Impact of T-Cell Dose on Outcome of T Cell–Replete HLA-Mismatched Allogeneic Peripheral Blood Stem Cell Transplantation

Rawan Mustafa MD, Dalia Al-Rimawi MSc, Dania Sarhan BSc, Hadeel Abdelkhaleq BSc, Khalid Halahleh MD
King Hussein Cancer Center, Amman, Jordan

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Background

The outcome of allogeneic hematopoietic cell transplantation (HCST) performed for hematologic malignancies relies on disease-related factors such as disease status and transplant-related factors including the conditioning regimen and immunotherapy exploiting the graft versus-tumor (GVT) effect, which is derived primarily from donor immune effector cells [1-2].

A complex interaction between the immune effector cells (antigen-presenting cells, CD3+ cells, CD4+ T cells, CD8+ T cells, regulatory T cells (Tregs), natural killer (NK) cells), is responsible for both the graft versus tumor (GVT) effect and the graft-versus-host disease(GvHD)[3]. Among these, the most well-studied cells are CD3+T cells [3].

CD3+T cells are the main player in GVT process, increasing the dose of these cells results in increasing the risk of acute GVHD [4]. In vivo and Ex vivo T cell depleted grafts are associated with reduction of GvHD but at the expense of increased relapses and infections [4]. Peripheral blood stem cell (PBSC) grafts which carry 10 to 15 times the higher quantity of CD3+T cells also have higher risk of GVHD, and chronic GvHD in particular compared with bone marrow (BM) grafts [5-7]. Although, several trials have been made to separate GVT effect from GVHD(CD34+T cell selection, naïve T cell depletion, post-transplantation cyclophosphamide, micro transplantation, and NK cell graft engineering), there are only few single-center studies that have evaluated the role of CD3+T cell dose with respect to both relapse, GVHD and survival outcomes post- HCT; however, these studies varied significantly in terms of selection criteria, different types of donors, different disease, and different conditioning regimens[8-11].. The optimum cutoff CD3+T cell dose that can potentially avoid GVHD while still preserving the GVT effect are unknown and there is no consensus in the transplant community [12]. Some experts hypothesized that there is a T cell dose range that enhance GVT without increased GvHD risk, and subsequent non-relapse mortality (NRM) [13].

Objective

We aimed to study whether the T-cell dose of allogeneic peripheral blood stem cell (PBSC) products influences transplantation outcomes in our patient population.

Methods

This is a retrospective chart review study including patients over 18 years of age, diagnosed with AML, ALL, or MDS, who underwent PBSC mismatched allogeneic transplant, including haploidentical, one-antigen or 2-alleles mismatched related transplants at the King Hussein Cancer Center's bone marrow transplant program between January 2010 and December 2020. We calculated the median CD3 cell dose and divided all patients into 2 groups (Low and High dose groups) and then measured the cumulative incidence of acute and chronic GVHD, 1- and 2-year overall survival (OS).

