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Retrospective Study

Impact of conditioning regimen on peripheral blood hematopoietic cell transplant

Michael Burns, Anurag K Singh, Carrie C Hoefer, Yali Zhang, Paul K Wallace, George L Chen, Alexis Platek, Timothy B Winslow, Austin J Iovoli, Christopher Choi, Maureen Ross, Philip L McCarthy, Theresa Hahn

ORCID number: Michael Burns (0000-0002-8281-0036); Anurag K Singh (0000-0002-0712-6517); Yali Zhang (0000-0002-0074-8663); Paul K Wallace (0000-0002-8361-204X); George L Chen (0000-0002-7036-2109); Austin J Iovoli (0000-0003-2089-8789); Christopher Choi (0000-0003-0166-6712); Philip L McCarthy (0000-0002-9577-3879); Theresa Hahn (0000-0002-3835-8855).

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Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Michael Burns, Carrie C Hoefer, Yali Zhang, George L Chen, Maureen Ross, Philip L McCarthy, Theresa Hahn, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, United States

Anurag K Singh, Alexis Platek, Timothy B Winslow, Austin J Iovoli, Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, United States

Paul K Wallace, Department of Flow Cytometry, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, United States

Christopher Choi, Center for Immunotherapy, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, United States

Corresponding author: Anurag K Singh, MD, Professor, Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, NY 14263, United States. anurag.singh@roswellpark.org

Telephone: +1-716-8451180

Fax: +1-716-8457616

Abstract

AIM

To investigate infused hematopoietic cell doses and their interaction with conditioning regimen intensity +/- total body irradiation (TBI) on outcomes after peripheral blood hematopoietic cell transplant (PBHCT).

METHODS

Our retrospective cohort included 247 patients receiving a first, T-replete, human leukocyte antigen-matched allogeneic PBHCT and treated between 2001 and 2012. Correlations were calculated using the Pearson product-moment correlation coefficient. Overall survival and progression free survival curves were generated using the Kaplan-Meier method and compared using the log-rank test.

RESULTS

Neutrophil engraftment was significantly faster after reduced intensity TBI based conditioning [reduced intensity conditioning (RIC) + TBI] and $> 4 \times 10^6$ CD34+ cells/kg infused. A higher total nucleated cell dose led to a higher incidence of grade II-IV acute graft-versus-host disease in the myeloablative + TBI regimen group ($P = 0.03$), but no significant difference in grade III-IV graft-versus-host disease. A higher total nucleated cell dose was also associated with increased incidence of moderate/severe chronic graft-versus-host disease, regardless of

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conditioning regimen. Overall and progression-free survival were significantly better in patients with a RIC + TBI regimen and total nucleated cell dose $> 8 \times 10^8$ /kg (3 years, overall survival: 70% *vs* 38%, $P = 0.02$, 3 years, progression free survival: 64% *vs* 38%, $P = 0.02$).

CONCLUSION

TBI and conditioning intensity may alter the relationship between infused cell doses and outcomes after PBHCT. Immune cell subsets may predict improved survival after unmanipulated PBHCT.

Key words: Total body radiation; Peripheral blood hematopoietic cell transplant; Total nucleated dose; Neutrophil engraftment; Graft-versus-host-disease

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Core tip: This study investigated infused hematopoietic cell doses and their interaction with conditioning regimen intensity on outcomes after peripheral blood hematopoietic cell transplant. Our retrospective cohort included 247 patients receiving a first, T-replete, human leukocyte antigen-matched allogeneic peripheral blood hematopoietic cell transplant. Neutrophil engraftment was significantly faster after reduced intensity total body irradiation and $> 4 \times 10^6$ CD34+ cells/kg infused. Overall and progression-free survival was significantly better in patients with a reduced intensity conditioning and total body irradiation regimen and total nucleated cell dose $> 8 \times 10^8$ /kg.

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INTRODUCTION

Peripheral blood hematopoietic cell transplant (PBHCT) is the most commonly used allogeneic hematopoietic cell source due to its faster rate of neutrophil engraftment^[1-4]. The optimal CD34+ cell dose range to minimize time to neutrophil and platelet recovery without increasing risk of acute graft-versus-host disease (GvHD) is $4-10 \times 10^6$ /kg^[5-11]. Some studies have reported a higher CD34+ cell dose yields improved overall survival (OS)^[9,12-14], while others have found no significant association^[7,10,15-18].

A higher total nucleated cell (TNC) dose has been reported to improve survival after PBHCT^[14,16], but analyses of specific T-cell subsets (CD4+, CD8+, natural killer cells) have been inconsistent^[17-19]. Factors such as T-cell depletion, conditioning regimen intensity, use of total body irradiation (TBI), and donor age may be interacting with graft cell doses to generate different effects on PBHCT outcomes. In addition, flow cytometric enumeration of cell doses are not standardized (except for CD34+ cell dose) and may also lead to differences in results between studies.

