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Comparison of Total Body Irradiation-Based Conditioning Regimens vs Chemotherapy-Based Protocols in Haploidentical Stem Cell Transplants in a Pakistani Cohort – A Single-Center Experience

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Abstract

Objective: To compare the outcomes of total body irradiation (TBI)-based and chemotherapy (CT)-based conditioning regimens in patients undergoing haploidentical hematopoietic stem cell transplantation (Haplo-HSCT).

Methodology: This retrospective single-center comparative study included 50 consecutive patients who underwent Haplo-HSCT at Shifa International Hospital, Islamabad, between January 2016 and September 2023. Patients received either TBI-based conditioning (n=21) or CT-based conditioning (n=29). Primary endpoints were overall survival (OS), progression-free survival (PFS), and graft-versus-host disease/relapse-free survival (GRFS). Secondary outcomes included neutrophil and platelet engraftment, transplant-related mortality (TRM), non-relapse mortality (NRM), relapse, engraftment failure, and graft-versus-host disease (GvHD). Survival outcomes were analyzed using Kaplan-Meier methods.

Results: The mean age was 23.4±12.2 years in the TBI group and 28.7±11.9 years in the CT group; 76% of patients were male. Median follow-up was 11.5 months. Two-year OS was 37.0% in the TBI group and 41.4% in the CT group, while two-year PFS was 37.0% and 41.4%, respectively. GRFS was similarly low in both groups (12.7% vs. 13.8%). Neutrophil engraftment occurred significantly earlier with TBI-based conditioning (median Day +13 vs. Day +14; p=0.032), whereas platelet engraftment was comparable. TRM (38.1% vs. 41.4%), NRM (14.3% vs. 13.7%), relapse (14.3% vs. 13.7%), and acute or chronic GvHD rates were similar between groups. Primary engraftment failure occurred only in the TBI group (9.5%).

Conclusion: TBI- and CT-based conditioning regimens produced comparable survival outcomes following Haplo-HSCT. Although TBI-based conditioning resulted in significantly faster neutrophil engraftment, it was associated with a higher incidence of primary engraftment failure. Larger prospective multicenter studies are needed to confirm these findings.

Keywords: Hematopoietic Stem Cell Transplantation, Haploidentical Transplantation, Whole-Body Irradiation, Conditioning Regimen

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Introduction

Allogeneic haematopoietic stem cell transplantation (Allo-HSCT) constitutes the definitive therapeutic modality for a wide variety of benign and malignant haematological disorders.[1] However, only approximately a third of eligible patients possess an available matched related donor (MRD) within Pakistan's resource-constrained healthcare environment.[2] Matched unrelated donor (MUD) accessibility remains unavailable in our setups due to the absence of an established registry. Haploidentical HSCTs (Haplo-HSCTs) have seen an increase in utilization in recent years in Pakistan: 22 such procedures were performed in 2021, while the number more than doubled to 52 in 2022.[2] Primary engraftment failure and amplified risk of acute/chronic graft-versus-host disease (GvHD) in Haplo-HSCT represent the principal clinical challenges with this modality.[3,4] Despite these limitations, haploidentical sibling HSCTs remain a viable therapeutic option for patients with aggressive haematological disorders.

Clinical debate persists regarding the optimal pre-transplant conditioning regimen to maximize therapeutic outcomes while minimizing treatment-related toxicity. Disease relapse risk increases when total body irradiation (TBI)-based regimens using 400cGy dose are utilized, while chemotherapy (CT)-based conditioning regimens

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carry elevated toxicity profiles; both regimes are associated with significant morbidity and mortality at present albeit from different causes.[5] However, there is an added advantage of sanctuary site clearance from residual disease with TBI-based regimens, where chemotherapeutic agents have difficulty penetrating. Multiple investigations have evaluated outcomes comparing TBI-based regimens versus CT-based regimens in HLA-matched HSCT, with clinical outcomes of TBI versus CT-based conditioning demonstrating comparable efficacy in patients undergoing these transplants.[6] However, only limited studies have assessed the efficacy of TBI-based versus CT-based conditioning in Haplo-HSCT and, while equivalent survival rates and chronic GvHD risks have been observed in related Haplo-HSCT when compared with MRD and MUD transplantations in some studies, the role of type of conditioning remains unclear.[6,7] TBI-based regimens are postulated to be associated with reduced treatment-related toxicity and accelerated neutrophil engraftment, which may help in facilitating expedited hospital discharge and decreased overall procedural costs associated with Allo-HSCT.[8,9] As a consequence, transplantation centers are transitioning from CT- to TBI-based conditioning protocols, particularly due to the therapeutic advantage of transplanting elderly patients and those with compromised performance status.

