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Autologous Peripheral Blood Stem Cell Transplantation Among Lymphoproliferative Disease Patients: Factors Influencing Engraftment

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ABSTRACT

Objectives: Autologous peripheral blood stem cells transplantation (APBSCT) is a therapeutic option which can be used in various hematological, neoplastic disorders including lymphoproliferative disease (LPD). Differences in patient populations and treatment modalities in different transplant centers mean it is important to improve the knowledge of the different factors affecting engraftment after APBSCT for the success of this procedure. We sought to determine the factors influencing neutrophil and platelet engraftment after APBSCT in patients with LPD. ***Methods***: We conducted a retrospective review of 70 patients with LPD (35 with lymphoma and 35 with multiple myeloma) who had undergone APBSCT between January 2008 and December 2016. Data obtained included disease type, treatment, and stem cell characteristics. Kaplan-Meier analysis was performed for probabilities of neutrophil and platelet engraftment occurred and was compared by the log-rank test. The multivariate Cox proportional hazards regression model was used for the analysis of potential independent factors influencing engraftment. A p-value < 0.050 was considered statistically significant. ***Results:*** Most patients were ethnic Malay, the median age at transplantation was 49.5 years. Neutrophil and platelet engraftment occurred in a median time of 18 (range 4–65) and 17 (range 6–66) days, respectively. The majority of patients showed engraftment with 65 (92.9%) and 63 (90.0%) showing neutrophil and platelet engraftment, respectively. We observed significant differences between neutrophil engraftment and patient's weight (< 60/≥ 60 kg), stage of disease at diagnosis, number of previous chemotherapy cycles (< 8/≥ 8), and pre-transplant radiotherapy. While for platelet engraftment, we found significant differences with gender, patient's weight (< 60/≥ 60 kg), pre-transplant radiotherapy, and CD34+ dosage (< 5.0/≥ 5.0 × 10^6/kg and < 7.0/≥ 7.0 × 10^6/kg). The stage of disease at diagnosis ($p = 0.012$) and pre-transplant radiotherapy ($p = 0.025$) were found to be independent factors for neutrophil engraftment whereas patient's weight (< 60/≥ 60 kg, $p = 0.017$), age at transplantation (< 50/≥ 50 years, $p = 0.038$), and CD34+ dosage (< 7.0/≥ 7.0 × 10^6/kg, $p = 0.002$) were found to be independent factors for platelet engraftment. ***Conclusions:*** Patients with LPD who presented at an early stage and with no history of radiotherapy had faster neutrophil engraftment after APBSCT, while a younger age at transplantation with a higher dose of CD34+ cells may predict faster platelet engraftment. However, additional studies are necessary for better understanding of engraftment kinetics to improve the success of APBSCT.

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Lymphoproliferative diseases (LPDs) such as multiple myeloma (MM) and lymphoma are a group of hematological malignancies, which are growing in number and a challenge to treat. There are various specific treatment protocols available, and these are not uniform among health institutions. One treatment option is autologous hematopoietic stem cell transplantation, but this procedure is limited to certain eligible patients. Autologous peripheral blood stem cell transplantation (APBSCT) has dramatically increased worldwide involving peripheral blood stem cells as a source of hematopoietic stem cells[1] for the treatment of hematological neoplasms particularly in patients with LPD.[2]

APBSCT has become the standard of care for patients newly diagnosed with MM, which has prolonged the median survival rate to five to six years[3] and in patients with relapsed high-risk diffuse large B-cell lymphoma.[4] The Hospital Universiti Sains Malaysia (USM) started APBSCT therapy for MM and lymphoma patients in 2008 and is the referral transplant center for the east coast states of Malaysia. To date, there is no available local data/study to see the successful engraftment in patients with hematological malignancies patients treated with APBSCT.

APBSCT has resulted in a substantial survival advantage for patients with MM[5] and high-grade lymphomas where it is associated with faster hematological engraftment, less erythrocyte and platelet transfusions, fewer febrile days, less antibiotic use, and reduced treatment-related costs. There is also a lower risk of tumor contamination compared to bone marrow transplantation.[6] Besides the source of hematopoietic stem cell, there are many factors influencing engraftment that have been studied in many institutions. Many studies agree that the most important factor for successful engraftment is the CD34+ cell count.[7–9] The threshold of CD34+ cells necessary for engraftment ranges between 1.0–2.5 $\times 10^6$ cells/kg[10] while a cell dose of more than 2.0 $\times 10^6$ cells/kg results in rapid platelet recovery.[11] Other studies reported that higher CD34+ cell dose (> 5.0 $\times 10^6$ cells/kg and > 7.0 $\times 10^6$ cells/kg)[11,12] were associated with faster engraftment while dose > 10.0 $\times 10^6$ cells/kg had less risk for poor engraftment.[13] However, with differences in patient populations and treatment modalities in different transplant centers, it is important to improve the knowledge of the different factors affecting engraftment after APBSCT for the success of this procedure.

