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Introduction

- The optimal CD34+ cell dose in peripheral blood allogeneic hematopoietic cell transplantation (alloHCT) is unknown.
- Higher cell dose is associated with improved short-term outcomes such as engraftment.
- Higher cell dose may be associated with increased risk of graft-versus-host disease (GVHD).
- A standard dose of $>2 \times 10^6$ CD34+ cells/kg has been adopted by most institutions.
- Aim: Examine the impact of CD34+ cell dose on overall survival (OS) in patients undergoing alloHCT with peripheral blood stem cell (PBSC) graft source.**

Methods

Design: Retrospective cohort study

Setting: Single academic medical center

Patient population: 377 adults with hematological malignancies who received myeloablative or reduced-intensity conditioning alloHCT with matched sibling donor PBSC from 2002-2015

Key Outcomes Measured:

- Overall survival (OS) at 5 years
- ANC engraftment at 42 days
- Platelet engraftment at 6 months
- Acute GVHD stages 3-4
- Chronic GVHD
- Relapse at 5 years
- Transplant related mortality at 5 years

Analysis: Patients were classified into three groups based on tertile of CD34 cell dose (Table 1). Kaplan-Meier method was used to estimate the probability of OS and the log-rank test was used to compare the curves. The Cox proportional hazard regression model was used for multivariate analysis.

Demographics

Recipient, Donor, Graft and Transplant Characteristics Grouped by CD34 Cell Dose Tertile					
		T1 $<5.0 \times 10^6$ /kg N=110	T2 $[5.0, 7.5 \times 10^6]$ /kg N=172	T3 $\geq 7.5 \times 10^6$ /kg N=95	P value
Recipient Characteristics					
Age	Median (Min-Max)	55.1 (19.0-74.2)	52.4 (18.8-73.1)	49.3 (22.3-71.6)	<0.01
Weight (kg)	Median (Min-Max)	87.2 (50.9-183.4)	84.0 (50.7-147.5)	80.0 (41.5-155.7)	0.08
BMI	Median (Min-Max)	28.6 (18.2-55.5)	28.3 (17.9-46.7)	27.2 (16.9-47.5)	0.08
	N of Observed	109	171	94	
	N of Missing	1	1	1	
Sex					0.45
	Male	73 (66.4%)	109 (63.4%)	55 (57.9%)	
	Female	37 (33.6%)	63 (36.6%)	40 (42.1%)	
CMV Status					0.21
	Neg	39 (35.5%)	79 (45.9%)	41 (43.2%)	
	Pos	71 (64.5%)	93 (54.1%)	53 (55.8%)	
	Missing	0	0	1 (1.1%)	
HCT-CI					0.21
	0	37 (33.6%)	61 (35.5%)	46 (48.4%)	
	1-2	38 (34.5%)	55 (32.0%)	24 (25.3%)	
	≥ 3	35 (31.8%)	56 (32.6%)	25 (26.3%)	
Disease					0.30
	Leukemia	77 (70.0%)	107 (62.2%)	71 (74.7%)	
	Lymphoma	26 (23.6%)	50 (29.1%)	19 (20.0%)	
	Other	7 (6.4%)	15 (8.7%)	5 (5.3%)	
DRI					0.94
	LOW	16 (14.5%)	29 (16.9%)	15 (15.8%)	
	INTERMEDIATE	78 (70.9%)	114 (66.3%)	66 (69.5%)	
	HIGH/VERY HIGH	16 (14.5%)	29 (16.9%)	14 (14.7%)	
Donor Characteristics					
Age					<0.01
	N of Observed	109	172	95	
	Median (Min-Max)	53.0 (22.7-75.9)	51.6 (16.9-72.7)	47.2 (18.4-69.1)	
	N of Missing	1	0	0	
Sex					0.08
	Male	54 (49.1%)	84 (48.8%)	59 (62.1%)	
	Female	56 (50.9%)	88 (51.2%)	36 (37.9%)	
Age*Sex					0.05
	Donor female & age ≥ 60	14 (12.7%)	14 (8.1%)	3 (3.2%)	
	Donor others	96 (87.3%)	158 (91.9%)	92 (96.8%)	
	Median (Min-Max)	2.0 (1.0-7.0)	2.0 (1.0-6.0)	1.0 (1.0-5.0)	<0.01
Graft/Transplant Characteristics					
Total CD3 cells $\times 10^6$ /kg	Median (Min-Max)	3.1 (0.3-10.0)	2.7 (0.8-7.6)	2.8 (1.4-7.7)	0.40
Female-to-Male					<0.01
	Yes	37 (33.6%)	59 (34.3%)	15 (15.8%)	
	No	73 (66.4%)	113 (65.7%)	80 (84.2%)	
Conditioning					0.05
	MAC	43 (39.1%)	89 (51.7%)	52 (54.7%)	
	RIC	67 (60.9%)	83 (48.3%)	43 (45.3%)	
Conditioning + ATG					0.09
	MAC	43 (39.1%)	89 (51.7%)	52 (54.7%)	
	RIC-ATG	12 (10.9%)	22 (12.8%)	8 (8.4%)	
	RIC: No ATG	55 (50.0%)	61 (35.5%)	35 (36.8%)	
Time to Death/Last follow up	Median Days (Min-Max)	542.0 (25-5428)	1082.0 (14-5493)	904.0 (20-5362)	<0.01