Results

		CD3+ cell dose		
	Value	Low	high	P-value
		18(51.43%)	17(48.57%)	
Recipient-Gender	Female	6(50.0%)	6(50.0%)	0.903
	Male	12(52.2%)	11(47.8%)	
Recipient-Age(present)	Mean(std)	30.3(12.5)	30.1(10.2)	0.766
	Median(Range)	27.5(17.0,58.0)	29.0(17.0,53.0)	
Recipient/Donor Sex Match	F/F	3(42.9%)	4(57.1%)	0.017
	F/M	3(75.0%)	1(25.0%)	
	M/F	1(11.1%)	8(88.9%)	
	M/M	11(73.3%)	4(26.7%)	
Recipient/Donor CMV Serostatus, Match	-ve/+ve	1		
	+ve/-ve		1	
	+ve/+ve	17(53.1%)	15(46.9%)	
Recipient/Donor ABO Match	Bidirectional	2(66.7%)	1(33.3%)	0.845
	Major mismatch	5(62.5%)	3(37.5%)	
	Match	8(44.4%)	10(55.6%)	
	Minor mismatch	3(50.0%)	3(50.0%)	
	Positive	18(52.9%)	16(47.1%)	
Donor GCSF primed BM	No	14(45.2%)	17(54.8%)	0.104
	Yes	4		
Donor GCSF PBSC	No	4		0.104
	Yes	14(45.2%)	17(54.8%)	
CD3+ cell dose	Mean(std)	13.7(5.9)	29.7(16.7)	0.000
	Median(Range)	15.6(2.8,19.7)	25.9(19.8,93.1)	
CD34+ cell dose	Mean(std)	6.8(3.2)	6.4(2.1)	0.632
	Median(Range)	6.9(2.2,15.6)	6.0(3.7,11.0)	
Disease Dx	ALL	6(60.0%)	4(40.0%)	0.711
	AML-MDS-Others	12(48.0%)	13(52.0%)	
Type of Transplant	Haploidentical	17(60.7%)	11(39.3%)	0.041
	Mismatched related	1(14.3%)	6(85.7%)	
Conditioning Regimen	Myeloablative	17(56.7%)	13(43.3%)	0.209
	Reduced Intensity	1(25.0%)	3(75.0%)	
	Reduced Toxicity		1(100%)	
TBI in conditioning	Yes	9(56.3%)	7(43.8%)	0.600
ATG in conditioning	Yes	2(28.6%)	5(71.4%)	0.228
GvHD Prophylaxis	CSA/TAC + Post-infusional Cytoxan (PTcy)	16(51.6%)	15(48.4%)	1.000

Table-1: Patients' Characteristics

Results

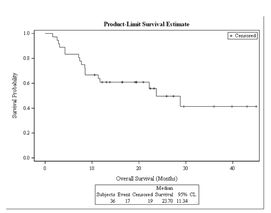
Thirty-five patients were stratified according to the median CD3+ cell dose into the Low CD3 group, which included 18 (51%) patients with a mean dose of 13.7×107/kg (range: 2.8–19.7), and the High CD3 group, which included 17 (49%) patients with a mean dose of 29.7×107/kg (range: 19.8–93.1) (P-value: 0.000). **Table -1**

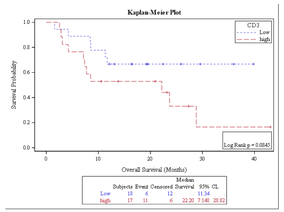
The cumulative incidence of acute GVHD was 60% (n=12) in the Low CD3 group and 40% (n=8) in the High CD3 group (P-value: 0.24). The cumulative incidence of chronic GVHD was 64% (n=9) in the Low CD3 group and 35% (n=5) in the High CD3 group (P-value: 0.26). **Table -2**

The overall survival for the cohort (n=35) at 12 months was 60.9% and reached 49.6% at 24 months. The 12-month OS for the Low and High CD3 groups was 66.7% and 52.9%, respectively. The 24-month OS for the Low and High CD3 groups was 66.7% and 33.1%, respectively (P-value: 0.084). **Figure -1**

		CD3+ cell dose		
	Value	Low	high	P-value
		18(51.43%)	17(48.57%)	
aGvHD	No	6(40.0%)	9(60.0%)	0.241
	Yes	12(60.0%)	8(40.0%)	
cGvHD	No	9(45.0%)	11(55.0%)	0.268
	Yes	9(64.3%)	5(35.7%)	

Table-2: The Cumulative Incidence of acute GVHD and chronic GVHD





TIMELIST	OS%
12 months	60.9(44.6,76.0)
24 months	49.6(30.8,68.5)

CD3	TIMELIST	OS%
Low	12 months	66.7(43.9,85.9)
Low	24 months	66.7(43.9,85.9)
high	12 months	52.9(29.8,75.5)
high	24 months	33.1(10.5,61.0)

Figure-1: Overall survival results.

Conclusion

Although the study showed a trend toward better OS in the Low CD3+ dose group, the difference was not statistically significant. Increasing the number of participants or longer follow up time can help elucidate these findings. The study also failed to show a difference in the incidence of both acute or chronic GVHD.

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