Our objective was to establish a comparison of outcomes between TBI-based regimens and CT protocols in Haplo-HSCT patients. This analysis between the two conditioning regimens will provide valuable insights into their efficacy in our hitherto unstudied patient population due to limited TBI facility availability in most transplantation centers within Pakistan. Additional patient-, donor-, and transplant-related variables influencing Haplo-HSCT outcomes were also evaluated. Considering this as the singular regional representative investigation, this study may serve as the foundation for future multicentric prospective studies capable of generating data on this critical subject with the potential to modify clinical practice in this patient cohort.

Methodology

This was a retrospective cohort study, conducted on patients and their records starting from Dec 1, 2016 to Sep 9, 2023 in the Department of Clinical Hematology and Stem Cell Transplant Unit, Shifa International Hospital, Islamabad. A total of 50 patients who underwent Haplo-HSCT were included, after obtaining a consent waiver and clearance from institutional IERB. Patients of both genders between the ages of 5 and 50 years undergoing their first Haplo-HSCT were included. Patients were followed for HSCT outcomes and those who were lost to follow up were excluded. All patients were followed via telephone, out-patient appointments or email till Mar 5, 2025.

Patients were sorted to one of two groups on the basis of pre-transplant conditioning regimen received: those who received CT-based conditioning were placed in the CT group while those who received TBI were grouped together. All data were collected from the hospital electronic and physical medical records using patients medical record number as well as through patient interviews and follow-ups. Donors were selected after testing with the Luminex screen and Single Antigen Bead (SAB) assay for HLA Class I and II antibodies in the recipient, and were selected if the MFI was less than 3000. The different CT- and TBI-based conditioning protocols received by the patients during our study period are shown in Table-I.

Table I: Different CT- and TBI-based conditioning protocols used during the study period.

Conditioning Regimen	Total
TBI-Based	21
$Flu^{150}/Cy^{30}/TBI^{400}/PT\text{-}Cy^{80}$	10
$Flu^{150}/Cy^{30}/ATG^{15}/TBI^{400}/PT\text{-}Cy^{80}$	9
$Flu^{150}/Bu^{12.8}/TBI^{400}/PT\text{-}Cy^{80}$	1
$Bu^{16}/Cy^{30}/TT/ATG^{2}/TBI^{400}/PT\text{-}Cy^{80}$	1
CT-Based	29
$Flu^{150}/Bu^{9.6}/Cy^{30}/PT\text{-}Cy^{80}$	2
$Bu^{16}/Cy^{50}/ATG^{2}$	1
$Flu^{150}/Bu^{16}/PT\text{-}Cy^{80}$	1
$Flu^{150}/Bu^{9.6}/Mel^{140}/PT\text{-}Cy^{80}$	23
$Flu^{150}/Bu^{12.8}/Cy^{30}/ATG^{2}/PT\text{-}Cy^{80}$	2

With regards to GvHD prophylaxis, after twenty-four hours of post-transplant cyclophosphamide (PT-Cy) completion, IV Cyclosporine (CSA) 3 mg/kg was administered twelve hourly to maintain a trough level of between 200 and 300 ng/mL. All patients also received Mycophenolate Mofetil (MMF) 15 mg/kg twelve hourly, which was started along with CSA. Rabbit Anti-Thymocyte Globulin (rATG) was given as GvHD prophylaxis at a dose of 1 mg/kg once daily for two days in some patients in whom increased incidence of GvHD

was expected, while patients who were being transplanted for aplastic anemia were give rATG at a dose of 3.75 mg/kg for four days.

Operational Definitions:

- Overall Survival (OS) was defined as time from the date of infusion of stem cells to the time of death or last follow-up.
- Progression-Free Survival (PFS) was the total duration from date of infusion of stem cells until the disease progression/relapse, death or last follow-up.
- GvHD Free Relapse free survival (GRFS) was the point from date of infusion of stem cells till the occurrence of any of the following events: grade III/IV acute GVHD/ chronic GvHD requiring systemic treatment/ disease relapse, death due to any cause or till last follow-up, which ever event came first.
- Non-Relapse Mortality (NRM) was defined as death post-transplant not caused by recurrence or progression of primary disease for which transplant was done.
- Transplant-Related Mortality (TRM) was defined as death due to any cause before Day +100 from date of infusion of stem cells.
- Neutrophil engraftment was defined as an absolute neutrophil count of ≥500/cubic mm on the first day of three consecutive days post-transplant conditioning.
- Platelets engraftment was defined as independence from platelets transfusion for at least 7 days with a platelet count of >20×10^9/L on the first day of three consecutive days post-transplant conditioning.
- Acute GvHD grading was done using Glucksberg scoring system, while chronic GvHD was assessed using the National Institute of Health Consensus Criteria for Organ scoring of Chronic graft versus host disease.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables, including age, were summarized as mean ± standard deviation (SD), whereas non-normally distributed variables, including time to neutrophil and platelet engraftment, $CD34^+$ stem cell dose, and survival duration, were expressed as median with interquartile range (IQR). Categorical variables, including sex, diagnosis, pre-transplant cytomegalovirus (CMV) serostatus, mortality, and conditioning regimen, were summarized as frequencies and percentages. Comparisons between groups were performed using the independent-samples *t*-test or Mann–Whitney *U* test for continuous variables, as appropriate, and the Chi-square test or Fisher's exact test for categorical variables. Overall survival (OS), progression-free survival (PFS), and graft-versus-host disease/relapse-free survival (GRFS) were estimated using the Kaplan–Meier method and compared between groups. A two-tailed *p* value of ≤0.05 was considered statistically significant.

Results

We analyzed fifty consecutive Haplo-HSCT patients of which 21 (42.0%) received TBI-based- and 29 (58.0%) received CT-based conditioning. The patients' pre-transplant characteristics are displayed in Table-II. The majority of the cohort were young males (n=38, 76.0%). Acute myeloid leukemia was the most common indication for transplant (n=22, 44.0%). All the malignant diseases were in complete remission when taken to the transplant.

Table II: Patient Characteristics prior to Haplo-HSCT.

Characteristic	TBI-Based (n=21)	CT-Based (n=29)	*p*-value
Recipient Age	23.38 ± 12.19	28.66 ± 11.92	0.213
Recipient Gender			
Male	18 (85.7)	20 (69)	0.201
Female	3 (14.3)	9 (31)	
Recipient CMV Status			
Positive	20 (95.2)	29 (100)	0.42
Negative	1 (4.8)	0	
Donor Age	25.71 ± 14.05	30.66 ± 13.58	0.292
Donor Gender			
Male	11 (52.3)	16 (55.1)	0.845
Female	10 (47.6)	13 (44.9)	
Donor Gender Match			
Yes	12 (57.1)	13 (44.8)	0.39
No	9 (42.9)	16 (55.2)	
Donor CMV Status			
Positive	20 (95.2)	28 (96.6)	1.00
Negative	1 (4.8)	1 (3.4)	
Diagnosis			
Malignant	11 (52.4)	27 (93.1)	
Benign	10 (47.6)	2 (6.9)	
Disease Type			
B-ALL	3 (14.3)	3 (10.3)	

T-ALL	3 (14.3)	0	
ETP-ALL	2 (9.5)	0	
AML	3 (14.3)	18 (62.1)	
AML (Familial)	0	1 (3.4)	
MPAL	0	1 (3.4)	
CML	0	1 (3.4)	
Aplastic Anemia	6 (28.6)	2 (6.9)	
Paroxysmal Nocturnal Hemoglobinuria	2 (9.5)	0	
Fanconi Anemia	1 (4.8)	0	
Myelodysplastic Syndrome	0	1 (3.4)	
Beta Thalassemia Major	1 (4.8)	0	
Hodgkin's Lymphoma	0	2 (6.9)	

We documented patients for different transplant characteristics as shown in the Table-III.

Table III. Transplant Characteristics.

Characteristic	TBI-Based (n=21)	CT-Based (n=29)	*p*-value
Conditioning			
NMA	20 (95.2)	4(13.7)	-
MAC	1 (4.8)	25 (86.2)	-
Stem Cells Source			
Peripheral Blood	19 (90.5)	29 (100)	0.17
Bone Marrow	2 (9.5)	0	
CD34 stem cell dose	10.0±5.07	6.8±3.33	0.029
Engraftment			
Neutrophil (days)	13±2.06	14±1.44	0.032
Platelets	13±8.7	13±12.7	0.26
GVHD Prophylaxis			
Anti-Thymocyte Globulin (ATG)	10 (47.6)	3 (10.3)	0.004
PT-Cy	21 (100)	28 (96.5)	1.00