In our retrospective study, we explored whether the collected and infused CD34+, CD3+, CD4+, CD8+, or TNC dose influenced engraftment, OS, progression free survival (PFS), and incidence of acute and chronic GvHD, and whether the results were affected by conditioning regimen intensity or use of TBI.

MATERIALS AND METHODS

Study design

This retrospective cohort study included 247 consecutive adult (≥ 18 years old) patients receiving their first allogeneic PBHCT between January 2001 and September 2012. Patients receiving syngeneic, human leukocyte antigen (HLA)-mismatched, T-cell depleted, or bone marrow transplants were excluded from this analysis. This study was reviewed and approved by the Institutional Review Board of Roswell Park

Cancer Institute.

Conditioning regimens

Four conditioning regimen groups were defined a priori as (1) myeloablative (MA) without TBI (MA-noTBI), (2) myeloablative with TBI (MA + TBI), (3) reduced intensity conditioning (RIC) without TBI (RIC-noTBI) and (4) RIC with TBI (RIC + TBI). These are described in Table 1. Conditioning regimens were assigned based on institutional standards including: (1) patients aged ≥ 60 years: received RIC regimens, (2) patients aged 41-59 years: a RIC regimen was preferred for patients with any of the following criteria: HLA mismatch, Karnofsky Performance Score (KPS) < 70 , extensive co-morbidities, recent smoking history, (3) patients aged 19-40 years: a myeloablative regimen was preferred unless the patient had an HLA mismatched donor, KPS < 70 , severe co-morbidity, and (4) patients aged ≤ 40 years with acute lymphoid leukemia: TBI regimen.

PBHC mobilization and collection

Donor marrow was stimulated with 10 mg/kg of granulocyte-colony stimulating factor for a minimum of 2 d and continued until white blood cell count was $> 8000 \times 10^9/L$; the attending bone marrow transplant physician provided a target CD34+ cell dose to be collected and, for related donors, approved the final dose collected and the end of apheresis. Most donors underwent apheresis for 1 d.

Cell dose definitions

Apheresis product cell doses were determined using multi-parameter flow cytometry. CD34+ cell counts were obtained using the ISHAGE protocol^[20], substituting 7-aminoactinomycin D with TO-PRO. CD3+, CD4+, and CD8+ cell counts used standard methodology^[21]. TNC doses were determined by multiplying the white blood cell count ($\times 10^8/mL$) on the day of apheresis by the volume of the product. Each cell count in the final infused product was divided by the actual recipient weight in kilograms measured within 2 d of the start of conditioning regimen to calculate the cell dose infused.

CD34+ cell dose was analyzed using previously published categories of < 4 , 4-8, $> 8 \times 10^6/kg$. CD3+, CD4+, and CD8+ cell doses were analyzed above and below the respective median cell doses in the study population. TNC dose was analyzed as above and below the median cell doses and also with various doses ranging from $7-10 \times 10^8$ cells/kg to determine an optimal TNC dose threshold.

Post-transplant outcome definitions

Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $> 0.5 \times 10^9/L$. Platelet engraftment was defined as the first date with a platelet count $> 20 \times 10^9/L$ after 7 consecutive days with no platelet transfusions. PFS was calculated as the time from PBHC infusion to date of first disease progression post-PBHCT or date of death from any cause; survivors without disease progression were censored at date of last follow-up. OS was calculated as the time from PBHC infusion to date of death from any cause with survivors censored at date of last follow-up. Acute and chronic GvHD were graded using standard definitions^[22-23].

Statistical analysis

The statistical methods of this study were reviewed by Yali Zhang from Roswell Park Comprehensive Cancer Center. Correlations between TNC dose and CD3+ dose, CD4+ dose, CD8+ dose, and CD34+ dose were calculated using the Pearson product-moment correlation coefficient. The cumulative incidence of acute and chronic GvHD was analyzed adjusting for the competing risk of disease relapse. Univariable analysis of OS and PFS were analyzed as time-to-event; survival curves were generated using the Kaplan-Meier method and were compared using the log-rank test. Multivariable analyses tested each cell dose while adjusting for significant factors in the univariate analysis, first in all patients and then stratified by the four conditioning regimen groups. Variables included in the multivariable analyses were age ($\geq / < 40$ years), KPS ($\geq / < 80$) at time of transplant, and BMI ($\geq / < 35$ kg/m²). All analyses were performed using SAS version 9.4.

RESULTS

The cohort consisted of 135 sibling and 112 unrelated donor transplant recipients. Sibling donors were 6/6 HLA-matched at HLA-A, -B, and -DRB1. Unrelated donors were 10/10 HLA-matched at HLA-A, -B, -C, -DRB1, and DQB1 (3 patients were 8/8

Table 1 Conditioning regimen descriptions

Conditioning regimen	Number of patients	Protocol
Myeloablative without TBI (MA-noTBI)	38	Bu 12.8 mg/kg intravenous total dose and Cy 120 mg/kg total dose
Myeloablative with TBI (MA + TBI)	51	Cy 120 mg/kg total dose and TBI 1000-1350 cGy
Reduced intensity conditioning without TBI (RIC-noTBI)	118	Flu 125 mg/m ² total dose and Mel 140 mg/m ² total dose
Reduced intensity conditioning with TBI (RIC + TBI)	40	Flu 160 mg/m ² total dose, Mel 50-75 mg/m ² total dose, and TBI 400 cGy

Bu: Busulfan; Cy: Cyclophosphamide; Flu: Fludarabine; MA: Myeloablative; Mel: Melphalan; TBI: Total body irradiation.