Table 1: Patient and treatment characteristics

Results

Multivariable analysis (Table 2) demonstrated that high CD34 cell dose was associated with superior 5-year OS (Figure 1) and more rapid platelet engraftment. Higher CD34 cell doses were also associated with improved absolute neutrophil count engraftment. There was no association between CD34 cell dose and TRM or relapse at 5 years. Although higher CD34 cell doses were not associated with acute GVHD stages II-IV, they were associated with chronic GVHD.

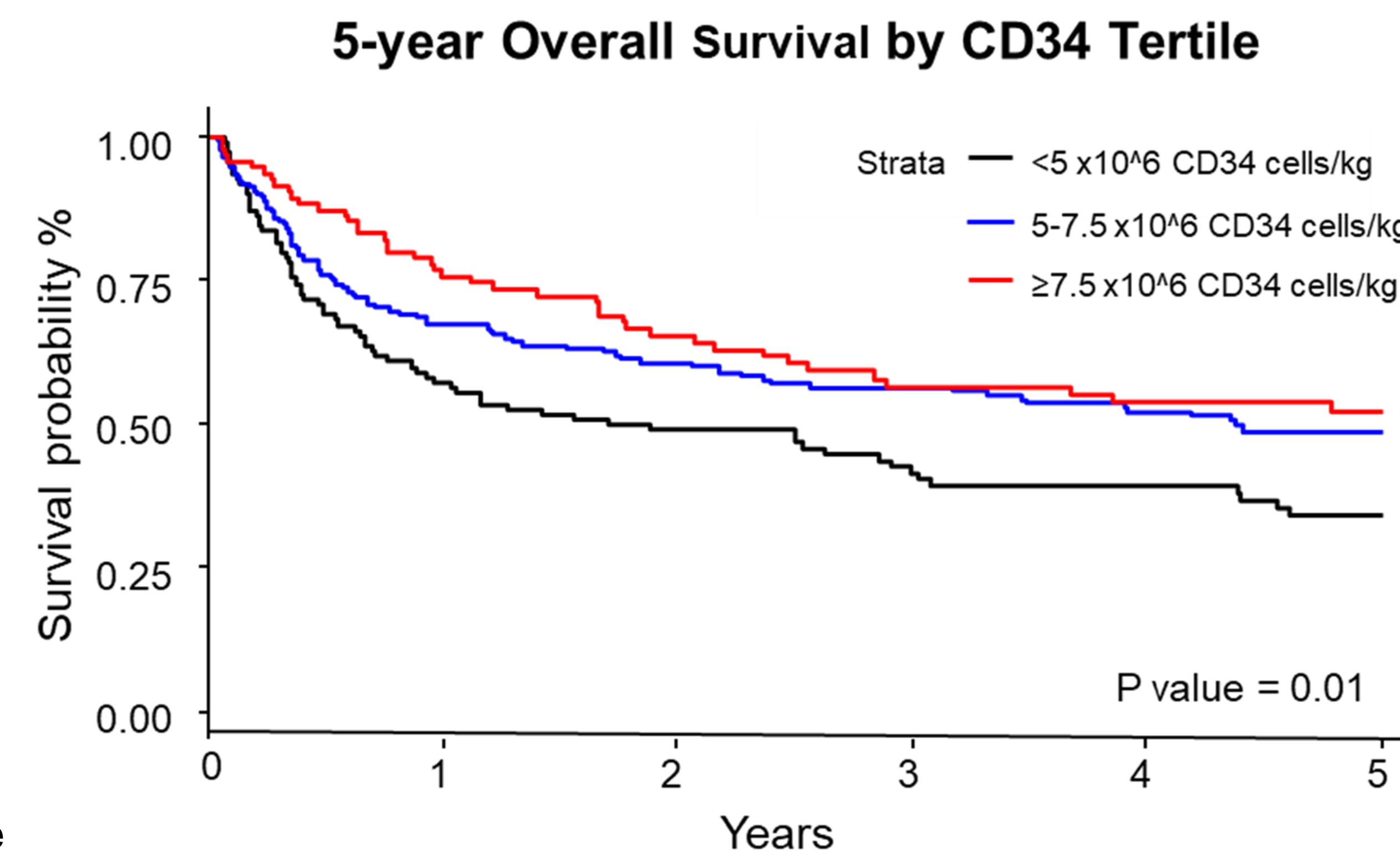


Figure 1: Unadjusted Kaplan-Meier estimates for overall survival (OS) by CD34 cell dose tertile. Log-rank test P value is shown.

Results (continued)

