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POSTER ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Selecting the Right Alternative Donor: Comparison of Outcomes of HLA-Mismatched Alternative Donor Hematopoietic Cell Transplantations in Adult Patients with Acute Lymphoblastic Leukemia Regarding KIR-Ligand Mismatch

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Background: Allogeneic hematopoietic cell transplantation from cord blood (CBT) or haploidentical donor (HIDT) has proved to be a viable option for patients unable to find a human leukocyte antigen (HLA)-matched conventional donor. However, few single-centered studies have compared outcomes of the two alternative donor transplantations in adult acute lymphoblastic leukemia (ALL).
Aim: Our aim is to compare outcomes of adult ALL patients treated with CBT with those treated with HIDT. Secondly, we tried to find out factor that could be considered in selecting donor for alternative donor transplantation to improve clinical outcomes.
Methods: We compare outcomes of adult ALL patients treated with CBT (n=134) between 2008 and 2022 with those treated with HIDT (n=47) between 2018 and 2022.Conditioning regimen for CBT consisted of total body irradiation (12Gy) plus cytarabine (9g/m ^{2}) plus fludarabine (150mg/m ^{2}). Graft-versus-host disease (GVHD) prophylaxis was attempted using tacrolimus and mycophenolate mofetil. For HIDT, we used reduced toxicity conditioning (RTC) regimen including fludarabine (150mg/m ^{2}) plus busulfan (6.4mg/kg). GVHD prophylaxis was done with ATG 1.5mg for 4 days plus short course methotrexate (MTX) (15mg/m ^{2}) plus tacrolimus. Killer cell immunoglobulin-like receptor (KIR) ligand mismatch was calculated in both GVH and HVG direction using HLA-KIR ligand database, and its effect on clinical outcomes of alternative donor transplantation was investigated.
Results: In HIDT, CD34+ cell count (´10 ^{6}/kg) was significantly higher (7.4 vs. 0.1, P<0.001), and the patients were older (49 vs. 33.5, P<0.001) compared to CBT. Other characteristics, such as cytogenetic risk and leukocyte count at diagnosis, did not show significant difference between the two groups. Incidence of acute GVHD II-IV (51.1% vs. 50.0%), III-IV (25.5% vs. 17.9%), and moderate to severe chronic GVHD (10.8% vs. 11.0%) between HIDT vs. CBT were similar. After median follow-up of 39.4 months (range: 5.5-167.4), HIDT showed higher cumulative incidence of relapse (CIR) compared to CBT (47.9% vs. 18.9%, P<0.001), which remained true even after stratifying by age subgroup (Age<40: P=0.033, Age≥40: P=0.002). Conversely, CBT showed higher non-relapse mortality (NRM) than HIDT (22.8% vs. 9.0%, P=0.038), but the same was true only in the older age subgroup (Age<40: P=0.484, Age≥40: P=0.002). These effects summed up to produce comparable results in estimated 3-year disease-free survival (DFS) of CBT and HIDT (58.4% vs. 43.5%, P=0.103), especially in the older subgroup (38.7% vs. 40.7%, P=0.897). Multivariate analysis also revealed that HIDT was related with higher relapse (HR 3.47; 95%CI 1.92-6.27, P<0.001), and CBT with higher NRM (HR 4.18; 95%CI 1.42-12.3, P=0.009).
GVH direction KIR ligand mismatching worked for lower 3-year DFS in CBT (40.3% vs. 74.4%, P=0.007), although CIR and NRM did not show significant difference (27.8% vs. 15.6%, P=0.178; 35.0% vs 18.4%, P=0.057, respectively). On the other hand, the mismatch resulted in lower incidence of acute GVHD II-IV (32.0% vs. 54.2%, P=0.011). The trend remained when such effect was investigated separately in CBT and HIDT, but it was not statistically significant (33.3% vs. 53.1%, P=0.082; 28.6% vs. 57.6%, P=0.053, respectively).
Conclusions: Our data shows higher NRM in CBT, and unexpected higher relapse rate in HIDT. Age of the patient should be considered when choosing CBT, because in older patients CBT showed notably worse NRM compared to HIDT. Higher incidence of relapse in HIDT may be attributable to ALL disease characteristics itself or insufficient elimination of leukemic cells by RTC regimen with stronger GVHD prophylaxis.

Similar to what is known in acute myeloid leukemia, GVH direction KIR incompatibility showed protective effect against acute GVHD in ALL. However, the mismatch resulted in worse DFS in ALL patients treated with CBT, but not in those treated with HIDT. Possible explanation to this phenomenon is that the number of NK cells in cord blood was insufficient for mismatch-induced graft-versus-leukemia effect, while its immune response against infected cells was suppressed by the same mechanism that resulted in lower acute GVHD.

Keywords: Acute lymphoblastic leukemia, Cord blood transplantation, Haploidentical donor transplantation, HLA-mismatched transplantation, Killer-cell immunoglobulin like receptor

Disclosures No relevant conflicts of interest to declare.