HLA-matched at HLA-A, -B, -C, -DRB1). Patients who received a MA regimen were significantly younger, had a higher KPS, more commonly had a sibling donor, tacrolimus/methotrexate GvHD prophylaxis regimen, and were treated for different diseases than patients who received a RIC regimen (Table 2).

Peripheral blood apheresis cell doses

Median (range) cell doses for the whole cohort were $264.3 (10.4-1137.5) \times 10^6/\text{kg}$ for CD3+, $166.2 (8.3-590.9) \times 10^6/\text{kg}$ for CD4+, $103.7 (2.2-590.9) \times 10^6/\text{kg}$ for CD8+, $6.5 (0.9-27.6) \times 10^6/\text{kg}$ for CD34+, and $8.3 (1.4-21.4) \times 10^8/\text{kg}$ for TNC. Graft composition for conditioning subgroups are detailed in Supplementary Table 1.

Neutrophil engraftment

The cumulative incidence of neutrophil engraftment was 99% at day 28 post-PBHCT. Six patients died on days 3, 5, 12, 20, 26, and 36 before neutrophil engraftment. Overall, patients who received a CD34+ cell dose $> 4 \times 10^6/\text{kg}$ experienced faster neutrophil engraftment (median 13 d *vs* 15 d, $P = 0.05$) as compared to patients who received a CD34+ cell dose $< 4 \times 10^6/\text{kg}$. Analysis by conditioning regimen demonstrated significantly faster neutrophil engraftment for an infused CD34+ cell dose $> 4 \times 10^6/\text{kg}$ in the RIC + TBI group (median 15 d *vs* 18 d, $P = 0.01$) and no statistically significant differences by CD34+ cell dose for the other three conditioning regimen groups (Table 3). There were no significant differences in time to neutrophil engraftment by CD3+, CD4+, CD8+, and TNC dose either overall or in any conditioning subgroup (Supplementary Table 2).

Platelet engraftment

Five patients did not nadir their platelet count below 20000/mm³ post-PBHCT and were excluded from the analysis of platelet engraftment. The cumulative incidence of platelet engraftment was 89% at day 40 post-PBHCT. One patient failed to engraft platelets and had a second transplant on day 44. Ten patients died before day 40, three patients died between days 41 to 100, and one patient died 6 mo post-PBHCT without platelet engraftment. Overall, patients who received a CD34+ cell dose $> 4 \times 10^6/\text{kg}$ experienced significantly faster platelet engraftment (median 16 d *vs* 20 d, $P = 0.001$) as compared to patients with a CD34+ cell dose $< 4 \times 10^6/\text{kg}$. Analysis by conditioning regimen demonstrated significantly faster platelet engraftment in patients with a CD34+ cell dose $> 4 \times 10^6/\text{kg}$ for the MA + TBI group (median 20 d *vs* 34 d, $P = 0.001$), and the RIC-noTBI group (median 17 d *vs* 22 d, $P = 0.01$), but no statistically significant differences in time to platelet engraftment by CD34+ cell dose for the other two conditioning regimen groups (Table 3). Platelet engraftment was significantly faster in patients who received a higher CD3+ or CD8+ cell dose in the RIC-noTBI group, but not in any of the other conditioning regimen groups. CD4+ and TNC cell doses were not significant (Supplementary Table 2).

Graft-versus-host disease

In the MA + TBI conditioning regimen group, there was a higher incidence of grade II-IV acute GvHD in patients who received a TNC dose $> 8 \times 10^8/\text{kg}$, however there was no difference in grade III-IV acute GvHD (Figure 1A and 1B). Conversely, there was a higher incidence of grade III-IV acute GvHD in patients who received a lower CD34+ cell dose ($\leq 8 \times 10^6/\text{kg}$), however there was no difference in grade II-IV acute GvHD by CD34+ cell dose (Figure 1C and 1D). These effects with TNC and CD34+ dose in MA + TBI were not seen in any of the other conditioning regimen groups. There were no statistically significant associations of CD3+, CD4+, or CD8+ dose with acute GvHD overall or in any conditioning regimen subgroup.

