Short Communication

Blood Cell Therapy
The official journal of APBMT

GVHD relapse-free survival after peripheral blood hematopoietic cell transplantation for hematologic malignancies

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Abstract

The preferred choice for hematopoietic cell transplantation (HCT) donors in India is a matched related donor (MRD) followed by a haploidentical (haplo) donor for patients with hematological malignancies. International data in the haplo-HCT setting is mainly using bone marrow as a source. Almost all HCTs in India use peripheral blood stem cells (PBSC), which increases the risk of graft-versus-host disease (GVHD). In this single-center prospective study from 2017 to 2021, we sought to compare these outcomes prospectively in adult patients with hematological malignancies. Patient, disease, donor, and HCT details were prospectively recorded. GVHD prophylaxis included cyclosporine + methotrexate in MRD-HCT and post-transplant cyclophosphamide (PTCy) based in haplo-HCT. The primary endpoint GVHD relapse-free survival (GRFS) was defined as the time post-HCT without any of the following events: grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse, or death from any cause. A total of 41 MRD and 33 haplo-HCT recipients were included in the study. Both cohorts were matched for age, sex, diagnosis, disease risk index, donor age, sex and CMV mismatches, and CD34 counts. A lower proportion of MRD-HCT recipients than haplo-HCT received myeloablative conditioning (39% vs. 76%, p = 0.002). There was no difference in the cumulative incidence of grade III-IV acute GVHD (16% vs. 27%, p = 0.2) or moderate-to-severe chronic GVHD (58% vs. 71%, p = 0.5). The one-year GRFS was not significantly different (53% vs. 38%, p = 0.2), with median GRFS of 420 and 274 days. The relapse incidence (22% vs. 19%, p = 0.6) and non-relapse mortality (25% vs. 35%, p = 0.4) did not differ. There was no difference in overall survival at one year (60% vs. 52%, p = 0.3). Despite a higher proportion of myeloablative conditioning in the haplo-HCT cohort, all outcomes, including GRFS, were comparable to those of the MRD-HCT cohort. This should encourage patients without an MRD to undergo haplo-HCT.

Key words GRFS, PBSC, HCT

Submitted September 28, 2022; Accepted February 27, 2023; Published online May 19, 2023; Issued online August 25, 2023

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Introduction

Haploidentical (haplo) hematopoietic cell transplantation (HCT) using peripheral blood stem cells (PBSC) and post-transplant cyclophosphamide (PTCy) is the preferred alternative donor transplant in the absence of a fully matched related donor (MRD) HCT for patients with hematological malignancies in India. MRD includes matched sibling donors (MSD) and an ~10% probability of a full match with parents/children[1]. Haplo-HCT is preferred over matched unrelated donor (MUD)-HCT because of the low likelihood of full matching in local registries and the high costs. In addition, data showing comparable outcomes between MRD-, MUD-, and haplo-HCT have increased confidence in offering haplo-HCT when MRD is not available[2, 3]. However, most international data use bone marrow as a source, as it has a lower risk of chronic GVHD[4]. Our preliminary experience with PBSC haplo-HCT using PTCy revealed a high incidence of chronic GVHD[5]. Therefore, GVHD-relapse-free survival (GRFS), which reflects the true success of HCT as sur-

Table 1. Comparison of characteristics and HCT outcomes between MRD and haplo-HCT

