

Background

Haploidentical hematopoietic stem cell transplant (haplo-HSCT) has risen in popularity over the past several years, as it has simplified the process of matching patients with hematologic diseases with HSCT donors. Through traditional HLA-matched HSCT, a patient needs a 7/8 or 8/8 HLA-matched donor, which can especially pose a challenge for ethnic minority groups. Haplo-HSCT mitigates this issue by requiring only a 50% HLA match, thus broadening the donor pool. In the past, haplo-HSCT often failed due to high rates of graft-failure and graft-versus-host disease (GVHD). However, the success rates of haplo-HSCT have improved with the advent of technologies such as T-cell depletion, the GIAC strategy and high-dose post-transplant cyclophosphamide¹.

Still, the field of haplo-HSCT is new, and the ideal dosing of CD34+ stem cells in haploidentical allogeneic stem cell transplant is unclear. Investigators have previously shown better outcomes with high dosing of CD34+ stem cells², but there is concern for higher rates of cytokine release syndrome (CRS) as dosing increases.

Furthermore, ideal CD3+ T cell dosing and CD34+/CD3+ ratio are not well-defined, but they are believed to impact haplo-SCT outcomes.

Objective

To determine if higher CD34+ stem cell doses resulted in increased rates of CRS, and to determine whether dosing affected graft-versus-host-disease-free, relapse-free survival (GRFS) at a 1-year timepoint and overall survival (OS). We also aimed to establish how CD3+ dose and CD34+/CD3+ ratio impacted these measures.

Methods

We performed a retrospective chart review of all adult patients who underwent haplo-HSCT with high-dose post-transplant cyclophosphamide at the USC Norris Cancer Center (NCCC) between 2015 and 2020. We analyzed differences in GRFS, OS and CRS based on CD34+ dose, CD3+ dose and ratio of CD34+/CD3+ cells used. We also assessed overall rates of acute and chronic GVHD and transplant-related mortality (TRM).

Results

In total, 103 haplo-HSCT cases were included in the study. One patient had 2 recorded transplant attempts at NCCC, which were reviewed as separate cases.

Patient Population

The age range was 21- 71 years old (median=51). Of the cases, 55% were male and 45% were female. The majority (62%) were Hispanic, 20% were Caucasian, 11% were Asian, and the rest were of other racial backgrounds. Most patients had AML (40.8%) or ALL (34.1%).