There was no significant association of chronic GvHD incidence with a TNC dose of $> 8 \times 10^8/\text{kg}$ either overall or by conditioning regimen. There was a significantly

Table 2 Patient characteristics for each of four conditioning regimen groups, n (%)

	MA-noTBI (n = 38)	MA+TBI (n = 51)	RIC-noTBI (n = 118)	RIC+TBI (n = 40)	P
Age at BMT					< 0.0001
Median-years (range)	47 (26-58)	36 (19-51)	54 (23-73)	61 (23-71)	
< 40	6 (16)	29 (57)	22 (19)	3 (8)	
≥ 40	32 (84)	22 (43)	96 (81)	37 (93)	
Gender					NS
Female	21 (55)	19 (37)	45 (38)	22 (55)	
Male	17 (45)	32 (63)	73 (62)	18 (45)	
Diagnosis					< 0.0001
ALL	0	20 (39)	7 (6)	6 (15)	
AML	11 (29)	28 (55)	58 (49)	14 (35)	
CML	7 (18)	1 (2)	3 (3)	1 (3)	
MDS/MPD	11 (29)	1 (2)	23 (19)	10 (25)	
NHL/CLL/PLL	8 (21)	1 (2)	25 (21)	8 (20)	
Other	1 (3)	0	2 (2)	1 (3)	
Karnofsky Performance Status					0.03
≤ 70	8 (21)	8 (16)	35 (30)	13 (33)	
80	13 (34)	15 (29)	51 (43)	14 (35)	
≥ 90	17 (45)	28 (55)	32 (27)	13 (33)	
BMT Regimen					< 0.0001
BuCy	36 (95)	0	0	0	
CyTBI	0	47 (92)	0	0	
FluCy	0	0	12 (10)	0	
FluMel	0	0	102 (86)	0	
FluMelTBI	0	0	0	40 (100)	
Other	2 (5)	4 (8)	4 (3)	0	
Sex Match					NS
Matched	24 (63)	30 (59)	70 (59)	27 (68)	
Mismatched	14 (37)	21 (41)	48 (41)	13 (33)	
Donor					< 0.0001
HLA Matched Related	33 (87)	31 (61)	54 (46)	17 (43)	
HLA Matched Unrelated	5 (13)	20 (39)	64 (54)	23 (58)	
GvHD Prophylaxis					< 0.0001
TacMtx	18 (47)	35 (69)	33 (28)	0	
TacMMF	4 (11)	2 (4)	18 (15)	0	
TacmMtxMMF	15 (39)	7 (14)	64 (54)	40 (100)	
Single Agent	1 (3)	7 (14)	3 (3)	0	
CMV Status					NS
R+D+	6 (16)	8 (16)	28 (24)	9 (23)	
R+D-	14 (37)	12 (24)	35 (30)	12 (30)	
R-D+	0	8 (16)	18 (15)	4 (10)	
R-D-	18 (47)	23 (45)	37 (31)	15 (38)	
BMI kg/m ²					NS
Normal (< 30)	15 (39)	25 (49)	34 (29)	13 (33)	
Overweight (25-< 30)	12 (32)	14 (27)	40 (34)	15 (38)	
Obese (≥ 30-< 35)	7 (18)	7 (14)	28 (24)	7 (18)	
Morbid (≥ 35)	4 (11)	5 (10)	16 (14)	5 (13)	

MA: Myeloablative; TBI: Total body irradiation; RIC: Reduced intensity conditioning; ALL: Acute lymphoid leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; MDS: Myelodysplastic syndrome; MPD: Myeloproliferative disorder; NHL: Non-Hodgkin lymphoma; CLL: Chronic lymphocytic leukemia; PLL: Prolymphocytic leukemia; Bu: Busulfan; Cy: Cyclophosphamide; Flu: Fludarabine; Mel: Melphalan; Tac: Tacrolimus; Mtx: Methotrexate; mMtx: Micro dose methotrexate; MMF: Mycophenylate mofetil ; R: Recipient; D: Donor; BMI: Body mass index; NS: Not significant ($P > 0.05$).

higher incidence of moderate to severe chronic GvHD in all patients who received a

Table 3 Time to neutrophil and platelet engraftment by CD34+ dose for each conditioning regimen group

	Conditioning group			
	MA-noTBI (n = 38)	MA + TBI (n = 51)	RIC-noTBI (n = 118)	RIC + TBI (n = 40)
Median days to engraftment (range)				
Absolute neutrophil count > 500/mm ³				
CD34+ dose > 4 × 10 ⁶ /kg	14 (10-22)	14 (9-28)	14 (3-36)	15 (10-22)
CD34+ dose < 4 × 10 ⁶ /kg	14.5 (12-19)	19 (13-28)	15 (10-21)	18 (16-24)
P	NS	NS	NS	0.01
Platelet count > 20000/mm ³				
CD34+ dose > 4 × 10 ⁶ /kg	17 (3-171)	20 (13-81)	17 (3-1515)	17 (10-866)
CD34+ dose < 4 × 10 ⁶ /kg	19.5 (15-32)	34 (20-228)	22 (14-275)	18 (11-20)
P	NS	0.001	0.01	NS

MA: Myeloablative; TBI: Total body irradiation; RIC: Reduced intensity conditioning; NS: Not significant ($P > 0.05$).