	MRD-HCT N = 41 N (%), median (IQR)	Haplo-HCT N = 33 N (%), median (IQR)	*p*-value
Age	33 (19-45)	28 (15-35)	0.2
Males	24 (59%)	26 (79%)	0.08
Females	17 (41%)	7 (21%)	
Diagnoses			
Acute myeloid leukemia/myelodysplastic syndrome	20 (49%)	15 (45%)	0.3
Acute lymphoblastic leukemia	13 (32%)	15 (45%)	
Other	8 (19%)	3 (10%)	
Modified Disease Risk Index			
Low	10 (24%)	5 (15%)	0.3
Intermediate	14 (34%)	8 (24%)	
High/very high	17 (42%)	20 (61%)	
Myeloablative conditioning	16 (39%)	25 (76%)	
Reduced-intensity conditioning	25 (61%)	8 (24%)	0.002
Donor age	33.5 (19.7 – 45.2)	28 (20.5 – 39.5)	0.4
Donor Sex mismatch	22 (54%)	14 (42%)	0.3
Female to male	10 (24%)	11 (33%)	
Male to female	12 (30%)	3 (9%)	
Recipient/Donor cytomegalovirus status			
Match (+/+, −/−)	38 (93%)	26 (79%)	0.09
Mismatch (+/−, −/+)	3 (7%)	7 (21%)	
CD34 counts ($\times 10^6$/kg recipient weight)	6.3 (4.3 - 7.6)	7.4 (5.2 – 9.8)	0.1
Neutrophil engraftment	13 (11 – 15.2)	14.5 (13.2 – 18)	0.003
Platelet engraftment	13 (12 – 14)	13 (12 – 23)	0.4
Cumulative incidence of grade III-IV acute GVHD	16%	27%	0.2
Cumulative incidence of moderate-severe chronic GVHD @ 1-year	59%	71%	0.5
Cumulative incidence of relapse @ 1-year	22%	19%	0.6
GRFS @ 1-year	53%	38%	0.2
Median GRFS	420 days	274 days	0.2
Non-relapse mortality @ 1-year	25%	35%	0.4
Overall survival @ 1-year	60%	52%	0.3
Median overall survival	512 days	721 days	0.3

MRD, matched related donor; HCT, hematopoietic cell transplantation; IQR, interquartile range; GVHD, graft versus host disease; GRFS, GVHD-relapse-free-survival

vival without ongoing morbidity/mortality, would be necessary for this setting. As no data are available comparing outcomes after PBSC haplo-HCT versus MRD in India, we sought to compare these outcomes prospectively in this study.

Methods

This single-center, prospective study enrolled all consecutive patients aged ≥ 12 years with hematological malignancies undergoing either MRD or haplo-HCT using PBSC between 2017 and 2021. The intensity of the conditioning regimen was based on the patient's age, comorbidities, and organ function according to the institutional criteria. Myeloablative conditioning regimens included busulfan (12.8 mg/kg)-based regimens for myeloid malignancies, and TBI (12 Gy)-based regimens for lymphoid malignancies. Reduced-intensity regimens (RIC) included fludarabine-melphalan 140 mg/m^2 for MRD-HCT and the Johns Hopkins regimen fludarabine-cyclophosphamide-TBI (200 cGy) for haplo-HCT. GVHD prophylaxis included cyclosporine (CSA) + methotrexate for MRD-HCT and PTCy + CSA + mycophenolate for haplo-HCT. Immunosuppressive therapy was tapered and stopped between day +60 and day +120, depending on the disease and GVHD risk. All the patients received azole and acyclovir prophylaxis. The CD34 dose was capped in the MRD-HCT at 8 × 10^6/kg, while it was uncapped for haplo-HCT[6]. Acute and chronic GVHD were scored according to established criteria[7, 8]. The eGVHD app was used to score the severity of GVHD[9]. The primary endpoint of this study was GRFS, defined as the time after HCT without any of the following events: grade III-IV acute GVHD,

