

Conference Abstracts

Myeloablative is Not Always Better: Dismantling the One-Size-Fits-All Approach to Haploidentical Conditioning Intensity

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Background

Haploidentical hematopoietic cell transplantation provides critical donor options for ethnically diverse patients, expanding the donor pool for patients in need of this life-saving procedure who do not have access to suitable matched related or unrelated donors. The potent graft-versus-leukemia (GVL) effect challenges the historical superiority of myeloablative conditioning (MAC). While reduced intensity (RIC) and nonmyeloablative (NMA) regimens reduce toxicity, it remains unclear if they provide sufficient disease control across all age groups. We aimed to define the optimal intensity across age-stratified disease groups.

Methods

We analyzed 5,143 adult patients using a publicly available CIBMTR dataset with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myeloproliferative neoplasm/myelodysplastic syndromes (MPN/MDS) between 2017-2021. Age was stratified using clinically relevant, data-guided cut-offs tailored to each disease. Conditioning regimens were stratified into, MAC with total body irradiation (TBI), MAC-no TBI, RIC/NMA fludarabine/cyclophosphamide/ TBI (Flu/Cy/TBI), and a composite of all other RIC regimens (RIC/other). Our primary endpoint was overall survival (OS).

Results

In multivariable analysis, OS was similar across all conditioning intensities and all subgroups, shifting the clinical focus entirely to the distinct trade-offs between relapse and NRM.

In younger patients, the reduction in NRM offered by RIC/NMA regimens was counterbalanced by higher relapse risk. In AML patients (≤ 55 years), Flu/Cy/TBI was associated with half the NRM risk (HR 0.50, $p = 0.017$), but at the cost of nearly double the relapse risk (HR 1.98, $p < 0.001$). Similarly, in ALL patients (≤ 40 years), the RIC/NMA platform was associated with reduced NRM (HR 0.22, $p = 0.046$) but more than double the risk of relapse (HR 2.32, $p = 0.002$). MDS/MPN (≤ 60 years) patients showed a similar trend, where Flu/Cy/TBI was associated with increased relapse (HR 1.90, $p = 0.057$) but reduced NRM (HR 0.59, $p = 0.054$). In young patients, RIC/all regimens showed comparable relapse and NRM rates across all diseases, compared to MAC.

In older cohorts, the trade-off favored de-escalation. In AML patients (> 55 years), MAC-chemo was associated with a higher risk of NRM (HR 2.16, $p = 0.003$) without a significant difference in relapse. In ALL patients (> 40 years), Flu/Cy/TBI was associated with half the risk of NRM (HR 0.50, $p = 0.034$) and comparable

relapse rates to MAC. In MDS/MPN patients (>60 years), RIC/Other regimens were associated with reduced relapse (HR 0.31, $p=0.002$) with no difference in NRM, and Flu/Cy/TBI showed reduced relapse (HR 0.69, $p=0.30$) and NRM (HR 0.70, $p=0.40$) rates without statistical significance, compared to MAC.

Conclusion

Since OS is comparable across regimens, the choice of conditioning intensity represents a strategic management of competing risks rather

than a survival imperative. Our data characterize the specific relapse/NRM profile of each regimen by age and disease. Compared to MAC/TBI, RIC/other showed comparable relapse/NRM profile in younger patients across all diseases. While RIC/NMA was associated with comparable or superior outcomes in older patients across all diseases, challenging the notion that higher intensity equates to better outcomes and warrant a paradigm shift toward risk-adapted regimen selection.

AML ≤ 55 years	OS	p-value	Relapse	p-value	NRM	p-value
MAC/TBI	ref		ref		ref	
MAC/no TBI	0.99 (0.86, 1.14)	0.90	1.03 (0.76, 1.39)	0.85	1.01 (0.70, 1.46)	0.96
Flu/Cy/TBI	0.93 (0.78, 1.11)	0.44	1.98 (1.42, 2.74)	< 0.001	0.50 (0.29, 0.89)	0.017
RIC/ other	1.00 (0.83, 1.19)	0.97	0.84 (0.57, 1.25)	0.40	1.26 (0.79, 2.00)	0.33
AML > 55 years						
MAC/no TBI	0.98 (0.78, 1.23)	0.87	0.66 (0.42, 1.03)	0.07	2.16 (1.30, 3.59)	0.003
Flu/Cy/TBI	1.02 (0.83, 1.24)	0.88	0.99 (0.70, 1.41)	0.95	1.03 (0.64, 1.66)	0.91
RIC/ other	1.07 (0.87, 1.32)	0.51	0.65 (0.45, 0.95)	0.025	1.40 (0.86, 2.28)	0.17
MPN/MDS ≤ 60 years						
MAC/no TBI	1.13 (0.86, 1.48)	0.38	1.12 (0.57, 2.20)	0.75	0.75 (0.44, 1.28)	0.29
Flu/Cy/TBI	1.07 (0.81, 1.42)	0.62	1.90 (0.98, 3.70)	0.057	0.59 (0.35, 1.01)	0.054
RIC/ other	1.12 (0.85, 1.47)	0.41	1.23 (0.62, 2.42)	0.55	0.64 (0.38, 1.08)	0.10
MPN/MDS > 60 years						
MAC/no TBI	1.10 (0.72, 1.70)	0.66	0.32 (0.13, 0.76)	0.010	1.25 (0.51, 3.07)	0.63
Flu/Cy/TBI	1.13 (0.77, 1.67)	0.53	0.69 (0.34, 1.39)	0.30	0.70 (0.30, 1.62)	0.40
RIC/ other	1.21 (0.82, 1.79)	0.34	0.31 (0.15, 0.65)	0.002	1.09 (0.47, 2.51)	0.84
ALL ≤ 40 years						
MAC/no TBI	0.92 (0.69, 1.22)	0.57	1.44 (0.78, 2.69)	0.25	1.18 (0.63, 2.21)	0.61
Flu/Cy/TBI	1.05 (0.78, 1.42)	0.73	2.32 (1.37, 3.92)	0.002	0.22 (0.05, 0.97)	0.046
RIC/ other	0.98 (0.73, 1.32)	0.91	0.91 (0.46, 1.82)	0.80	1.21 (0.55, 2.65)	0.64
ALL > 40 years						
MAC/no TBI	1.05 (0.78, 1.43)	0.74	0.86 (0.48, 1.55)	0.62	1.02 (0.51, 2.04)	0.95
Flu/Cy/TBI	1.18 (0.93, 1.51)	0.18	0.86 (0.53, 1.37)	0.52	0.50 (0.26, 0.95)	0.034
RIC/ other	1.02 (0.78, 1.33)	0.90	0.73 (0.43, 1.24)	0.25	1.39 (0.77, 2.50)	0.28

Table 1. Multivariable Analyses