Class	Multivariate Analysis			Class	Multivariate Analysis		
	HR (CI 95%)	P-value			HR (CI 95%)	P-value	
5-year OS				ANC Engraftment			
CD34 tertile				CD34 tertile			
	T1	1	0.01		T1	1	<0.01
	T2	0.68 (0.49-0.93)			T2	1.51 (1.18-1.94)	
	T3	0.58 (0.39-0.86)			T3	1.49 (1.12-1.98)	
DRI				CD3 cell dose			
	Low	1	<0.01		<2.1	1.00	
	Intermediate	2.21 (1.35-3.62)			[2.1, 2.8]	0.90 (0.68-1.21)	0.27
	High/V.High	3.60 (2.07-6.29)			[2.8, 3.7]	0.94 (0.70-1.26)	
HCT-CI					≥ 3.7	0.76 (0.57-1.01)	
	0-1	1	0.08	Conditioning			
	2	1.42 (0.93-2.18)			MAC	1	<0.01
	2+	1.37 (1.00-1.86)			RIC-ATG	5.33 (3.57-7.95)	
Recipient age					RIC:No ATG	5.34 (4.02-7.08)	
	≤ 52	1	0.99	HCT-CI			
	≥ 52	1.00 (0.75-1.33)			0-1	1	0.04
					2	1.30 (0.93-1.80)	
					2+	1.33 (1.05-1.68)	
aGVHD Grade II-IV				Recipient age			
CD34 tertile					≤ 52	1	0.41
	T1	1	0.24		≥ 52	1.11 (0.87-1.43)	
	T2	1.13 (0.77-1.66)		PLT Engraftment			
	T3	0.81 (0.51-1.27)		CD34 tertile			
CD3 cell dose					T1	1	<0.01
	<2.1	1	0.23		T2	1.12 (0.84-1.50)	
	[2.1, 2.8]	1.19 (0.78-1.81)			T3	1.68 (1.27-2.24)	
	[2.8, 3.7]	0.72 (0.44-1.19)		CD3 cell dose			
	≥ 3.7	0.91 (0.59-1.41)			<2.1	1	0.14
Conditioning					[2.1, 2.8]	1.30 (0.95-1.77)	
	MAC	1	0.13		[2.8, 3.7]	1.13 (0.81-1.58)	
	RIC-ATG	0.80 (0.47-1.37)			≥ 3.7	0.92 (0.66-1.28)	
	RIC:No ATG	0.71 (0.51-1.00)		cGVHD			
CD34 tertile					T1	1	<0.01
	T1	1	0.04		Conditioning		
	T2	1.68 (1.12-2.52)			MAC	1	
	T3	1.50 (0.94-2.38)			RIC-ATG	2.17 (1.34-3.52)	
CD3 cell dose					RIC:No ATG	3.51 (2.63-4.67)	
	<2.1	1.00	0.30	Recipient age			
	[2.1, 2.8]	1.32 (0.86-2.02)			≤ 52	1	0.27
	[2.8, 3.7]	0.88 (0.54-1.43)			≥ 52	0.86 (0.66-1.12)	
	≥ 3.7	0.91 (0.59-1.43)		5-year TRM			
Conditioning				CD34 tertile			
	MAC	1	0.42		T1	1	0.31