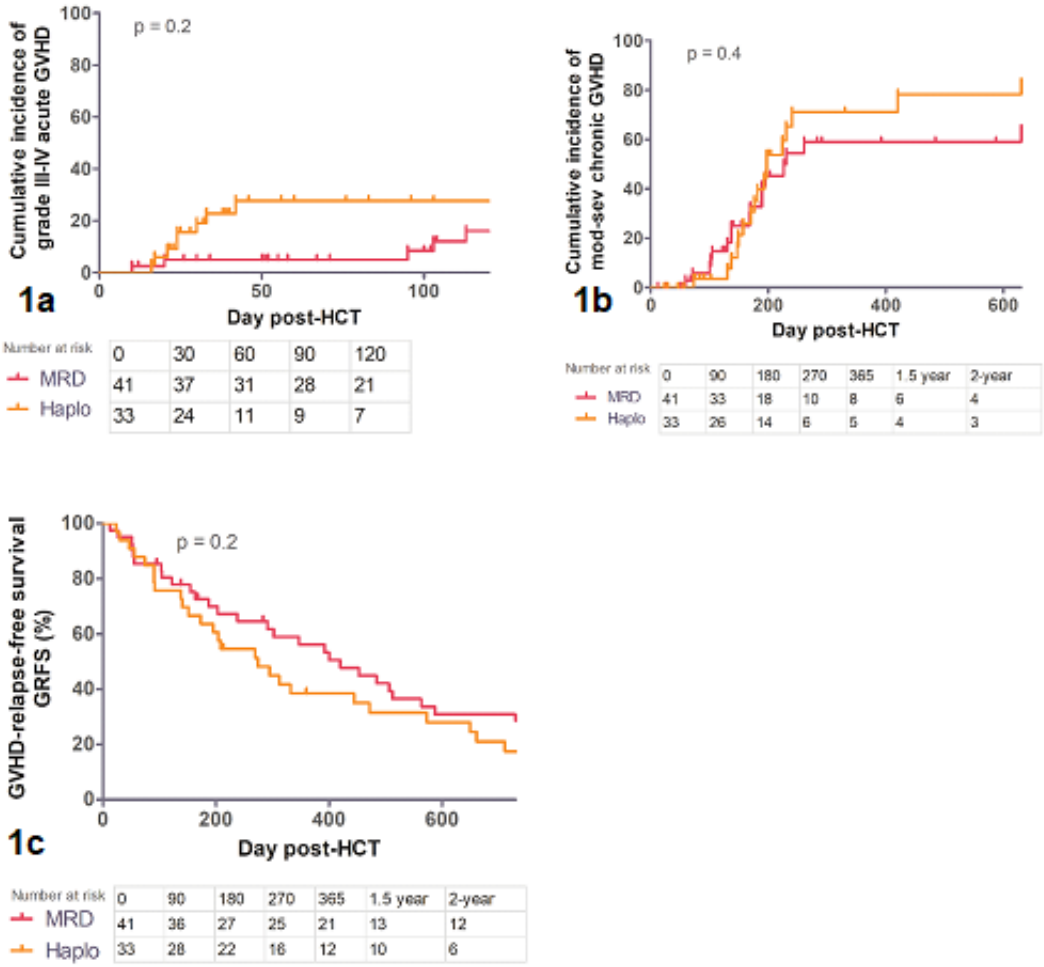

Figure 1. Comparison of outcomes between MRD and haplo-HCT
1a. Cumulative incidence of grade III-IV acute GVHD, 1b. Cumulative incidence of moderate-severe chronic GVHD, 1c. GVHD-relapse-free survival cumulative incidence of relapse

chronic GVHD requiring systemic immunosuppressive treatment, disease relapse, or death from any cause[10]. Non-relapse mortality (NRM) was defined as death from any cause other than relapse. OS was defined as the time from transplantation to death from any cause. The cumulative incidences of GVHD and NRM were calculated using relapse as the competing risk. NRM, relapse incidence, and OS were secondary endpoints. Patient, disease, donor, HCT factors, and outcomes were compared between the MRD and haplo-HCT cohorts using either a Mann-Whitney test or a chi-square or Fisher's exact test. The Kaplan-Meier method was used to compare survival outcomes using the log-rank test. A p-value < 0.05 was used for statistical significance.