Thus, our study aimed to determine the predictive factors influencing engraftment in patients with LPD who underwent APBSCT. Hopefully, the results obtained may be useful for hematologists to predict and choose patients who may benefit from undergoing APBSCT and optimize their management.

METHODS

Our study was a retrospective record review study of all lymphoma and MM patients who had undergone APBSCT between January 2008 and December 2016 in the Stem Cell Transplantation Unit, Department of Medicine, Hospital USM. We retrieved data related to the factors that might affect engraftment including patient characteristics, disease, treatment, and stem cell characteristics of 71 patients who underwent APBSCT. Patients reviewed in the study included 35 with MM, 19 with non-Hodgkin lymphoma (NHL), and 16 with Hodgkin lymphoma (HL). One of the patients with MM was excluded due to incomplete data. We applied the International Staging System (stage I, II, III) for MM[14] and the Lugano classification (stage I, II, III, IV) for lymphoma.[15] The disease was categorized into early stage (stage I and II MM and lymphoma) and advanced stage (stage III MM and stage III/IV lymphoma).[14,15] All patients received high-dose chemotherapy as conditioning therapy prior to hematopoietic stem cell infusion; patients with MM received high-dose melphalan 200 mg/m^2 (MEL-200 SCT) and all patients with NHL and HL received carmustine-etoposide-cytarabine-melphalan (BEAM). Patient's pre-transplant characteristics are shown in Table 1.

Written consent was obtained from all patients before the initiation of APBSCT treatment. This study was approved by the Human Research Ethics Committee, USM (protocol number USM/JEPeM/140362).

All patients with MM were mobilized by daily stimulation with a combination of granulocyte colony-stimulating factor (G-CSF) and cyclophosphamide, and patients with NHL and HL with the combination of G-CSF and etoposide (VP16) or salvage chemotherapy regime ifosfamide-

Table 1: Pre-transplantation patient characteristics (n = 70).

Characteristics	Frequency n (%)	Median (range)
Gender		
Male	32 (45.7)	
Female	38 (54.3)	
Race		
Malay	64 (91.4)	
Non-Malay	6 (8.6)	
Age, years		
At diagnosis		46.5 (12–70)
At mobilization		49.0 (13–71)
At transplantation		49.5 (15–71)
Weight, kg		56.0 (34–109)
Diagnosis		
MM	35 (50.0)	
NHL	19 (27.1)	
HL	16 (22.9)	
Disease stage at diagnosis		
Early	21 (30.0)	
Advanced	49 (70.0)	
Disease status at transplantation		
CR	16 (22.9)	
VGPR/PR	43 (61.4)	
SD	8 (11.4)	
PD	3 (4.3)	
BM infiltration, (except MM)		
Yes	2 (5.7)	
No	33 (94.3)	
Plasma cells at diagnosis, % (except lymphoma)		41.0 (8.5–75)
Received radiotherapy		
Yes	12 (17.1)	
No	58 (82.9)	

MM: multiple myeloma; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; BM: bone marrow.

carboplatin-etoposide (ICE). Daily peripheral blood CD34+ cells counts were measured, and leukapheresis was carried out when peripheral blood CD34+ cell counts were more than 20 cells/μL. The leukapheresis procedure was performed using the Spectra Optia (Terumo BCT Lakewood, CO USA) separator.

The peripheral blood CD34+ cells and CD34+ dose of collected product was determined using single-platform flow cytometric method based on ISHAGE gating strategy using BD TruCOUNT™ Stem Cell Enumeration kit with CellQuest™ Pro program in BD FACSCalibur™ flow cytometer (Becton Dickinson, San Jose, CA).[16] For cryopreservation, the apheresis products were adjusted with autologous plasma to a calculated volume. The product was divided into cryobags and a cryoprotectant, dimethyl sulfoxide (DMSO) was added to achieve final concentration of 10% of the total suspension. The products were frozen in a cryopreservation controlled-rate freezer and stored at -196 °C in liquid nitrogen until infusion.

For infusion, the cryopreserved unit was thawed rapidly in a 37 °C water bath and infused immediately through the central venous catheter. After infusion, all patients received post-transplant granulocyte colony-stimulating factor along with antibacterial, antiviral, and antifungal chemoprophylaxis. Daily full blood count was sent from the day of stem cell infusion to monitor white blood cell count, absolute neutrophil count, and platelet count using the hematology analyzer Sysmex XE-5000 (Sysmex Corporation, Kobe, Japan).

The day of neutrophil engraftment was defined as the first day when the absolute neutrophil count was > 0.5×10^9/L for three consecutive days, while the day of platelet engraftment was defined as the first day when platelet count was > 20×10^9/L for three consecutive days without transfusion support.[11,17] Rapid engraftment was defined when both neutrophil and platelet engraftment occurred within 12 days of stem cell infusion.[18]

The data were analyzed using SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Descriptive results were expressed as percentage, median and range. The outcome examined was days to neutrophil and platelet engraftment. Kaplan-Meier analysis was performed for probabilities of neutrophil and platelet engraftment and the difference between engraftment time and factors analyzed was compared by log-rank test. The multivariate Cox proportional hazards regression model was used for the analysis of potential independent factors influencing neutrophil and platelet engraftment. A *p*-value of < 0.050 was considered statistically significant.