TNC dose > 9 × 10⁸/kg ($P = 0.004$) but was not statistically significant in any conditioning regimen subgroup. There was no association of CD34+, CD3+, CD4+, or CD8+ cell dose with chronic GvHD either overall or in any conditioning regimen group.

Overall and progression-free survival

Median follow-up in all patients was 4.8 years (range 1.6-12 years). CD34+, CD3+, CD4+, and CD8+ cell doses were not associated with either OS or PFS in all patients or stratified by conditioning regimen. TNC dose showed no significant difference in OS or PFS when analyzed in all patients (Figure 2A). However, a significant improvement in OS was seen in patients with TBI-based conditioning regimens who received higher (> 8 × 10⁸/kg) TNC doses (Figure 2B). Further analysis showed this effect was restricted to the RIC + TBI (Figure 2D) group with no significant difference in the MA + TBI group (Figure 2C). Similar results were found with PFS: a higher (> 8 × 10⁸/kg) TNC dose was associated with improved PFS in patients who received TBI-based conditioning regimens, which was driven by the RIC + TBI subgroup.

Multivariate analysis

Based on the univariate analysis, age, KPS, and BMI were included as covariates in the multivariable analysis of each cell dose with OS, and KPS and BMI were included as covariates in the multivariable analysis of each cell dose with PFS (Table 4). Similar to the univariate analysis, TNC dose > 8 × 10⁸ cells/kg was associated with improved OS and PFS in patients who received TBI-based conditioning regimens. However, upon further stratification, this finding was statistically significant only in the RIC + TBI conditioning group.

Correlations between cell populations

To investigate potential correlations between cell types, Table 5 summarizes the matrix of Pearson correlations between cell doses. While most cell doses are significantly and positively correlated with the others ($P < 0.001$), most correlation coefficients were low. Pearson $r^2 < 0.5$ means < 50% of the difference between cell doses can be explained by the linear relationship between the two. CD3+ cell dose is correlated with CD4+, CD8+, and TNC cell doses (r^2 : 0.5-0.83, Table 4), however CD34+ cell dose is not correlated with any of the other cell types ($r^2 < 0.05$) and is thus an independent cell type.

DISCUSSION

The effect of infused cell dose on post-transplant outcomes is complex. Our single center study is the first to analyze the relationship of conditioning regimen intensity and use of TBI with infused cell doses. A recent study demonstrated that in reduced intensity transplant without TBI, TNC dose was associated with improved PFS and OS similar to our results in reduced intensity conditioning with or without TBI^[24]. Martin *et al*^[24] reported that higher TNC dose was also associated with decreased relapse and increased incidence of chronic GvHD.

Our results indicate that overall CD34+ cell dose is not associated with OS or PFS in