Principle mode of stem cell harvest was from peripheral blood (n=48, 96.0%) and only two patients received bone marrow harvest stem cells. Median stem cell dose infused in the TBI-based group was higher, (p=0.029). Forty-nine (98.0%) patients received PT-Cy as GvHD prophylaxis, of whom 12 (24.0%) received a combination of ATG and PT-Cy, while only 1 (2.0%) received ATG alone because they received a high cumulative dose of cyclophosphamide prior to stem cell infusion, precluding PT-Cy use. Neutrophil engraftment was achieved one day earlier in the TBI-based group and the difference was statistically significant (p=0.032). Platelets engraftment was observed at a median of 13 days in both groups (p=0.26).

The cumulative incidence of grade II-IV acute GvHD was 6 (28.6%) in the TBI-based group and 13 (44.8%) in the CT-based group (p=0.24), while grade III-IV acute GvHD occurred in 3 (14.2%) and 6 (20.6%), respectively (p=0.71). The incidence of chronic GvHD was 6 (28.6%) with TBI-based conditioning and 9 (31%) with CT-based conditioning, (p= 1.0).

At two years, the cumulative incidence of relapse was 14.3% (n=3) in the TBI-based group vs 13.7% (n=4) in the CT-based group (p=1.00), while non-relapse mortality was 14.3% (n=3) and 13.7% (n=4), respectively (p=1.0). TRM was 38.1% (n=8) in the TBI-based group and 41.4% (n=12) in the CT-based group (p=0.81). The most common causes that led to TRM were infections and early relapse. Rest of the causes are outlined in Table-IV.

Table-IV. Outcomes.

Characteristic	TBI-Based (n=21)	CT-Based (n=29)	*p*-value
Cause of Death			
NRM	3 (14.3)	4 (13.7)	1.00
Relapse	3 (14.3)	4 (13.7)	1.00
TRM	8 (38.1)	12 (41.3)	0.815
Acute GvHD			
Grade I	1 (4.7)	4 (13.7)	0.148
Grade II	3 (14.2)	7 (24.1)	0.488
Grade III	2 (9.5)	4 (13.7)	0.694
Grade IV	1 (4.7)	2 (6.8)	1.00
No GvHD	10(47.6)	14 (48.2)	0.963
Chronic GvHD			
Yes	6 (28.6)	9 (31)	1.000
No	15 (71.4)	20 (69)	
Broad Cause of Death			
Primary Engraftment Failure	2 (9.5)	0	0.171
Acute GvHD	1 (4.7)	3 (10.3)	0.630
Sepsis	1 (4.7)	4 (13.7)	0.383
Hemorrhagic cystitis	0	2 (6.8)	0.503
Cytokine release syndrome	1 (4.7)	3 (10.3)	0.630
Others (Infections/ICB/ progressive disease)	8 (38.1)	5 (17.2)	0.097
Chronic GvHD	0	1 (3.4)	1.00

Out of total 50 patients, 19 (38.0%) were alive at the time of the study. 02(4.0%) patients developed fatal complications of CMV reactivation. One patient died of chronic lung GvHD grade IV in the CT group.

Median OS was 11.5 months for the whole sample, with two-year OS was 41.4% (95% CI, 26.8% - 63.8%) in CT-based group vs 37% (95% CI, 21% - 65.4%) in the TBI-based group as shown in the Figure 1. Median PFS was 8 months, while the two-year PFS in the CT-based group

was 41.4% and 37% in the TBI-based group as demonstrated in Figure 2. The two-year GRFS was 13.8% in the CT-based group and 12.7% in the TBI-based group as shown in Figure 3.

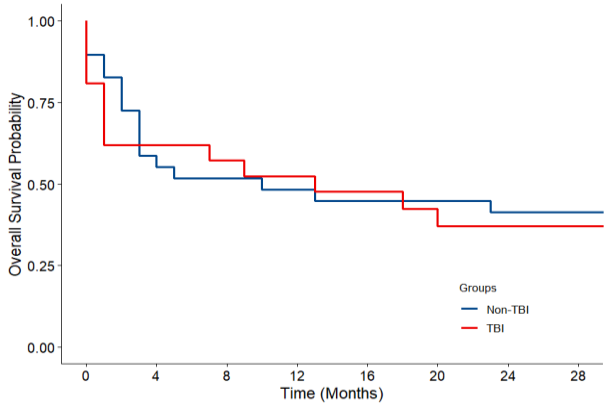

Figure 1. (Overall Survival)

