HSC transplant: role of amino acid substitutions in antigen binding sites

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Introduction

Robust evidence supports the adverse impact of donor-recipient HLA disparity on Hematopoietic Stem Cells Transplantation (HCT) outcomes and thus it is necessary to investigate the relationship between mismatches and transplant outcome as a 10/10 match cannot be found for all patients in need of transplantation. Interesting studies conducted on amino acid substitutions (AAS) in the antigen binding sites (Pidala et al., Blood, 2013) showed the relevance of the HLA-B mismatches in position 9 (chronic GvHD increase), HLA-C in position 99 (increase in transplant-related mortality), HLA-C in position 116 (acute GvHD increase). These mismatches are classified as nonpermissive if they lead to an amino acid change.

Objectives

We studied the impact of these AAS on the transplant outcome of donor-recipient pairs from 2005 to now in collaboration with the Transplant Center (Molinette of Turin).

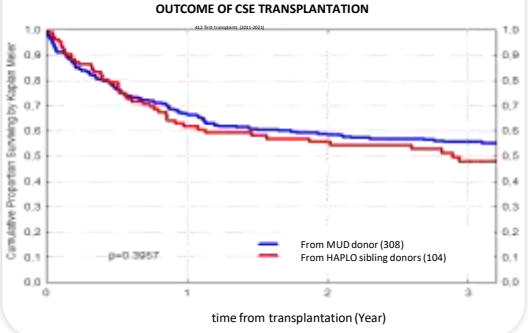
Methods

Patients and donors had completed high-resolution typing for HLA-A, B, C, DRB1, DQB1 (GenDx kits). In this period 931 patients underwent an HSC allografts, the study included 430 patients who received a first transplant from haploidentical sibling donors (HAPLO 106), MUD 10/10 (239), MUD 9/10 with a permissive mismatch at the loci HLA-B or HLA-C (P-MM 46), MUD 9/10 with a nonpermissive mismatch at the same loci (NP-MM 39).

Results

MUD and HAPLO sibling donors transplants were compared in the period from 2011 to 2021. We analysed patient survival related to different variables like gender, age, original disease of recipient, onset and severity of GvHD, source of HSC. The survival at 3 years in recipient of HAPLO and, MUD.

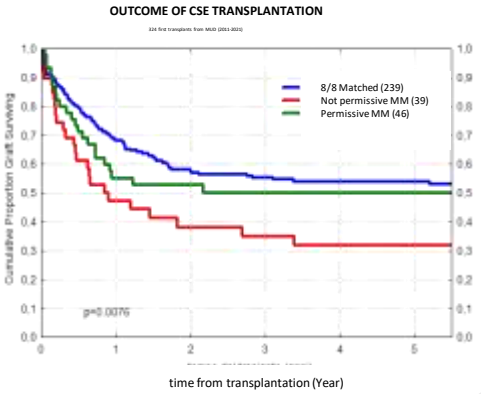
		From MUD donor	From HAPLO sibling donors	p-value
N. TX 2011-2021		315	114	
Gender recipient (M/F)		190/125	62/52	P=0.270
Age recipient (aa)		50,5±11,8	51,8±13,7	P=0.748
Underlying disease	AML	130 (41%)	67 (58.7%)	P=0.010
	Lymphoma	57 (18%)	11 (9.6%)	
	ALL	40 (13%)	18 (15.8%)	
	SAA	10 (3%)	0	
	MDS	48 (15%)	13 (11.4%)	
	Chronic myeloproliferative Disease	13 (4%)	5 (4.4%)	
	Myeloma	15 (5%)	0	
	Other	2 (0.6%)	2 (1.7%)	
Cellular source	Bone marrow	25 (8%)	45 (40%)	P<0.001
	Peripheral blood	289 (92%)	69 (60%)	
Age donor (aa)		38,9±9,6	34,2±12,7	P=0.013
Acute G-vHD		54.7%	51.4%	P=0.568



Results

We analysed patient survival related to different variables like gender, age, original disease of recipient, onset and severity of GvHD, source of HSC. The survival at 3 years in recipient of HAPLO, MUD and P-MM transplants is similar (53%), while it is less for NP-MM (34%).

		FIRST MUD TRANSPLANTS			
		8/8 MATCHED	PERMISSIVE MISMATCH	NOT PERMISSIVE MISMATCH	P-value
N. TX 2005-2021		239	46	39	
Gender recipient (M/F)		132/107	34/12	22/17	P=0.062
Cellular source	Bone marrow	24	5	4	P=0.999
	Peripherical bood	215	41	35	
Age donor (aa)		29,3 ±8,5	33,3±8,5	37,2±8,3	P=0.004
G-vHD acuta		52.7%	60.6%	44.4%	P=0.476
Underlying disease	AML	92	15	14	P=0.768
	Lymphoma	45	16	9	
	ALL	31	7	3	
	SAA	8	1	1	
	MDS	38	6	6	
	Chronic myeloproliferative Disease	10	0	2	
	Myeloma	15	1	4	



Discussion & Conclusion

The survival at 5 years for P-MM is 52% significantly better than for Not Permissive-MM transplants (32%, p = 0.04).
This relevant information will be provided to the Transplant Center as a tool for the selection of donors.

References

Pidala et al., Blood, 2013