Letters to the Editor

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Early Outcomes After Haploidentical Hematopoietic Cell Transplantation in Elderly Patients with Myeloid Malignancies in India: A Single Center Experience

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Dear Editor

A study published in the August issue of Blood Cell Therapy has shown significantly higher non-relapse mortality (NRM) after myeloablative (MAC) allogeneic hematopoietic cell transplant (allo-HCT) in South Asians, compared to other Asians and whites older than 45 years[1]. Allo-HCT is the only curative option for intermediate to adverse-risk and relapsed acute myeloid leukemia (AML). While it is challenging for older individuals to find a human leukocyte antigen (HLA)-matched family donor or an unrelated donor in Indian donor registries, most patients have a haploidentical (haplo) child, making haplo-HCT a time-efficient and economically feasible option in India[2]. Studies from India on outcomes after haplo-HCT in younger patients have shown higher non-relapse mortality (NRM) rates ranging from 30% to 40%[3,4]. There is a gap in the outcome data for elderly Indians (≥ 55 years), as most studies have not addressed this issue, and only a limited number of centers offer haplo-HCT to the elderly patient.

After review and approval of the Institutional Ethical Committee (IEC code: 2025-253-IMP-EXP-66) with waiver of informed consent, we retrospectively analyzed the early outcomes following haplo-HCT in elderly patients (chronological age ≥ 55 years) with myeloid malignancies. Patient demographics and clinical parameters were obtained retrospectively from electronic medical records and follow-up notes. All data were collected up to September 30, 2025.

Between December 2024 and May 2025, four patients with AML and one patient with *de novo* chronic myeloid leukemia (CML) in myeloid blast crisis, aged 55 years or older, underwent haplo-HCT at our institution. The peripheral blood stem cell graft was obtained from an HLA haploidentical son for each patient. The characteristics of the patients, stem cell donors, the allo-HCT procedures, and outcomes are summarized in **Table 1**.

Patients aged between 55 and 59 years received sequential reduced intensity conditioning (RIC) regimen (preconditioning: plerixafor 0.24 microgram/kg via subcutaneous route at 10 hours before cytarabine on day -9, cytarabine 1.5 g/m^2/day with cladribine 5 mg/m^2/day on day -9, -8, and conditioning: plerixafor 0.24 microgram/kg via subcutaneous route at 10 hours before treosulfan on day -6, treosulfan 7 g/m^2/day from day -6 to day -4 with fludarabine 30 mg/m^2/day from day -6 to day -3). Patients aged ≥ 60 years received sequential RIC (preconditioning: plerixafor 0.24 microgram/kg via subcutaneous route at 10 hours before cytarabine on day -9, cytarabine 1.5 g/m^2 with cladribine 5 mg/m^2 on day -9, thymoglobulin 2.5 mg/kg/day on day -8, -7, and conditioning: plerixafor 0.24 microgram/kg via subcutaneous route at 10 hours before treosulfan on day -6, treosulfan 5 g/m^2/day from day -6 to day -4 with fludarabine 30 mg/m^2/day from day -6 to day -3). The graft versus host disease (GVHD) prophylaxis regimen was comprised of intravenous bortezomib (1.3 mg/m^2 at +6 and + 48 hours), post-transplant cyclophosphamide (PTCy) on day +3 and +4 (50 mg/kg/day for age 55-59 years and 25 mg/kg/day for age ≥ 60 years), cyclosporine (target trough level 200-350 ng/mL), and mycophenolate mofetil from day +5. Those receiving intermediate dose PTCy (25 mg/kg/day) received a