Results

A total of 41 MRD and 33 haplo-HCT recipients were included in the study. The median follow-up in both cohorts was 347 days (IQR 146-937) and 274 days (IQR 139-1,036), respectively, (p = 0.8). The median ages were 33 years (IQR 19-45 years) and 28 years (IQR 15-35 years) (p = 0.2) (**Table 1**). Male patients were predominant in both cohorts (59% vs. 79%, p = 0.08). An equal proportion of patients had acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) (49% vs. 45%, p = 0.3) and acute lymphoblastic leukemia (ALL) (32% vs. 45%). The disease risk index was also matched between both cohorts: low-risk (24% vs. 15%), intermediate-risk (34% vs. 24%), and high/very high-risk in 42% and 61% (p = 0.3), respectively. A lower proportion of MRD-HCT recipients received the MAC regimen than did the haplo-HCT (39% vs. 76%, p = 0.002). The median donor ages of 33.5 years (19.7-45.2) vs. 28 years (20.5-39.5) were comparable in both cohorts (p = 0.4). Both cohorts had similar proportions of recipient-donor gender-mismatch transplants (54% vs. 42%, p = 0.3) and CMV-matched transplants (93% vs. 79%, p = 0.09). The median CD34 counts were similar despite capping in the MRD-HCT cohort (6.3×10^6/kg vs. 7.4×10^6/kg, p = 0.1). Neutrophil