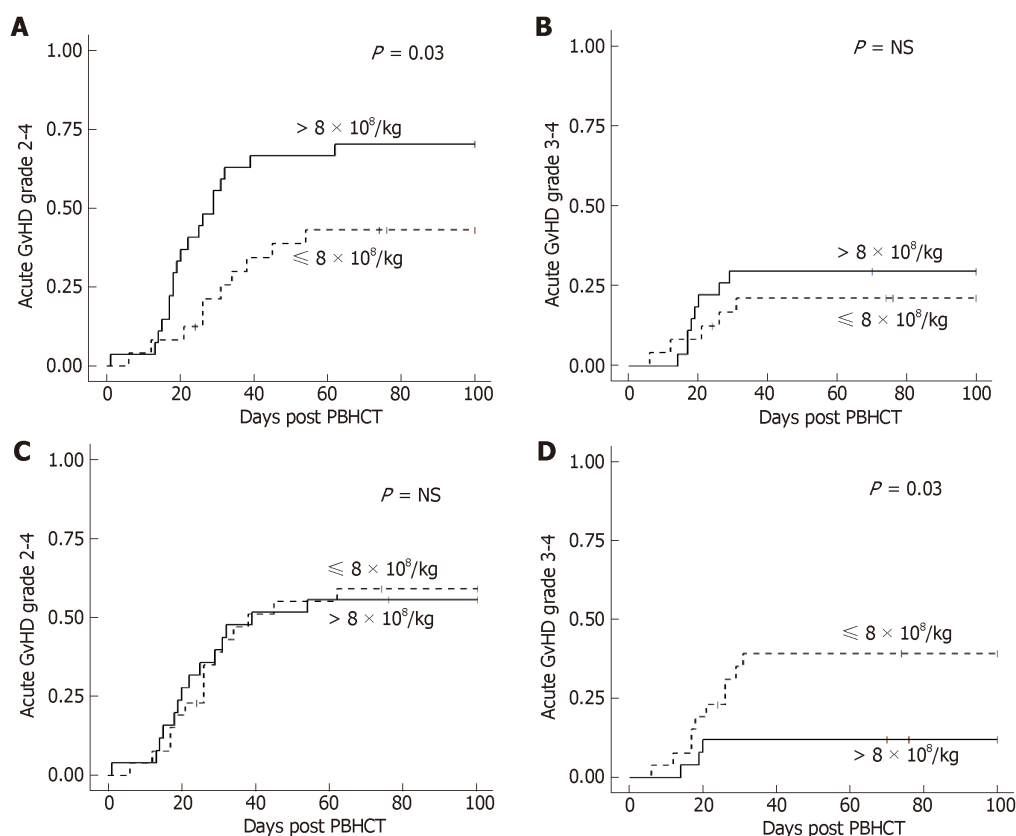


Figure 1 Cumulative incidence of acute GvHD by total nucleated cell dose in myeloablative + total body irradiation conditioning. A: Higher total nucleated cell dose had a higher incidence of acute GvHD grade II-IV; B: Total nucleated cell dose is not associated with acute GvHD grade III-IV; C: CD34+ cell dose is not associated with acute GvHD grade II-IV; D: Lower CD34+ cell dose has a higher incidence of acute GvHD grade III-IV. GvHD: Graft-versus-host disease.

our patient population as observed in other studies^[9,11-13,24]. This differs from a study in T-cell depleted transplants after myeloablative TBI conditioning, which reported CD34+ doses between $4-8 \times 10^6/\text{kg}$ were optimal for OS, and anything above or below this range resulted in increased mortality^[25]. Gorin *et al*^[16] demonstrated RIC + TBI patients receiving a TNC dose $> 9.1 \times 10^8/\text{kg}$ had improved PFS, which was similar to our results.

There was no association in patients with higher CD3+, CD4+, CD8+, or CD34+ doses and OS or GvHD, however recent studies indicated that an optimal CD34+ cell dose can lead to improved survival, less GvHD, and improved engraftment^[5-11]. Our results demonstrated an association with TNC dose, which could indicate there is another graft cell subset that may better predict these outcomes. One candidate is the natural killer (NK) cell. A low donor NK cell dose was associated with significantly longer time to engraftment and worse OS^[16]. NK cells have also been implicated as an important modulator of GvHD and the graft *vs* leukemia effect^[26]. It is possible that increasing the donor NK cell dose could allow for a more robust graft *vs* leukemia effect without increasing risk of GvHD^[27]. Focusing on the recipient, previous work demonstrated that host NK cells are relatively radiation-resistant and may decrease the incidence and severity of GvHD^[28-30]. Thus, in the setting of low dose TBI, host NK cells could be preserved and mediate a decrease in GvHD while allowing for an improved graft *vs* leukemia effect, translating into an improved PFS/OS.

Further confirmation of our results in a larger, multi-center registry study could be performed. In addition, analysis of other cell populations (*i.e.*, NK cell dose) could explain our findings. Further understanding of the impact of graft composition on post-transplant outcomes, and their potential interactions with conditioning regimens could allow physicians to better target certain cell doses in order to improve post-transplant survival outcomes.

Table 4 Multivariable analysis shows no association of cell doses with overall survival or progression free survival, except for total nucleated cell dose in the reduced intensity conditioning + total body irradiation group

Variable	Overall survival ¹					Progression free survival ²				
	All patients (n = 247)	MA-noTBI (n = 38)	MA + TBI (n = 51)	RIC-noTBI (n = 118)	RIC + TBI (n = 40)	All patients (n = 247)	MA-noTBI (n = 38)	MA + TBI (n = 51)	RIC-noTBI (n = 118)	RIC + TBI (n = 40)
CD3+ cell dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	1.1	1.0	0.5	1.3	0.8	1.0	1.1	0.4	1.4	0.6
95%CI	0.8-1.5	0.4-2.6	0.2-1.1	0.8-2.1	0.3-2.2	0.7-1.4	0.4-2.6	0.2-1.0	0.8-2.2	0.2-1.7
P	NS	NS	NS	NS	NS	NS	NS	0.05	NS	NS
CD4+ cell dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	1.2	1.1	0.6	1.2	2.0	1.1	1.1	0.5	0.3	1.5
95%CI	0.8-1.7	0.4-2.6	0.2-1.3	0.8-1.0	0.7-6.0	0.8-1.6	0.5-2.6	0.2-1.2	0.8-2.1	0.5-4.3
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CD8+ cell dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	1.2	1.5	1.0	1.3	0.5	1.1	1.1	0.9	1.2	0.7
95%CI	0.8-1.6	0.5-4.2	0.4-2.3	0.8-2.1	0.2-1.8	0.8-1.5	0.5-2.8	0.4-2.0	0.8-2.0	0.2-2.0
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
TNC dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	0.8	1.0	0.7	0.9	0.2	0.8	1.1	0.7	1.1	0.2
95%CI	0.6-1.2	0.4-2.4	0.3-1.9	0.5-1.5	0.1-0.8	0.6-1.2	0.4-2.5	0.3-1.6	0.6-1.8	0.1-0.8
P	NS	NS	NS	NS	0.02	NS	NS	NS	NS	0.02
CD34+ cell dose										
< 4 × 10 ⁶ /kg HR	1	1	1	1	1	1	1	1	1	1
4-8 × 10 ⁶ /kg HR	1.0	0.5	1.3	1.1	0.6	0.8	0.7	1.2	1.0	0.6
95%CI	0.6-1.5	0.2-1.4	0.4-4.4	0.6-1.9	0.1-2.3	0.6-1.4	0.2-2.1	0.4-4.0	0.6-1.8	0.2-2.6
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
> 8 × 10 ⁶ /kg HR	1.0	1.3	0.7	1.1	0.5	0.9	1.5	0.6	1.1	0.5
95%CI	0.6-1.5	0.4-4.0	0.2-2.3	0.5-2.0	0.1-2.4	0.6-1.4	0.5-4.6	0.2-2.0	0.6-2.0	0.1-2.6
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

