most commonly characterized by an encephalopathy syndrome (CRES). Incidence, timing and severity of these toxicities differ across the three major CAR T-cell products, but are manageable and reversible in the large majority of cases. Ongoing areas of investigation include use of anti- CD19 CAR T-cells in additional NHL histologies, understanding mechanisms of resistance, biomarkers of response and toxicity, and optimization of the CAR construct and combination strategies.





- Date/Time: November 3rd/ 16:25-17:15
- Venue: Room 102

Overview of Immune Checkpoint Inhibitors in Hematologic Malignancies

Speaker: Chien-Chin Lin, M.D. Affiliation: National Taiwan University Hospital

Speech Summary

During the past few years, we have witnessed significant progress of cancer immunotherapies that activate patients' immune systems against tumor cells. Immune-checkpoint inhibitors block the interaction between checkpoint ligands and their cognate receptors on the effector cells to augment a potent and durable tumor-killing response. The findings support the notion that cancer patients' immunity has the capacity to react selectively to their tumors through recognition of tumor-specific antigens. Programmed death 1 (PD-1) is considered as the most important checkpoint pathways currently and the blockade has been approved by FDA for treating several solid cancers and Hodgkin lymphoma. However, the effects of PD1 blockade in various hematologic malignancies are still under investigation. Traditional treatment for hematologic malignancies include chemotherapy, radiotherapy, target therapy and allogeneic stem cell transplant. For those patients relapse or refractory to above treatment, their prognoses were poor during the past decades. In current era, immune checkpoint blockade may provide an alternative option and opportunity for them. In today's presentation, current status and studies about immune checkpoint inhibitors in hematologic malignancies will be reviewed.





- Date/Time: November 3rd/ 16:25-17:15
- Venue: Room 103

CAR T: a substitute or a complement to the transplant?

Speaker: Prof. Alvaro Urbano-Ispizua Affiliation: University of Barcelona

Speech Summary

Several American and Chinese groups have shown impressive results with Anti-CD19 directed CAR Tcell therapy in relapsed/refractory (R/R) B cell acute lymphoblastic leukemia (B-ALL), B cell non-Hodgkin lymphoma (B- NHL), and chronic lymphocytic leukemia. It was not a surprise that the U.S. Food and Drug administration (FDA) approved very fast the use of Anti CD19- CAR T in pediatric and young adults with ALL and R/R diffuse large B-NHL. CAR T cells targeting BCMA is also showing outstanding results in multiple myeloma (MM) patients previously treated with >3 lines of anti-MM regimens. Both FDA and the European Medical Agency are currently evaluating the approval of such an anti-BCMA CAR T cell. There is much enthusiasm and hope around CAR Ts. The tremendous effectiveness of the CAR T cells also raises the question of whether they will eventually substitute the hematopoietic stem cell transplantation (HSCT) or will be used as a bridge to it, or of whether they will be indicated just in case of a relapse after HSCT. To answer these questions, we need longer follow up of those patients treated with CAR T cells, and also to see how CAR Ts behave in earlier phases of these diseases. Clinical trials are already being evaluated this aspect, and results will be available in the near future. The published cost of this treatment per patient (ranging between 375.000 and 450.000 \$) also raises the concern of its affordability for all European patients who might need it. Production and distribution of academic CAR T cells might be part of the solution to this economic problem. Unfortunately, less than 10% of worldwide academic CAR Ts are produced in Europe. In this presentation, the dilemma of CAR Ts vs HSCT will be discussed, together with European academic initiatives in this fascinating field of gene cell therapy.





Ex vivo T cell-depleted haploidentical hematopoietic cell transplantation in children with non-malignant disorders

Speaker: Ho Joon Im

Affiliation: Asan Medical Center Children's Hospital, University of Ulsan College of Medicine

Speech Summary

The outcomes of allogeneic hematopoietic cell transplantation (HSCT) using an HLA-haploidentical family donor have significantly improved in both T cell-depleted or T cell-replete transplants. The ex vivo techniques for removal of T cells have evolved from the selection of CD34+ hematopoietic stem cell progenitors towards the depletion of CD3+ cells and to the depletion of $\alpha\beta$ + T cells more recently. The most recent depletion technique targeting $\alpha\beta$ + T cells produces grafts containing many $\gamma\delta$ + lymphocytes and other effector cells including NK cells. While $\alpha\beta$ + T cells are known to be associated with the initiation of GVHD, $\gamma\delta$ + T cells can enhance immune reconstitution and are not implicated in GVHD. The $\alpha\beta$ + T cell depletion is the current approach applying in haploidentical HSCT at our center. More than 150 cases of haploidentical HSCT including 28 CD3-depleted transplants have been performed so far at our center. The recent emerging evidence for haploidentical HSCT has provided additional therapeutic options for pediatric patients with malignant and non-malignant diseases curable with HSCT but do not have a suitable related or unrelated donor. In this presentation, I will introduce our experience with ex vivo T cell-depleted haploidentical HCT in children and adolescents with non-malignant disorders, including bone marrow failure syndrome, primary immunodeficiency, hemophagocytic lymphohistiocytosis, and metabolic diseases.



