



The Impact of CD34+ Cell Dose on the Outcome of Allo-HSCT in Adult SAA Patients Conditioned with a Non-ATG-Based Regimen with Post-Transplantation Cyclophosphamide from Fully Matched-Sibling Donors

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Background and Aim

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only treatment that may cure severe aplastic anemia (SAA) and restore effective hematopoiesis. Post-transplantation cyclophosphamide (PTCy) decreases the risk of acute and chronic graft-versus-host disease (GVHD) by reducing alloreactive CD4+ effector T-cell proliferation with the preferential recovery of CD4+ T regulatory cells¹. The outcome of PTCy in SAA is comparable to antithymocyte globulin rabbit^{2,3}. However, there is a paucity of research regarding the optimal dose of CD34+ cells required for successful engraftment in conditioning regimens utilizing PTCy for GVHD prophylaxis. In this study, we aimed at finding a preliminary cut-off for the optimal CD34+ dose required in patients receiving PTCy, without increased risk of acute or chronic GVHD. The primary outcome measures were 6-months TRM and 1-year overall survival (OS).

Patients and Methods

We retrospectively analyzed the data of 23 SAA patients aged 20 years and older who underwent Allo-HSCT at Nasser's Institute Hospital for research and treatment, Cairo, Egypt from 2017 to 2020. Patients were conditioned with fludarabine (40 mg/m²/d from d-3 to d-1), cyclophosphamide (25 mg/kg/d from d-5 to d-2), and PTCy (50 mg/kg/d from d+3 to d+4) (FLU/Cy/PTCy). All patients received PBSC. Cyclosporine (3 mg/kg/d) was started from d+5. Overall survival was estimated using Kaplan-Meier's method and 6-months mortality was represented by frequencies and proportions. To determine the CD34+ dose cut-off, we performed a logistic regression analysis to predict 6-months TRM, followed by a receiver-operator characteristics analysis to determine the Youden's index.

Results

The median age at transplantation was 31 years (range: 20–55 years), and the median CD34+ dose was $6.1 \times 10^6/\text{kg}$ (range: $2.9\text{--}7.0 \times 10^6/\text{kg}$). Neutrophil engraftment occurred in 15 patients (65.2%) and platelet engraftment in 12 patients (52.2%). The median time to engraftment was 18 days for neutrophils (range: 15–26 days) and 15 days for platelets (range: 9–27 days). Within the specified follow-up period, 12 patients died, where 7 deaths (58.3%) occurred before d+15.

The primary cause of death was septic shock, which occurred in 6 patients (50%). The median survival was 5.5 months. None of our patients had aGVHD, and only 2 patients (8.70%) had pulmonary cGVHD. ROC analysis identified a CD34+ dose of $6 \times 10^6/\text{kg}$ as an optimal cut-off to predict 6-month mortality with 66.7% sensitivity and 81.8% specificity (AUC: 0.75). CD34+ doses higher than $6 \times 10^6/\text{kg}$ correlated with lower 6-months TRM (30.8% vs. 80.0%, OR = 9.0, $p = 0.03$) and higher 1-year OS (69.2% vs. 20.0%, HR = 4.1, $p = 0.02$).