¹Adjusted for age, KPS and BMI;²Adjusted for KPS and BMI. KPS: Karnofsky performance score; BMI: Body mass index; HR: Hazard ratio; 95%CI: 95% confidence interval; MA: Myeloablative; TBI: Total body irradiation; RIC: Reduced intensity conditioning; NS: Not significant ($P > 0.05$).

Table 5 Summary of correlations between cell doses demonstrating low correlation between total nucleated cell dose and CD8+ and CD34+ cell doses and moderate correlation with CD3+ and CD4+ cell doses

	CD3+ dose	CD4+ dose	CD8+ dose	CD34+ dose
CD4+ dose				
R	0.91			
R ²	0.83			
P	< 0.0001			
CD8+ dose				
R	0.81	0.55		
R ²	0.66	0.30		
P	< 0.0001	< 0.0001		
CD34+ dose				
R	0.20	0.21	0.11	
R ²	0.04	0.04	0.01	
P	0.0012	0.0009	NS	
Total nucleated cell dose				
R	0.71	0.64	0.56	0.38
R ²	0.50	0.41	0.31	0.14
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001

R: Pearson product moment correlation coefficient, $R > 0.8$ indicates highly correlated cell doses, $R < 0.4$ indicates low correlation between cell doses, R^2 : The square of the Pearson correlation, $R^2: 0.83$ indicates 83% of the variance in one cell dose (e.g., CD3+) is determined by the other (e.g., CD4+); NS: Not significant ($P > 0.05$).

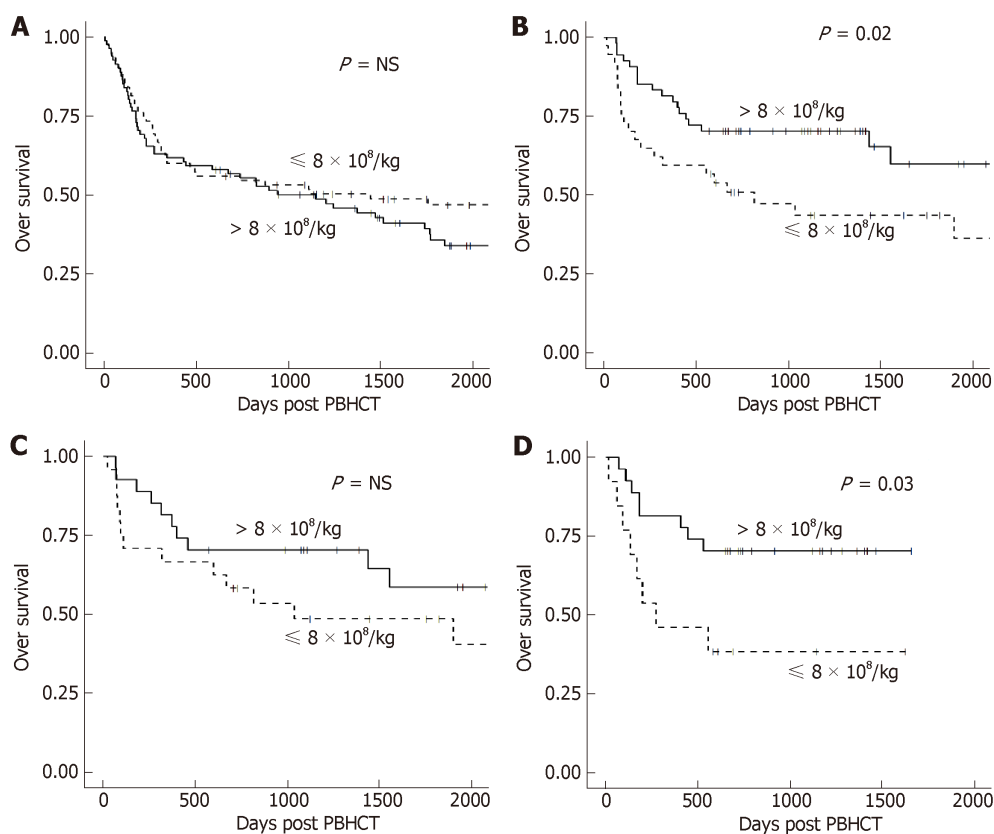


Figure 2 OS by total nucleated cell dose. A: OS was not significantly different in patients conditioned without TBI; B: OS was significantly better with a higher total nucleated cell dose in patients conditioned with TBI; C: OS was not significantly different in patients conditioned with myeloablative TBI; D: OS was significantly better with a higher total nucleated cell dose in patients conditioned with reduced intensity TBI. OS: Overall survival; TBI: Total body irradiation.