Table 1. Characteristics of patients and allogeneic transplantations

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, years	55	65	56	61	66
Gender	Female	Male	Male	Male	Female
Age-adjusted HCT-CI	1	2	1	3	1
KPS	80	90	90	50	80
Diagnosis, DRI	Relapsed AML, intermediate	AML, intermediate	AML, intermediate	Relapsed AML, intermediate	CML myeloid blast crisis, high
Molecular or cytogenetic aberration (method of detection)	CEBPA EXON 1 (NGS, VAF 55%) WT1 (NGS, VAF 54%)	FLT3-ITD (NGS, VAF 41%), IDH1 (NGS, VAF 48%), NPM1 (NGS, VAF 35%)	None identified	None identified	t (9;22) (FISH), ASXL-1 mutation (NGS, VAF 10%)
Number of prior lines of therapy	3	1	1	2	1
Disease status at transplant	CR3, MRD +ve (1.2%)*	CR1, MRD -ve*	CR1, MRD +ve (0.138%)*	CR2, MRD -ve*	CR1, MRD -ve**
Donor, gender (age, years)	Offspring, male (19)	Offspring, male (39)	Offspring, male (29)	Offspring, male (32)	Offspring, male (38)
Pre-transplant CMV serostatus	D+/R+	D+/R+	D+/R+	D+/R+	D+/R+
HSC source	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood
Pre-conditioning regimen	Plerixafor (0.24mcg/kg ×1), Ara-C (1.5g/m^2 ×2), Clad (5mg/m^2 ×2)	Plerixafor (0.24mcg/kg ×1), Ara-C (1.5g/m^2 ×1), Clad (5mg/m^2 ×1), r-ATG 2.5mg/kg ×2	Plerixafor (0.24mcg/kg ×1), Ara-C (1.5g/m^2 ×2), Clad (5mg/m^2 ×2)	Plerixafor (0.24mcg/kg ×1), Ara-C (1.5g/m^2 ×1), Clad (5mg/m^2 ×1), r-ATG 2.5mg/kg ×2	Plerixafor (0.24mcg/kg ×1), Ara-C (1.5g/m^2 ×1), Clad (5mg/m^2 ×1), r-ATG 2.5mg/kg ×2
Conditioning regimen	Plerixafor (0.24mcg/kg ×1), Flu (30mg/m^2 ×4), Treo (7g/m^2 ×3)	Plerixafor (0.24mcg/kg ×1), Flu (30mg/m^2 ×4), Treo (5g/m^2 ×3)	Plerixafor (0.24mcg/kg ×1), Flu (30mg/m^2 ×4), Treo (7g/m^2 ×3)	Plerixafor (0.24mcg/kg ×1), Flu (30mg/m^2 ×4), Treo (5g/m^2 ×3)	Plerixafor (0.24mcg/kg ×1), Flu (30mg/m^2 ×4), Treo (5g/m^2 ×3)
GVHD prophylaxis	Bz-1.3mg/m^2 at +6, +48 hours Cy-50mg/kg at day +3, +4 CSA+MMF from day +5	Bz-1.3mg/m^2 at +6, +48 hours Cy-25mg/kg at day +3, +4 CSA+MMF from day +5, abatacept 10mg/kg at day +14, +28	Bz-1.3mg/m^2 at +6, +48 hours Cy-50mg/kg at day +3, +4 CSA+MMF from day +5	Bz-1.3mg/m^2 at +6, +48 hours Cy-25mg/kg at day +3, +4 CSA+MMF from day +5, abatacept 10mg/kg at day +14, +28	Bz-1.3mg/m^2 at +6, +48 hours Cy-25mg/kg at day +3, +4 CSA+MMF from day +5, abatacept 10mg/kg at day +14, +28
$CD34^+$ cell dose, ×10^6/kg	13.68	13.07	11.04	13	13
Neutrophil engraftment, days	18	12	15	11	13
Platelet engraftment, days	28	12	21	11	13
Acute GVHD	None	None	None	None	None
Chronic GVHD, NIH grade	Mild (skin alone)	Moderate (skin and mouth)	Moderate (skin and mouth)	None	None
CMV viremia episodes	1	3	1	4	4
CMV disease	No	No	No	No	No
Reactivation of tuberculosis, site	Yes, lymphadenitis	Yes, pleural effusion	None	Yes, pulmonary Tuberculosis	None
Relapse, days	None	None	None	None	None
Surviving (post-HCT days)	Yes (298)	Yes (276)	Yes (249)	Yes (164)	Yes (119)
Ongoing systemic IST	No	Yes	Yes	No	Yes (tapering dose of cyclosporine)

HCT-CI, hematopoietic cell transplantation comorbidity-index; KPS, Karnofsky performance score; DRI, disease risk index; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; NGS, next generation sequencing; VAF, variable allele frequency; FISH, fiuorescent in situ hybridization; CR, complete remission; MRD, measurable residual disease; +ve, positive; -ve, negative; CMV, cytomegalovirus; D+, donor seropositive; R+, recipient seropositive; HSC, hematopoietic stem cell; Ara C, cytarabine; Clad, cladribine; r-ATG, rabbit antithymocyte globulin; Flu, fludarabine; Treo, treosulfan; Bz, bortezomib; Cy, cyclophosphamide; CSA, cyclosporine A; MMF, mycophenolate mofetil; GVHD, graft versus host disease; NIH, National Institute of Health; IST, immunosuppressive therapy.