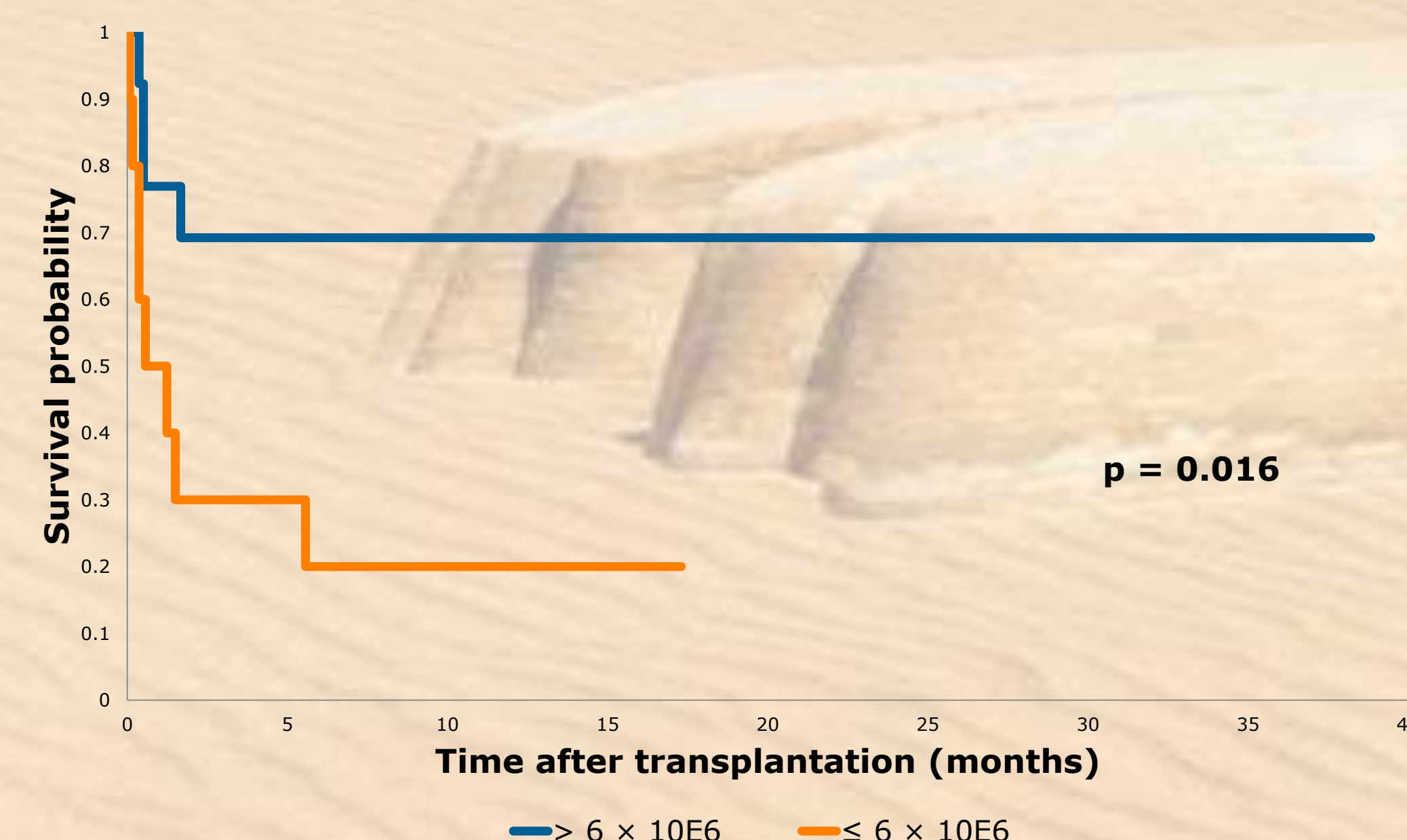


Figure 1. Overall survival with regards to the CD34+ dose

Table 1. Patients' characteristics with regards to the CD34+ dose

	CD34+ dose		p
	$\leq 6 \times 10^6$ (n=13)	$> 6 \times 10^6$ (n=10)	
Transplantation year:			
2017	2 (15.4%)	0 (0.0%)	
2018	2 (15.4%)	3 (30.0%)	
2019	8 (61.5%)	6 (60.0%)	
2020	1 (7.7%)	1 (10.0%)	
Age (yr):			0.71 ²
Mean (±SD)	30.7 (10.2)	32.3 (9.6)	
20-40	11 (84.6%)	7 (70.0%)	
> 40	2 (15.4%)	3 (30.0%)	
Gender:			0.07 ¹
Females	7 (53.8%)	1 (10.0%)	
Males	6 (46.2%)	9 (90.0%)	
Donor- recipient CMV IgG:			0.41 ¹
Donor-/recipient-	3 (23.1%)	0 (0.0%)	
Donor-/recipient+	1 (7.7%)	2 (20.0%)	
Donor+/recipient-	1 (7.7%)	0 (0.0%)	
Donor+/recipient+	8 (61.5%)	8 (80.0%)	
Donor-recipient sex:			0.21 ¹
Female-Female	5 (38.5%)	1 (10.0%)	
Female-Male	4 (30.8%)	5 (50.0%)	
Male-Female	2 (15.4%)	0 (0.0%)	
Male-Male	2 (15.4%)	4 (40.0%)	
Months from diagnosis to Tx:			0.46 ³
Median (Range)	6.5 (3.7-36.2)	9.0 (3.8-27.1)	
≤ 12 months	11 (84.6%)	6 (60.0%)	
> 12 months	2 (15.4%)	4 (40.0%)	