ARTICLE HIGHLIGHTS

Research background

Peripheral blood hematopoietic cell transplant (PBHCT) is the most commonly used allogeneic hematopoietic cell source due to its quick rate of neutrophil engraftment. A higher total nucleated cell (TNC) dose has been reported to improve survival after PBHCT, but analyses of specific T-cell subsets have been inconsistent. Factors such as T-cell depletion, conditioning regimen intensity, use of total body irradiation (TBI), and donor age may be interacting with graft cell doses to generate different effects on PBHCT outcomes. In addition, flow cytometric enumeration of cell doses are not standardized and may also lead to differences in results between studies.

Research motivation

While the optimal CD34+ cell dose range to minimize time to neutrophil and platelet recovery without increasing risk of acute graft-versus-host disease has been found to be $4\text{--}10 \times 10^6/\text{kg}$, some studies have reported a higher CD34+ cell dose yields improved overall survival while others have found no significant association. Further understanding of the impact of graft composition on post-transplant outcomes, and their potential interactions with conditioning regimens, could allow physicians to better target certain cell doses in order to improve post-transplant survival outcomes.

Research objectives

The objectives of this study were to examine whether the collected and infused CD34+, CD3+, CD4+, CD8+ or TNC dose influenced engraftment, overall survival, progression free survival, and incidence of acute and chronic GvHD, and whether the results were affected by conditioning regimen intensity or use of TBI.

Research methods

Four conditioning regimen groups were defined a priori as (1) myeloablative (MA) without TBI (MA-noTBI), (2) myeloablative with TBI (MA + TBI), (3) Reduced intensity conditioning (RIC) without TBI (RIC-noTBI) and (4) RIC with TBI (RIC + TBI). Correlations between TNC dose and CD3+ dose, CD4+ dose, CD8+ dose, CD34 dose were calculated using the Pearson product-moment correlation coefficient. The cumulative incidence of acute and chronic GvHD was analyzed adjusting for the competing risk of disease relapse. Univariable analysis of OS and progression free survival (PFS) were analyzed as time-to-event; survival curves were generated using the Kaplan-Meier method and were compared using the log-rank test. Multivariable analyses tested each cell dose while adjusting for significant factors in the univariate analysis, first in all patients and then stratified by the four conditioning regimen groups. These analyses allowed us to explore the interaction of conditioning regimen and allogeneic donor apheresis product composition in relation to outcomes after unmanipulated peripheral blood hematopoietic cell transplantation.

Research results

The cohort consisted of 135 sibling and 112 unrelated donor transplant recipients. Overall, patients who received a CD34+ cell dose $> 4 \times 10^6/\text{kg}$ experienced faster neutrophil engraftment and platelet engraftment as compared to patients who received a CD34+ cell dose $< 4 \times 10^6/\text{kg}$. Analysis by conditioning regimen demonstrated significantly faster neutrophil engraftment for an infused CD34+ cell dose $> 4 \times 10^6/\text{kg}$ in the RIC + TBI group. Overall and progression-free survival was significantly better in patients with a RIC + TBI regimen and TNC dose $> 8 \times 10^8/\text{kg}$. Our results indicated that overall CD34+ cell dose is not associated with OS or PFS in our patient population, similar to other studies. We did find an overall and progression-free survival benefit in patients with a RIC + TBI regimen and TNC dose $> 8 \times 10^8/\text{kg}$, which could indicate there is another graft cell subset that may better predict these outcomes.

Research conclusions

Our single center study is the first to analyze the relationship of conditioning regimen intensity and use of TBI with infused cell doses. Neutrophil engraftment was significantly faster after reduced intensity TBI based conditioning and $> 4 \times 10^6$ CD34+ cells/kg infused. In addition, overall and progression-free survival were significantly better in patients with a RIC + TBI regimen and TNC dose $> 8 \times 10^8/\text{kg}$. Our study suggested that TBI and conditioning intensity may alter the relationship between infused cell doses and outcomes after PBHCT. Our results demonstrated that immune cell subsets may predict improved survival after unmanipulated PBHCT.

Research perspectives

This study suggests that TBI and conditioning intensity may alter the relationship between infused cell doses and outcomes after PBHCT. Further confirmation of our results in a larger, multi-center registry study could be performed. In addition, analysis of other cell populations, such as NK cell dose, could explain our findings. Further understanding of the impact of graft composition on post-transplant outcomes, and their potential interactions with conditioning regimens could allow physicians to better target certain cell doses in order to improve post-transplant survival outcomes.

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