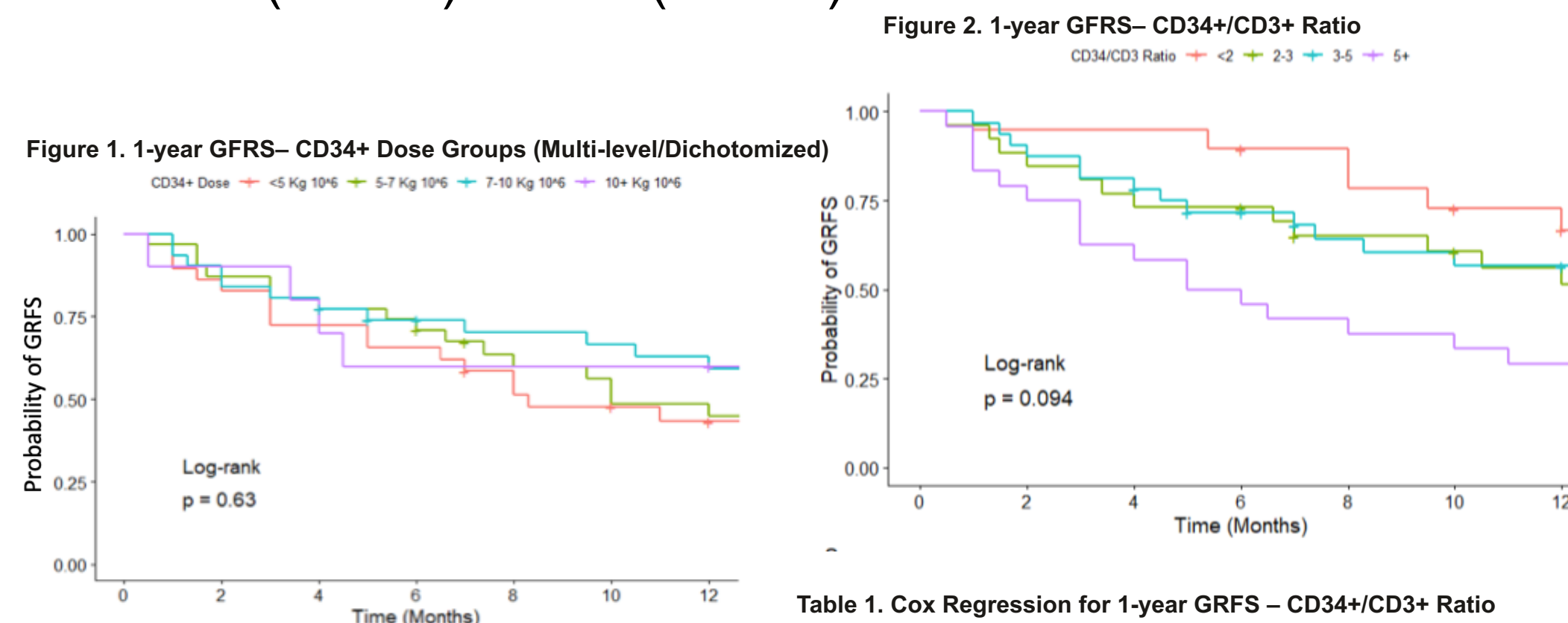


Table 1. Cox Regression for 1-year GRFS – CD34+/CD3+ Ratio

Variable	Coefficient	Hazard Ratio (95%CI)	P-value
CD34/CD3 Ratio			
<2	Reference	Reference	
2 – 3	0.566	1.76 (0.71 – 4.37)	0.222
3 – 5	0.565	1.76 (0.73 – 4.25)	0.209
5+	1.071	2.92 (1.21 – 7.05)	0.017*

CD34+ Dosing and CRS

Variable	N	CD34+ Dose		P-value
		<5x10 ⁶ cells/kg (n=30)	≥5x10 ⁶ cells/kg (n=73)	
Had CRS				0.194
No	25	10 (33.3%)	15 (21.1%)	
Yes	76	20 (66.7%)	56 (78.9%)	
Missing	2			
Had CRS Grade 3/4				0.567
No	74	20 (100%)	54 (93.1%)	
Yes	4	0	4 (6.9%)	
O ₂ Requirement due to CRS				0.030*
No	80	27 (100%)	53 (82.8%)	
Yes	11	0	11 (17.2%)	
Hypotension Requiring Fluid Bolus due to CRS within 7 days of SCT				0.215
No	77	25 (92.6%)	52 (80.0%)	
Yes	15	2 (7.4%)	13 (20.0%)	
Missing	11			
Took Pressors				0.313
No	96	30 (100%)	66 (94.3%)	
Yes	4	0	4 (5.7%)	
Missing	3			
ICU Transfer due to CRS				0.101
No	89	27 (100%)	62 (88.6%)	
Yes	8	0	8 (11.4%)	
Missing	6			

Figure 3. 1-year GRFS– CD3+ Dose

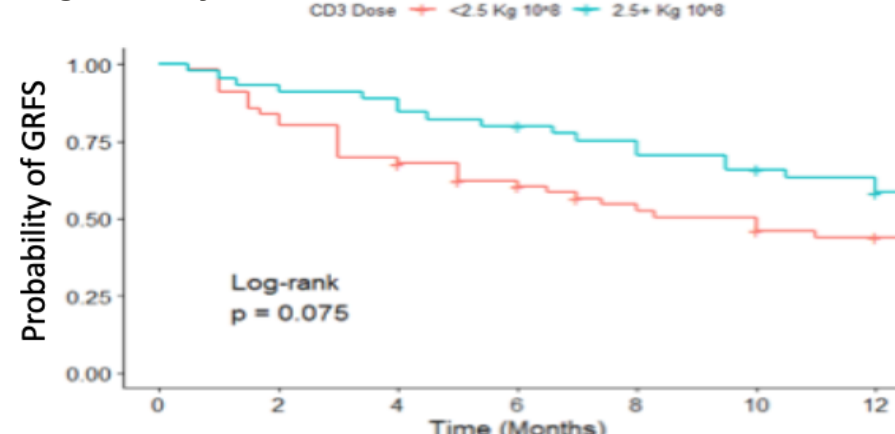
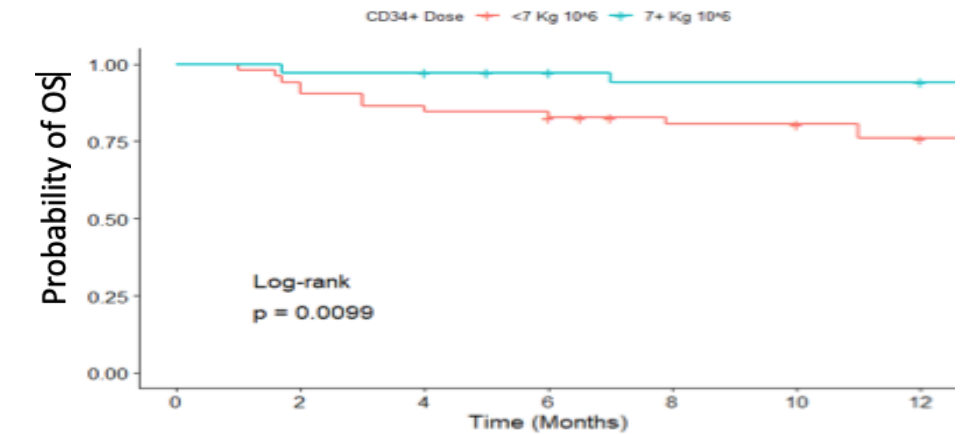