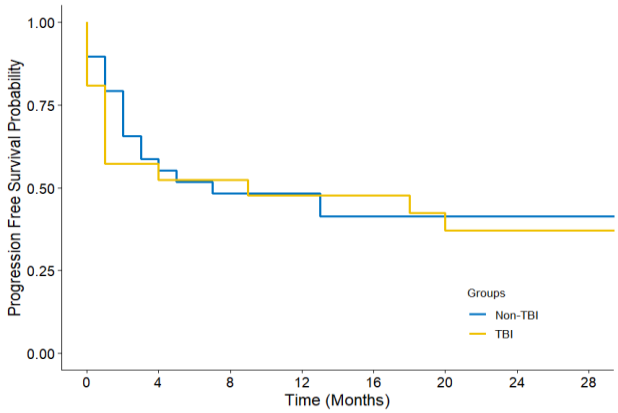

Figure 2. (Progression-Free Survival)

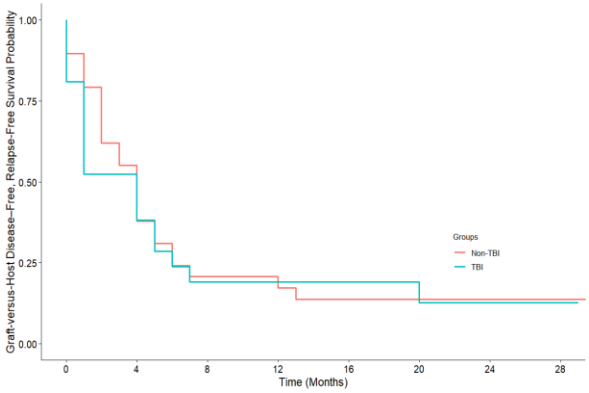

Figure 3. (Graft-versus-Host Disease-Relapse-Free Survival Probability)

Discussion

This single-center retrospective analysis represents the first comparative study of TBI-based versus CT-based conditioning regimens in Haplo-HSCT within the Pakistani population. Our findings demonstrate comparable two-year OS (37% vs 41.4%), PFS (37% vs 41.4%), and GRFS (12.7% vs 13.8%) between TBI-based and CT-based conditioning protocols, respectively. These outcomes provide important evidence for the feasibility of both conditioning approaches in resource-limited settings where certain chemotherapeutic regimens or TBI facilities may not be uniformly available.

The survival outcomes observed in our study cohort align with findings from several international studies examining conditioning regimens in haploidentical transplantation. Luznik et al., reported a similar OS of 36% and a slightly lower PFS of 26% at two years while using TBI-based conditioning in their study. Conversely, Klein et al., used the same TBI-based regimen in an AYA cohort with high-risk haematological malignancies and reported a higher OS of 52% and a PFS of 32% at three years [10,11], while Jaiswal et al., used CT-based regimen in a cohort aged two to twenty years and showed a better OS and PFS of 52.9% and 43.9% at eighteen months, respectively.[12] The variation in outcomes is likely attributable to the differences in the diagnoses of the different study cohorts and follow-up durations: whereas our report had a wide variety of patients, Jaiswal et al., was mainly focused on acute leukaemias and also used prophylactic donor lymphocyte infusions to improve PFS post-transplant. [12] This difference in outcomes is even more pronounced when our study is compared to studies such as Yun Lei et al., who used CT-based regimens for Haplo-HSCT in aplastic anemia with OS of 96.3% at two years.[13] Clearly, further disease specific study is required in the South-Asian before concrete conclusions can be drawn.

The low GRFS rates of 13.8% with CT-based and 12.7% with TBI-based conditioning in our study were substantially lower than those reported in international cohorts. Sanz et al. reported GRFS of 46% at two years in patients with acute lymphoblastic leukemia undergoing Haplo-HSCT using both TBI and CT-based regimens, while Xia Bi et al demonstrated GRFS of 65.8% at three years while using Donor Lymphocyte Infusion (DLI) at day-6 in conditioning protocol.[14,15.] This composite endpoint, which incorporates overall survival, disease progression, and significant GvHD, provides a comprehensive assessment of transplant success and quality of survival. The lower GRFS in our cohort reflects the cumulative impact of higher TRM, GvHD incidence,

and disease-related complications in our patient population. As before the heterogeneity of our study population in-terms of diagnosis makes a basis for comparison difficult.