1. Fisher's exact test.
2. Student's t-test.
3. Mann-Whitney's U test.
Tx: Transplantation, yr: Years.

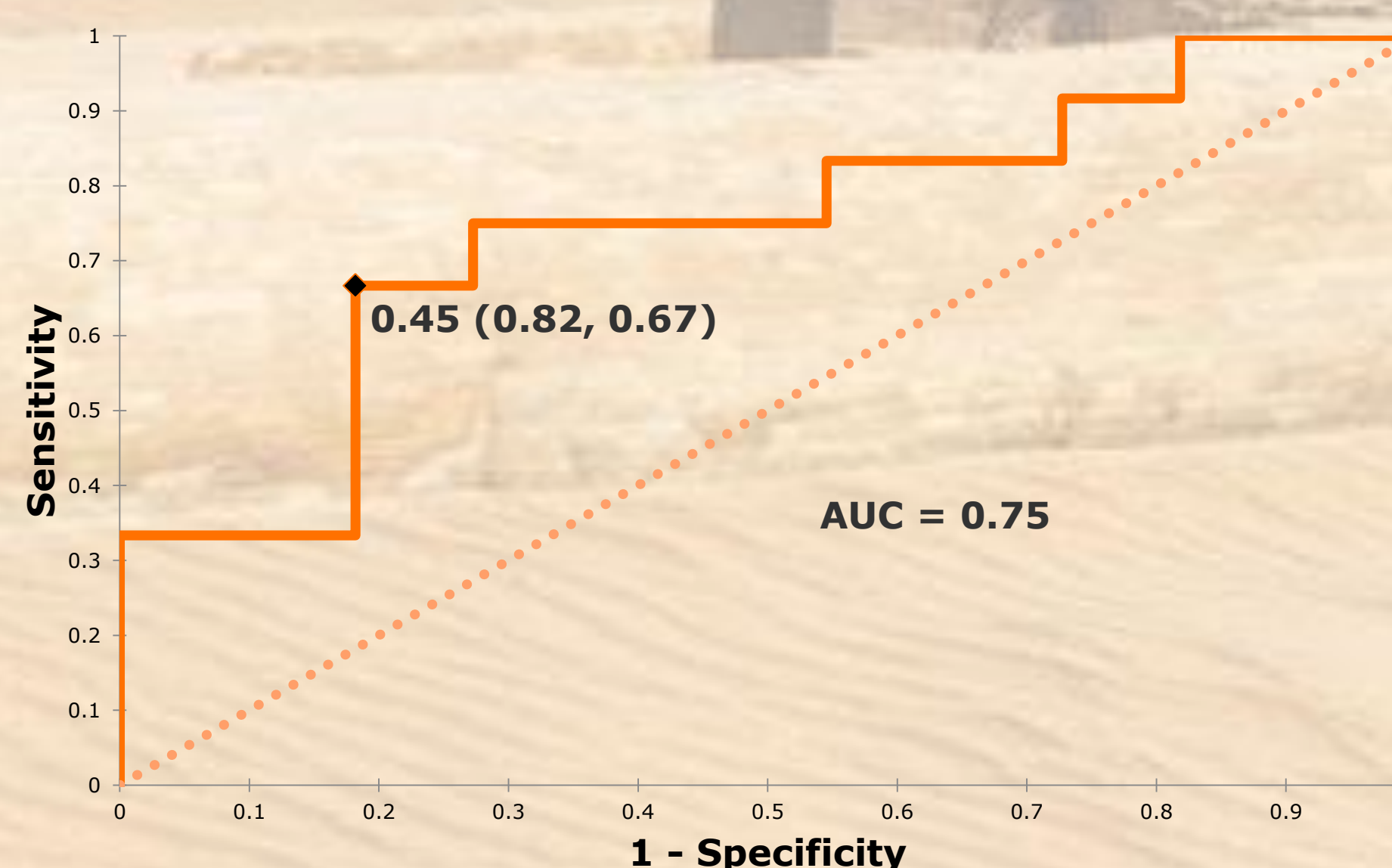


Figure 2. ROC curve (blue dot represents the Youden's index)

Conclusion

We found that a cut-off of 6×10^6 cells/kg correlated with superior survival outcome at 1-year post-transplantation and lower 6-month TRM, with no acute GVHD and acceptable incidence of chronic GVHD.

The CD34+ dose is critical to decide the success of transplantation. Several studies evaluated the optimal CD34+ dose needed for successful engraftment and superior outcome. However, studies evaluating the cut-off are heterogeneous. We believe that the optimal CD34+ depends on the conditioning regimen. Furthermore, regimens using PTCy require even higher doses.

Our cut-off is higher than that suggested by Acruri *et al.*⁴ who reported a CD34+ dose of at least 3.2×10^6 cells/kg for superior EFS in SAA patients undergoing haploidentical HSCT. However, our cut-off is close to that suggested by Elmariah *et al.*⁵ who described a cut-off of 5×10^6 cells/kg for superior OS and DFS in patients with hematological malignancies.

Hematopoietic stem cells are resistant to cyclophosphamide since they are rich in aldehyde dehydrogenase (ADH), which converts aldophosphamide -a toxic metabolite- to carboxy cyclophosphamide -a non-toxic metabolite-⁶. However, we hypothesize ADH is saturable at a certain dose of cyclophosphamide.

Our study is limited by its small number of patients, which limits the establishment and validation of a definitive cut-off.

References

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