Table 3. CRS and CD34+ Dose – 7 x 10⁶/kg Cutoff

Variable	N	CD34+ Dose		P-value
		<7x10 ⁶ cells/kg (n=62)	≥7x10 ⁶ cells/kg (n=41)	
Had CRS				0.139
No	25	18 (30.0%)	7 (17.1%)	
Yes	76	42 (70.0%)	34 (82.9%)	
Missing	2			
Had CRS Grade 3/4				0.312
No	74	43 (97.7%)	31 (91.2%)	
Yes	4	1 (2.3%)	3 (8.8%)	
O ₂ Requirement due to CRS				0.743
No	80	50 (89.3%)	30 (85.7%)	
Yes	11	6 (10.7%)	5 (14.3%)	
Hypotension Requiring Fluid Bolus due to CRS within 7 days of SCT				0.056
No	77	51 (89.5%)	26 (74.3%)	
Yes	15	6 (10.5%)	9 (25.7%)	
Missing	11			
Took Pressors				0.021*
No	96	61 (100%)	35 (89.7%)	
Yes	4	0	4 (10.3%)	
Missing	3			
ICU Transfer due to CRS				0.710
No	89	54 (93.1%)	35 (89.7%)	
Yes	8	4 (6.9%)	4 (10.3%)	
Missing	6			

Figure 4. 1-year OS– CD34+ Dose



GVHD, Relapse, and Survival

Median CD34+, CD3+ and CD34+/CD3+ ratio were 6.1 x 10⁶/kg, 2.27 x 10⁸/kg and 3.2, respectively. Median time to neutrophil, platelet and lymphocyte recovery were 17, 24 and 124 days, respectively. 1-year GRFS was 43.7% and TRM was 13.6%. Rates of aGVHD and cGVHD were 42.7% and 35.9%, respectively.

There was no statistically significant difference in GRFS (p= 0.28) and OS (p=0.141) between CD34+ dose <5 x 10⁶/kg and ≥5. There was no difference in 1- year GRFS and OS when multiple dose levels of CD34+ and CD3+ cells were compared.

When dichotomized CD34+ cell dose of ≥7 x 10⁶/kg was compared to <7, the higher dose had significant improvement in 1- year OS (p-value=0.01) but no difference in 1-year GRFS (p-value=0.24). HR for 1- year GRFS was 2.92 for CD34+/CD3+ ratio >5 compared to a ratio <2 (p-value= 0.01).

Summary

- We found higher rates of oxygen requirement when CD34+ dose ≥5 x 10⁶/kg was used compared to <5, and higher requirement for pressor support when a CD34+ dose ≥7 x 10⁶/kg was used compared to <7
- 1-year GRFS was 43.7%
- OS was significantly improved with CD34+ dose ≥7 x 10⁶/kg, and CD3+ dose <2.5 x 10⁸/kg showed a trend towards lower 1-year GRFS
- CD34+/CD3+ ratio >5 was associated with a higher hazard ratio for 1-year GRFS (2.92)

Discussion

- Our findings indicate that along with improved OS by using ≥7 x 10⁶/kg CD34+ cells, lower CD3+ <2.5 x 10⁸/kg and higher CD34+/CD3+ ratio >5 can improve 1-year GRFS in setting of haplo-HSCT
- However, higher CD34+ dose is also associated with higher rates of CRS, including oxygen and pressor requirements
- This is a single-center, retrospective study, and a prospective study should be conducted to better elucidate optimum CD34+ and CD3+ dosing

References

- Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. Nat Rev Clin Oncol. 2016; 13:10-24.
- Elmariah H, Naqvi SMH, Kim J, Nishihori T, Mishra A, Perez L, Faramand R, Lazaryan A, Liu HD, Khimani F, Nieder M, Anasetti C, Pidala J, Bejanyan N. Impact of infused CD34+ stem cell dosing for allogeneic peripheral blood stem cell transplantation with post-transplant cyclophosphamide. Bone Marrow Transplant. 2021 56:1683-1690.