	RIC-ATG	0.80 (0.47-1.37)			T2	1.11 (0.72-1.70)	
	RIC:No ATG	0.71 (0.51-1.00)			T3	0.77 (0.46-1.31)	
CD34 tertile				CD3 cell dose			
	0-1	1.00	0.42		<2.1	1	0.45
	2	1.18 (0.72-1.92)			[2.1, 2.8]	1.47 (0.87-2.45)	
	3+	1.28 (0.89-1.84)			[2.8, 3.7]	1.43 (0.84-2.42)	
Female-to-Male					≥ 3.7	1.39 (0.82-2.34)	
	Yes	1.00	0.46	DRI			
	No	0.84 (0.60-1.19)			Low	1	<0.01
DRI					Intermediate	1.68 (0.92-3.09)	
	Low	1	0.19		High/V.High	3.61 (1.86-7.02)	
	Intermediate	0.69 (0.47-1.03)		5-year Relapse			
	High/V.High	0.58 (0.33-1.02)		CD34 tertile			
					T1	1	0.09
					T2	0.58 (0.36-0.94)	
					T3	0.71 (0.41-1.23)	
5-year OS					<2.1	1	0.08
CD34 tertile					[2.1, 2.8]	0.43 (0.22-0.82)	
	T1	1	0.09		[2.8, 3.7]	0.66 (0.37-1.18)	
	T2	0.58 (0.36-0.94)			≥ 3.7	0.76 (0.44-1.30)	
	T3	0.71 (0.41-1.23)		DRI			
CD3 cell dose					Low	1	0.24
	<2.1	1	0.08		Intermediate	1.69 (0.88-3.25)	
	[2.1, 2.8]	0.43 (0.22-0.82)			High/V.High	1.28 (0.55-2.95)	
	[2.8, 3.7]	0.66 (0.37-1.18)		Total Collections			
	≥ 3.7	0.76 (0.44-1.30)			0-1	1	0.24
					2	0.60 (0.33-1.11)	
					3+	0.86 (0.58-1.28)	
				Recipient Age			
					≤ 52	1	0.98
					≥ 52	1.00 (0.69-1.46)	

Table 2: Summary of multivariate analysis.

Conclusions

- Higher CD34 cell dose ($>7.5 \times 10^6$ /kg) is associated with superior OS at 5 years and improved engraftment but does carry an increased risk of chronic GVHD.
- These data support a target CD34 cell dose goal of 7.5×10^6 /kg for peripheral blood sibling donors
- Further development of novel stem cell mobilization techniques (*i.e.*, G-CSF and plerixafor) in donors at high risk for low collection yield is warranted.
- Further studies should evaluate if cell dose has similar prognostic impact in alternative donor transplant.