*flowcytometric MRD **flowcytometric and molecular MRD

short course of abatacept (10 mg/kg on days +14 and + 28). All patients received mycophenolate mofetil till day +35. Cyclosporine dose tapering was initiated at a median time of 80 days (range, 70-110 days).

Neutrophil and platelet engraftment was achieved in all patients at a median time of 13 days (range, 11-18 days) and 13 days (range, 11-28 days), respectively. None of the patients developed grade 3-4 regimen-related toxicity. The chimerism analysis, performed using the short tandem repeat method on bone marrow aspirates at day +30 and peripheral blood samples at days +60 and +90, revealed 100% donor chimerism in all patients. The bone marrow was in complete morphologic remission, and flow cytometric measurable residual disease was undetectable in all patients at both day +30 and day +90. At a median follow-up of 249 days (range, 119-298 days), none of the patients developed acute GVHD, and two patients developed moderate chronic GVHD (National Institute of Health grading criteria) involving the skin and mouth. Weekly monitoring of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) was performed by quantitative polymerase chain reaction, starting on day +7 and continuing till day + 100. Although asymptomatic CMV viremia was detected in all patients, all viremia episodes responded to preemptive therapy with valganciclovir. None of the patients developed EBV reactivation. Three patients developed reactivation of *Mycobacterium tuberculosis (M.tuberculosis)* at a median time of 90 days (range, 80-140 days) after HCT and are currently receiving antitubercular therapy. Until the last date of data collection, none of the patients experienced disease relapse after HCT, and all are alive.

The leading causes of treatment failure after a melphalan-based RIC-haplo-HCT and PTCy-based GVHD prophylaxis in elderly patients (age $\geq$ 55 years) with AML are relapse and NRM. The day +100 NRM with this regimen was 21%[5]. A study by Shima et al. suggested that performance status is a predictor of survival outcome after geriatric allo-HCT (age $\geq$ 60 years)[6]. Notably, in our study, three out of five patients had a KPS < 90. A report on haplo-HCT in dyskeratosis congenita has demonstrated the feasibility and safety of a low-dose treosulfan-based RIC regimen in a patient genetically vulnerable to regimen-related toxicity[7]. Mobilization of leukemic stem cells using plerixafor during MAC for allo-HCT in AML is safe[8]. All patients in our cohort tolerated the plerixafor-containing low-dose treosulfan-based regimen without grade 3-4 regimen-related toxicity. We incorporated plerixafor to mobilize and sensitize the leukemic stem cells to the conditioning chemotherapy. However, a longer follow-up and a larger sample size are required to assess the efficacy of this strategy in preventing relapse. The absence of acute GVHD and extensive chronic GVHD potentially reflects the efficacy of our GVHD prophylaxis. The safety and effectiveness of short-course bortezomib-based GVHD prophylaxis have been demonstrated in HLA-mismatched unrelated donor RIC transplantation[9]. The combination of abatacept with PTCy and sirolimus has shown excellent GVHD-free survival after haplo-HCT in non-malignant diseases[10]. Our abatacept-containing GVHD prophylaxis arm differed in two key aspects: first, it included an intermediate-dose PTCy, and second, the abatacept course was shorter. Notably, three out of five patients developed reactivation of *M. tuberculosis*. The probable explanations for the higher incidence of tubercular reactivation in this cohort are the high endemicity of tuberculosis in India and impaired cellular immunity after haplo-HCT.

Despite the limitations of retrospective data, a small sample size, and a shorter follow-up period, our study provides real-world data from a low and middle-income country (LMIC) on outcomes during the most vulnerable period after haplo-HCT in the elderly.

In conclusion, our study demonstrates the feasibility and safety of haplo-HCT in elderly patients with myeloid malignancies living in LMICs. Plerixafor, combined with low-dose treosulfan-based conditioning, is well tolerated. The addition of bortezomib and abatacept to the PTCy-based GVHD prophylaxis is feasible and potentially effective.

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Author Contributions

SSR and CP contributed to the concept and design of the study. SSR and BV analyzed the data. SSR, CP, and BV drafted the original manuscript. SSR, CP, BV, MKS, MS, DC, KR, RG, and RK contributed to patient care. All authors critically reviewed and approved the final version of the manuscript.

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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