A significant finding from our study was the earlier neutrophil engraftment observed in the TBI-based conditioning (Day+13 vs Day+16 with CT-based conditioning, p=0.032). This accelerated engraftment has not been previously documented in Haplo-HSCT using TBI-based conditioning. Early neutrophil recovery has important clinical implications, including reduced duration of neutropenia, decreased risk of infectious complications, and the potential for early discharge from hospital with associated financial savings, which is particularly relevant in our resource-constrained healthcare setting.

However, the TBI-based conditioning was associated with a higher rate of primary engraftment failure (19% vs 0%, p=0.05). On the contrary Solomon et al showed 100% engraftment with TBI-based myeloablative conditioning in Haplo-HSCT.[16] Several factors may have contributed to this finding, including the relatively low TBI dose (400 cGy) used in our protocol, donor-specific antibody levels, and the degree and type of HLA mismatch. Further investigation is warranted to identify specific risk factors for engraftment failure in TBI-based Haplo-HSCT within our patient population.

The transplant-related mortality rate of 40% in our cohort though higher but still comparable to few international series. Yan et al. reported TRM of 33.3% in Haplo-HSCT for haematologic malignancies and Catherine et al showed a TRM of 40% in Haplo-SCT conducted in AML group.[17,18] The primary causes of mortality in our series were sepsis, cytomegalovirus viremia, and steroid-refractory acute GvHD. The high TRM likely reflects the advanced disease status of many patients at transplantation, with 58% having received myeloablative conditioning following multiple salvage regimens. The non-relapse mortality of 14% was predominantly infection-related and comparable to the 18% reported by Munchel et al. in haploidentical transplantation using non-myeloablative regimens. [19]

The incidence of acute grade III/IV GvHD was 14.2% in the TBI group and 20.6% in the CT group, with chronic GvHD rates of 33% and 31% respectively. These rates are consistent with published literature on Haplo-HSCT using PT-Cy-based GvHD prophylaxis. Chevallier et al. reported similar acute GvHD rates in Haplo-HSCT for haematologic malignancies, while chronic GvHD incidence has ranged from 25-40% in various series. [20] The comparable GvHD rates between our two conditioning groups suggest that the addition of TBI at 400 cGy does not significantly alter the immunologic milieu with respect to GvHD risk when combined with PT-Cy. Additionally, rabbit anti-thymocyte globulin was administered to 26% of patients as part of the conditioning regimen to further reduce GvHD risk in selected high-risk cases.

The relapse rate of 8% in our entire cohort was lower than anticipated given the high proportion of patients with advanced malignancies. This may reflect the benefit of both TBI-based and intensive CT-based conditioning in disease control, as well as the graft-versus-leukaemia effect following Haplo-HSCT. Historical data suggested that non-TBI-based regimens were associated with lower relapse rates in haematologic malignancies, as demonstrated by Rubio et al. in 2016. [21]

Several strengths characterize our study, which represents the first comparative analysis of TBI-based versus CT-based conditioning in Haplo-HSCT within the South Asian region. All our patients received uniform GvHD prophylaxis with PT-Cy and standardized supportive care measures, reducing variability in post-stem cell infusion treatment. Moreover, the evaluation of a contemporary cohort with an adequate follow-up duration allows for a useful assessment of both short-term and intermediate-term outcomes. Lastly, this analysis provides crucial data regarding the feasibility and safety of TBI-based conditioning in a resource-limited setting, which can serve as an important base for expanding access to Haplo-HSCT.

Several limitations warrant consideration in the interpretation of our findings. The retrospective nature of our study introduces selection bias, as the assignment to type of conditioning was not randomized. Additionally, heterogeneity in underlying diagnoses and disease status at transplantation may have confounded outcome comparisons, as patients with different malignancies and varying disease burden may respond differently to the same conditioning regimens. Finally, the single-center nature of this study may limit generalizability to other

transplant centers with different patient populations, disease patterns and supportive care practices.

Conclusion

Our findings demonstrate that both TBI-based and CT-based conditioning yield comparable two-year outcomes in Haplo-HSCT, with TBI associated with significantly earlier neutrophil engraftment, but higher rates of primary engraftment failure. These outcomes support the feasibility of expanding Haplo-HSCT in centers without TBI facilities. Future prospective, multi-center studies with larger patient cohorts are required to validate these findings, with emphasis on strategies to reduce primary engraftment failure with TBI, including optimization of dosing, role of rituximab in major ABO incompatibility, and refinement of donor selection criteria based on donor-specific antibody testing.

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