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ORAL ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Combined Effect of Unrelated Donor Age and HLA Peptide-Binding Motifs (PBM) Match Status on HCT Outcomes

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Background: HLA-mismatched unrelated donors (MMUDs) can be either matched or mismatched at protein binding motifs (PBM), while all HLA-matched donors are PBM-matched. A MMUD who is class I PBM-matched in the graft-vs-host (GVH) direction is preferred over a PBM-mismatched donor [*JCO.2023;41(13):2416*]. As donor age is also an important prognostic factor, we hypothesized that using a younger donor could compensate for the inferior overall survival (OS) associated with PBM-mismatches. Specifically, we tested if OS after transplantation with HLA-mismatched/PBM-matched/younger donors is similar to that with HLA-matched/older donors, and if OS is similar with HLA-mismatched/PBM-mismatched/younger donors as with HLA-mismatched/PBM-matched/older donors.
Methods: We analyzed the outcomes of patients with acute leukemia or myelodysplastic neoplasms who underwent HLA-matched or single class I MMUD HCT with a calcineurin inhibitor (CNI) for GVHD prophylaxis using a publicly available Center for International Blood and Marrow Transplant Research dataset. HLA class I MMUDs were categorized as "PBM-mismatched" if there was any GVH mismatch for the PBM, or "PBM-matched" if there was PBM-matching or only host-versus-graft mismatching. Donor age was dichotomized as "older" (> 35 years) or "younger" (< 35 years).
Six groups were compared: HLA-matched/younger donor (n=10,531), HLA-matched/older donor (n=3572), PBM-matched/younger donor (n=357), PBM-matched/older donor (n=257), PBM-mismatched/younger donor (n=616), and PBM-mismatched/older donor (n=339). The primary outcome of interest was OS.
Results: Median patient age was 50.3-56.2 years. Acute myeloid leukemia was the most common diagnosis in all groups (53-60%), most had early/intermediate disease (64-70%), most received myeloablative conditioning (60-69%) and peripheral blood (PB) graft (76-81%). A minority (18-23%) had T-cell epitope -DPB1 non-permissive GVH mismatched. All patients received CNI-based prophylaxis, without post-transplant cyclophosphamide (PTCy). Median follow-up among survivors was 48-61 months. In multivariate analysis, transplantation from HLA-matched/younger donors was associated with superior OS relative to any other group [**Figure**]. The notable findings of pairwise comparisons were three-fold. First, donor age significantly impacts OS in both HLA-matched and HLA-mismatched groups, but the negative impact of older donors relative to younger donors increases with increased mismatching for the PBM (18%, 25% and 35% increased mortality in older compared to younger donors within HLA-matched, PBM-matched and PBM-mismatched groups, respectively) [**Table**, pairwise comparison group 1]. Secondly, younger donors appear to negate the detrimental effect of PBM-mismatching [comparison group 2]. Specifically, the PBM-matched/younger donor group had similar OS as the HLA-matched/older donor group and the PBM-mismatched/younger donor group had similar OS as the PBM-matched/older donor group. Thirdly, HLA/PBM-matching is important within the younger and the older donor groups [comparison group 3]; however, the impact of PBM-mismatching was higher with older donors (25% and 62% increased risk of mortality with PBM-matched and PBM-mismatched, respectively than HLA-matched) than with younger donors (18% and 42% increased risk of mortality with PBM-matched and PBM-mismatched than HLA-matched).
Conclusion: Older unrelated donor age and PBM-mismatching confer similarly adverse effects on OS after transplantation with CNI prophylaxis and the impacts are additive. The preferred donor is HLA-matched, followed by HLA-mismatched/PBM-matched, and HLA-mismatched/PBM-mismatched. Transplantation from younger donors with inferior matching led to comparable outcomes as the older donors with better matching - a finding which may widen the "acceptable" donor pool. The best OS is observed with HLA-matched/younger donors and the worst with PBM-mismatched/older donors. Whether the use of PTCy modifies the impact of donor age and/or HLA/PBM-mismatching needs investigation.