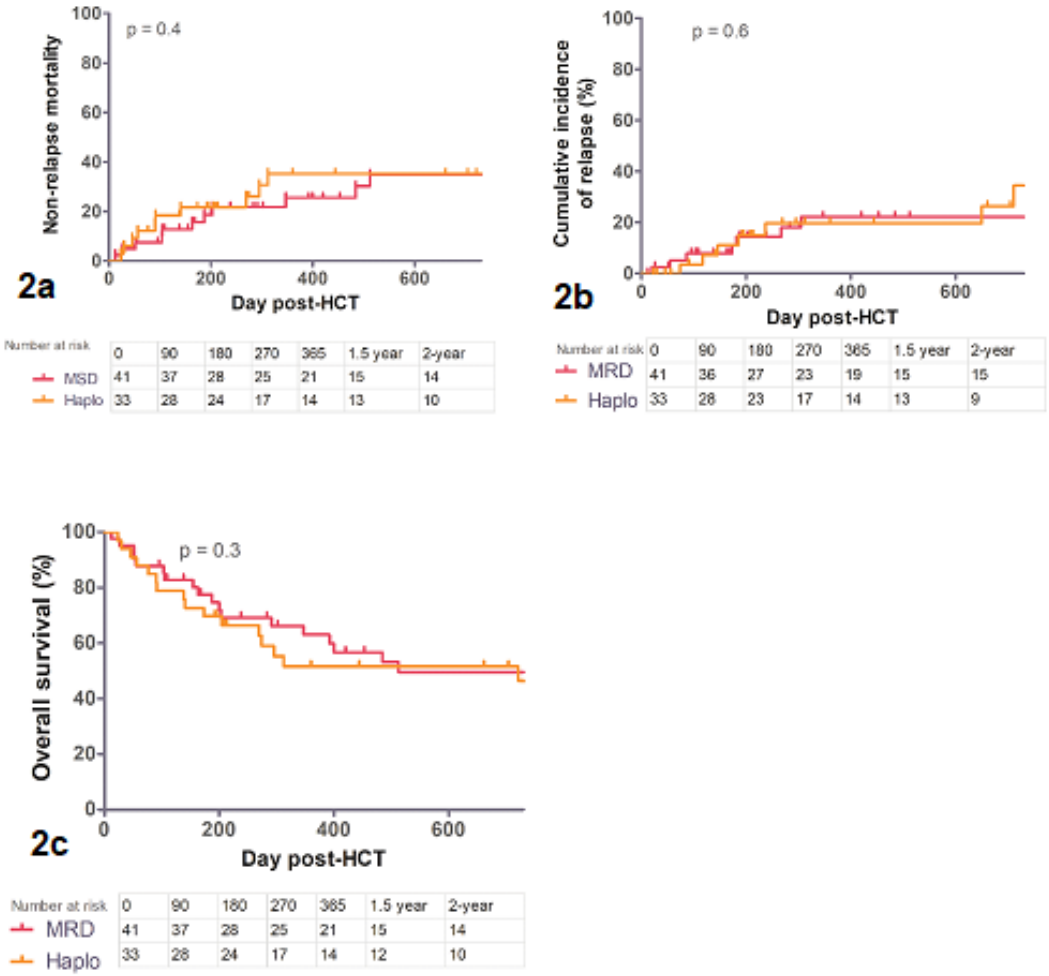

Figure 2. Comparison of outcomes between MRD and haplo-HCT
2a. Non-relapse mortality, 2b. Cumulative incidence of relapse, and 2c. Overall survival

engraftment was delayed in the haplo-HCT cohort by a median of 1.5 days (13 days vs. 14.5 days, p = 0.003). There was no difference in platelet engraftment between the cohorts (13 vs. 13 days, p = 0.4). The cumulative incidence of grade III-IV acute GVHD at day+100 (16% vs. 27%, p = 0.2) (**Figure 1a**) as well as moderate-to-severe chronic GVHD (58% vs. 71%, p = 0.5) (**Figure 1b**) at 1-year post-HCT was not significantly different between the cohorts. The primary endpoint GRFS was not significantly different (53% vs. 38%, p = 0.2), with median GRFS of 420 and 274 days, respectively (**Figure 1c**). The NRMs at one year were 25% and 35%, respectively (p = 0.4) (**Figure 2a**). The cumulative incidences of relapse at one year were 22% and 19%, respectively (p = 0.6) (**Figure 2b**). There was no difference in the overall survival at one year (60% vs. 52%, p = 0.3), with median OS of 512 and 721 days, respectively (**Figure 2c**).

Discussion

Registry studies from both EBMT and CIBMTR have reported similar survival outcomes with MRD and unmanipulated haplo-HCT for AML[11, 12] and ALL[13, 14]. These studies showed a higher risk of acute GVHD balanced by a lower risk of chronic GVHD with PTCy haplo-HCT. Our study had a higher incidence of moderate-to-severe chronic GVHD, mostly related to the use of PBSC, and a higher proportion of patients receiving MAC regimens in the haplo-HCT cohort. While overall survival is the true success measure of HCT, patients often feel deceived when they have to experience chronic issues of GVHD, as it significantly affects their quality of life. Despite this, our cohort's one-year GRFS of 53% with PBSC MRD and 38% with haplo-HCT were not significantly different. The two-year GRFS after MRD and haplo-HCT in the EBMT studies using predominantly bone marrow and RIC regimens were 50% vs. 47%, respectively, in the AML cohort[11] and 39% vs. 40%, respectively, in the

ALL cohort[13]. There is a need to delay immunosuppression discontinuation using a risk-model-based clinical application in haplo-HCT to balance the higher risk of chronic GVHD with PBSC. Early conventional tapering of immunosuppressive therapy around day +60 to day +120 is associated with more discontinuation failures due to GVHD without affecting relapse outcomes[15]. The major limitation of this study was the small sample size, with heterogeneous diagnoses and conditioning regimens. However, similar GRFS with MRD and haplo-HCT studies will help build confidence in offering PBSC haplo-HCT using PTCy for patients with hematological malignancies without a matched related donor.

Author Contributions

DPL and PC conceived the study. PC, KSK, and DPL analyzed the data and drafted the manuscript. All authors were involved in patient recruitment, clinical care, and manuscript writing. DPL and KSK confirmed full access to the data in the study and the final responsibility for the manuscript.

Financial Support

This work was performed as a part of the American Society of Hematology Global Research Award to DPL.

Ethics Approval

This study was approved by the Postgraduate Institute of Medical Education and Research Institutional Ethics Committee (IEC) letter no. INT/IEC/2021/SPL-982.

Informed Consent

Informed consent was obtained from all participants.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

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https://doi.org/10.31547/bct-2022-014