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Table 2. Uni- and multivariate analyses in adult ALL patients treated with alternative donor HSCT

Variables	DFS				NRM				CIR				Acute GVHD II-IV				Chronic GVHD (moderate to severe)			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	3-year DFS	*P*	HR (95% CI)	*P*	3-year NRM	*P*	HR (95% CI)	*P*	3-year CIR	*P*	HR (95% CI)	*P*	100-day incidence	*P*	HR (95% CI)	*P*	3-year incidence	*P*	HR (95% CI)	*P*
Age at diagnosis																				
<40 years (n=106)	64.1%	0.002	**1.00**		13.6%	0.014	**1.00**		22.5%	0.186			54.7%	0.043	**1.00**		12.5%	0.352	-	
≥40 years (n=75)	41.4%		**1.97 (1.26-3.08)**	**0.003**	27.9%		**3.40 (1.62-7.17)**	**0.001**	31.9%				38.7%		**0.72 (0.46-1.11)**	**0.130**	8.8%			
HCT-CI																				
0-2 (n=120)	53.2%	0.647			19.9%	0.779			27.5%	0.766			50.0%	0.520			9.3%	0.457	-	
≥3 (n=61)	58.0%				18.1%				24.0%				44.3%				14.1%			
Initial leukocyte count																				
<30×10^9/L (n=119)	62.3%	0.004	**1.00**		14.0%	0.014	**1.00**		24.4%	0.308			47.1%	0.410			12.0%	0.381	-	
≥30×10^9/L (n=62)	41.0%		**1.63 (1.03-2.58)**	**0.036**	29.2%		**2.08 (1.06-4.07)**	**0.032**	30.3%				50.0%				8.8%			
CR prior to transplantation																				
CR1 (n=155)	60.4%	<0.001	**1.00**		18.0%	0.213	**1.00**		22.0%	<0.001	**1.00**		49.0%	0.612			11.5%	0.637	-	
≥CR2 (n=26)	21.1%		**3.55 (2.09-6.01)**	**<0.001**	26.9%		**1.96 (0.78-4.94)**	**0.150**	52.0%		**3.76 (1.89-7.49)**	**<0.001**	42.3%				7.7%			
Ph-subgroup and MRD																				
Ph-negative ALL (n=108)	61.0%	0.019	**1.00**		16.0%	0.29			23.3%	0.344			52.8%	0.022	**1.00**		11.6%	0.917	-	
Ph-positive ALL, MRD-negative (n=39)	53.6%				22.1%				25.3%				30.8%		**0.47 (0.26-0.86)**	**0.015**	11.2%			
Ph-positive ALL, MRD-positive (n=34)	37.4%		**1.55 (0.92-2.62)**	**0.099**	26.5%				36.6%				52.9%		**0.98 (0.57-1.66)**	**0.930**	9.0%			
Karyotype																				
Standard-risk (n=77)	65.3%	0.016			13.3%	0.077			21.7%	0.229			55.8%	0.098			13.0%	0.33	-	
Poor-risk (n=104)	47.0%				23.9%				29.7%				42.3%				9.4%			
EMI at presentation																				
No (n=106)	54.7%	0.836			19.6%	0.937			26.2%	0.759			43.4%	0.123			11.6%	0.652	-	
Yes (n=75)	55.0%				19.0%				26.6%				54.7%				10.0%			
Source of stem cell																				
CBT (n=134)	58.5%	0.105			22.8%	0.048	**1.00**		18.9%	<0.001	**1.00**		47.8%	0.73			10.9%	0.904	-	
HIDT (n=47)	44.3%				9.0%		**0.23 (0.08-0.67)**	**0.007**	47.9%		**3.45 (1.91-6.23)**	**<0.001**	48.9%				10.8%			
GvH KIR ligand mismatch																				
No (n=121)	61.3%	0.040	**1.00**		16.1%	0.117			24.0%	0.283			54.2%	0.011	**1.00**		11.2%	0.93	-	
Yes (n=60)	38.1%		**1.53 (0.96-2.43)**	**0.075**	26.9%				35.0%				32.0%		**0.56 (0.32-0.97)**	**0.039**	10.0%			
HvG KIR ligand mismatch																				
No (n=111)	55.2%	0.99			18.5%	0.946			27.7%	0.957			48.8%	0.638			10.1%	0.594	-	
Yes (n=70)	54.1%				20.3%				25.6%				46.4%				12.7%			

Abbreviation: ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplantation; DFS, disease-free survival; NRM, non-relapse mortality; GVHD, graft-versus-host disease; CIR, cumulative incidence of relapse; HCT-CI, hematopoietic cell transplantation comorbidity index; CR, complete remission; Ph, Philadelphia chromosome; MRD, measurable residual disease; EMI, extramedullary involvement; CBT, cord blood transplantation; HIDT, haploidentical donor transplantation; GvH, graft versus host direction; HvG, host versus graft direction; KIR, killer-like immunoglobulin receptor.
*For multivariate analysis, variables were chosen using stepwise selection with Akaike's information criteria.

Figure 1