Plenary Session 6: Alternative donor transplantation (1): Haploidentical HSCT

- Date/Time: November 4th/ 09:50-11:00
- Venue: Room 201

Speech Title:

HLA-haploidentical PBSCT using posttransplant cyclophosphamide in Japan

Speaker: Takanori Teshima, MD Affiliation: Hokkaido University

Speech Summary

We conducted a series of prospective studies of HLA-haploidentical PBSCT using posttransplant cyclophosphamide (haploPBSCT; n=435). Outcome was comparable between reduced-intensity and myeloablative conditioning haploPBSCT. Survival outcomes of haploPBSCT were also comparable to those of unrelated transplantation.





Haploidentical Transplantation In Bone Marrow Failure

Speaker: Xiao-Jun Huang Affiliation: Peking University People's Hospital

Speech Summary

The recent development of haplo-HSCT in treating nonmalignant hematologic diseases, such as severe aplastic anemia (SAA), Fanconi anemia (FA), paroxysmal nocturnal hemoglobinuria (PNH) will be reviewed in this report.

In 2012, Xu et al. reported on 19 consecutive SAA patients who received haplo-HSCT using Beijing protocol. In this protocol, the conditioning regimen included busulfan, cyclophosphamide and ATG. The recipients received a combination of G-CSF-primed BM and G-CSF-mobilized PBSC from haploidentical family donors and CsA, mycophenolate mofetil and short-term MTX for GVHD prophylaxis. All patients achieved 100% donor myeloid engraftment, and the OS was 64% with a median 746 days follow-up for surviving patients. Using Beijing protocol, further studies on haplo-HSCT for pediatric and adult patients with SAA as a salvage or upfront therapy were performed, respectively. And favorable outcomes were achieved. We conclude that haplo-HSCT is an effective and feasible choice for both pediatric and adult patients with SAA as a salvage or even upfront therapy. In our center, the platform for haploidentical and unrelated donor transplantation from unmanipulated grafts in treating FA have been developed. And in this platform, the conditioning regimen includes fludarabine, dose-reduced pre-transplant CY and ATG, and without PTCY. All 5 patients including 2 haplo-HSCT recipients using this platform achieved complete donor chimerism, and 4/5 patients was alive until the date of follow- up, one haplo-HSCT recipient died of severe infection. Haplo-HSCT with Flu-containing RIC regimens may be a suitable option for FA patients without a matched related or unrelated donor.

In summary, favorable outcomes were acquired in haplo-HSCT using Beijing protocol for nonmalignant hematological diseases, and haplo-HSCT may be a reliable strategy for patients with bone marrow failure diseases who lack a suitable matched sibling or unrelated donor.



Transplant outcomes of haploidentical activities, GIAC- like versus PTCy-based, for hematological malignancies in Taiwan: Results from Taiwan Blood and Marrow Transplantation Registry (TBMTR)

Speaker: Chi-Cheng Li Affiliation: Hualien Tzu Chi Medical Center, Taiwan

Speech Summary

Haploidentical hematopoietic stem cell transplantation represents the most difficult transplant modality in history. It also marks a milestone that human being can overcome HLA barrier to engraft successfully with controllable graft-versus-host-disease (GvHD). In the past decade, there were two well- known and introduced protocols being applied, Baltimore-designed PTCy and Beijing-designed GIAC methods. Although standing on different strategies and pathophysiology to ensure engraftment kinetics and prevention of severe GvHD, both protocols have been proved to make a big breakthrough and save thousands of lives in need of transplantation to cure various hematological disorders. Taiwan, a beautiful island located between Taiwan Strait and the Pacific Ocean, has received different influences from China and America including in the medical fields. Both PTCy-based andG IAC-like haploidentical protocols have been introduced and practiced in Taiwan. The results have been registered to Taiwan Blood and Marrow Transplantation Registry. Updated comparison result is going to be presented to the 23rd Annual Congress of 2018 APBMT in Taipei.



Plenary Session 7: Pediatrics transplantation

- Date/Time: November 4th/ 09:50-11:00
- Venue: Room 102

Speech Title:

Reduced-intensity conditioning Stem Cell Transplantation for pediatric patients with Primary Immunodeficiency

Speaker: Prof. Amir Ali Hamidieh Affiliation:Tehran University of Medical Sciences

Speech Summary

Certain types of primary immunodeficiencies (PIDs) are fatal and Allogenic Hematopoietic Stem Cell Transplantation (HSCT) is the only life-saving treatment for them, especially if therapy is instituted early, prior to onset of infections.

Reduced intensity (RIC) and myeloablative (MAC) conditioning regimens are currently being used in the treatment of patients affected by PIDs. The conditioning regimen used for HSCT in PIDs is still a controversial issue.

Full donor chimerism can be achieved with the use of MAC, but this regimen can lead to a higher risk of infections in patients with PID who suffer from comorbid complications. RIC has offered many PID patients who are ineligible for MAC regimens a chance of cure. However, the beneficial role of RIC was questioned following reports suggesting higher chance of rejection and lower symptom resolution rate in mixed chimerism settings. Despite this fact, transplant based on RIC because of its low transplant-related mortality, has been increasingly utilized in recent years.

Based on currently available international data, as pre-transplant infections in pediatric patients with PIDs increase the rate of mortality, the use of MAC regimen requires careful attention, but using less-toxic regimen with RIC seems to be highly effective and will improve manifestation of PID with either full or mixed chimerism.