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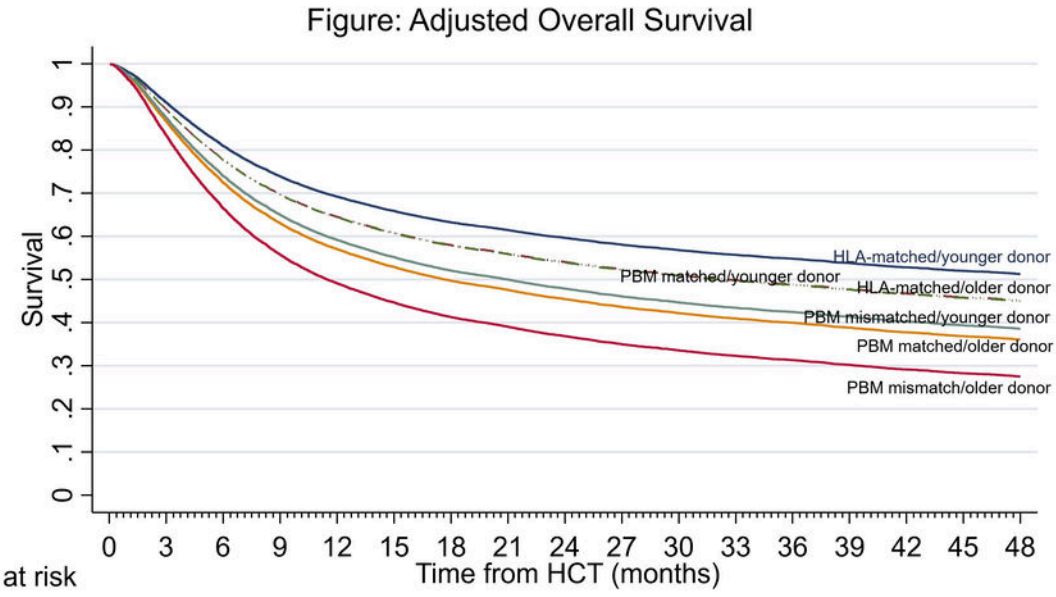

Number at risk

HLA-matched/younger donor	10531	8444	7069	6129	5215	4574	3955	3472	2969
HLA-matched/older donor	3572	2703	2193	1906	1634	1450	1273	1131	990
PBM-matched/younger donor	357	264	218	190	176	157	143	121	109
PBM-matched/older donor	257	176	138	118	106	94	81	72	65
PBM-mismatched/younger donor	616	439	346	297	246	226	196	176	149
PBM-mismatched/older donor	339	216	155	131	109	97	89	78	66

Table: Multivariate analysis: Overall Survival

	Donor groups	HR	95% CI		P-value
	HLA-matched/younger donor	*Ref*			
	HLA-matched/older donor	1.18	1.12	1.25	<0.001
	HLA-mismatched/PBM-matched/younger donor	1.18	1.02	1.37	0.03
	HLA-mismatched/PBM-matched/older donor	1.48	1.26	1.73	<0.001
	HLA-mismatched/PBM-mismatched/younger donor	1.42	1.27	1.58	<0.001
	HLA-mismatched/PBM-mismatched/older donor	1.91	1.67	2.18	<0.001
Group	***Pairwise comparisons***				
1	HLA-matched/older donor vs HLA-matched/younger donor (ref)	1.18	1.12	1.25	<0.001
	PBM-matched/older donor vs PBM-matched/younger donor (ref)	1.25	1.01	1.55	0.04
	PBM-mismatched/older donor vs PBM-mismatched/younger donor (ref)	1.35	1.14	1.59	<0.001
2	PBM-matched/younger donor vs HLA-matched/older donor (ref)	1.00	0.86	1.16	0.99
	PBM-mismatched/younger donor vs PBM-matched/older donor (ref)	0.96	0.80	1.16	0.67
3	PBM-matched/younger donor vs HLA-matched/younger donor (ref)	1.18	1.02	1.37	0.03
	PBM-mismatched/younger donor vs PBM-matched/younger donor (ref)	1.20	1.00	1.43	0.05
	PBM-matched/older donor vs HLA-matched/older donor (ref)	1.25	1.06	1.47	0.01
	PBM-mismatched/older donor vs HLA-matched/older donor (ref)	1.62	1.41	1.85	<0.001
	PBM-mismatched/older donor vs PBM-matched/older donor (ref)	1.29	1.06	1.58	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio; PBM, protein binding motifs; Ref, reference

Model adjusted for disease (MDS: HR 0.76, 95% CI 0.71-0.81, p<0.001), advanced stage (HR 1.71, 95% CI 1.62-1.80, p<0.001), KPS 90-100 (HR 0.81, 95% CI 0.77-0.84, p<0.001), HCT-CI ≥2 (HR 1.27, 95% CI 1.21-1.33, p<0.001), donor/recipient CMV -/+ (HR 1.11, 95% CI 1.06-1.16, p<0.001), time from diagnosis to HCT (6-12 months: HR 1.16, 95% CI 1.09-1.22, p<0.001), recipient age (40-55 yrs: HR 1.20, 95% CI 1.13-1.29, p<0.001; 55.1-65 yrs: HR 1.46, 95 % CI 1.37-1.56, p<0.001; >65 yrs: HR 1.62, 95% CI 1.50-1.73, p<0.001) and year of HCT (2010-12: HR 0.84, 95% CI 0.78-0.91, p<0.001; 2013-2015: HR 0.74, 95% CI 0.68-0.79, p<0.001; 2016-18: HR 0.64, 95% CI 0.59-0.69, p<0.001).

Figure 1

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