Table 2: Patient characteristics of transplantation (n = 70).

Characteristics	Frequency, n (%)	Median (range)	95% CI
No. of prior chemotherapy regime cycles		8.0 (3.0–14.0)	
Conditioning regime			
MEL-200	35 (50.0)		
BEAM	35 (50.0)		
Infused CD34+ dosage, × 10^6/kg		3.6 (0.7–15.9)	
Diagnosis to APBSCT interval, years		1.4 (0.5–10.1)	
Harvest preservation period, months		4.9 (0.4–18.8)	
Engraftment time, days			
Neutrophil		18.0 (4.0–65.0)	15.6–20.4
Platelet		17.0 (6.0–66.0)	14.6–19.4
Engraftment[a]			
Neutrophil (Yes/No)	65/5 (92.9/7.1)		
Platelet (Yes/No)	63/7 (90.0/10.0)		
Rapid engraftment, ≤ 12 days[b]			
Neutrophil (Yes/No)	16/53 (23.2/76.8)		
Platelet (Yes/No)	20/49 (29.0/71.0)		
Infection (Yes/No)	45/25 (64.3/35.7)		

CI: confidence interval; MEL-200: melphalan-200mg; BEAM: carmustine-etoposide-cytarabine-melphalan; APBSCT: autologous peripheral blood stem cell transplantation.
[a]Seven patients died before platelet and/or neutrophil engraftment occurred.
[b]One patient died within 12 days transplant before engraftment occurred.

RESULTS

In 70 patients with LPDs who underwent APBSCT, the median infused CD34+ cells dose was 3.6 × 10^6/kg (range 0.7–15.9). In all patients, neutrophil and platelet engraftment occurred in median time of 18.0 (range 4.0–65.0) and 17.0 (range 6.0–66.0) days, respectively. The details of other transplantation data were summarized in Table 2. The majority of patients showed engraftment, with 65 (92.9%) and 63 (90.0%) showing neutrophil and platelet engraftment, respectively. Only 16 (23.2%) and 20 (29.0%) patients were observed to have early (≤ 12 days) neutrophil and platelet engraftment, respectively. Seven patients died due to septicemia before platelet and/or neutrophil engraftment [Table 3]. All were infused with a CD34+ cell dose of > 2.5 × 10^6 cells/kg. We found that the majority were female (six patients), had a diagnosis of NHL (five patients), died within 30 days of transplant (six patients), and had neutropenic sepsis within the first week of transplantation. All had at least achieved partial remission before transplantation.

The effects of gender, age, type of diagnosis, weight, blood group, infused CD34+ dosage,

Table 3: Summary of patients who died before neutrophil and/or platelet engraftment occurred after APBSCT.

Diagnosis	Gender	Age at transplant, years	Stage of disease at diagnosis	Dose CD34+ cells infused (× 10^6/kg)	Engraftment status		Day of death (post-transplant
					Neutrophil	Platelet	
MM	Female	51	III	3.5	Yes (day 50)	No	159
MM	Female	69	II	5.3	No	No	26
NHL	Male	59	IV	2.6	No	No	14
NHL	Female	60	III	3.9	Yes (day 22)	No	33
NHL	Female	31	IV	3.1	No	No	13
NHL	Female	49	III	3.3	No	No	8
NHL	Female	52	IV	2.9	No	No	20

APBSCT: autologous peripheral blood stem cell transplantation; MM: multiple myeloma; NHL: non-Hodgkin lymphoma.

Table 4: Differences of median neutrophil and platelet engraftment time after APBSCT among patients with LPDs using Kaplan-Meier analysis (n = 70).

Variables	Frequency	Neutrophil engraftment time, days			Platelet engraftment time, days		
		Engraftment (%)	Median (95% CI)	*p*-value*	Engraftment (%)	Median (95% CI)	*p*-value*
Gender				0.397			0.016
Male	32	31 (96.9)	17 (13.0–21.0)		31 (96.9)	15 (11.8–18.2)	
Female	38	34 (89.5)	20 (17.7–22.3)		32 (84.2)	20 (14.3–25.7)	
Race				0.737			0.055
Malay	64	60 (93.8)	18 (15.5–20.5)		58 (90.6)	18 (15.8–20.2)	
Non-Malay	6	5 (83.3)	13 (5.8–20.2)		5 (83.3)	11(-)	
Age at transplantation, years				0.157			0.119
< 50	35	33 (94.3)	18 (16.1–19.9)		33 (94.3)	15 (10.9–19.1)	
≥ 50	35	33 (91.4)	19 (10.2–27.8)		30 (85.7)	18 (13.8–22.2	
Weight, kg				0.047			0.047
< 60	43	38 (88.4)	18.3-21.7		36 (83.7)	18 (15.6–20.4)	
≥ 60	26	26 (100)	13.0-19.0		26 (100)	15 (10.8–19.2)	
MM	35	34 (97.1)	15 (11.6–18.4)	0.486	33 (94.3)	17 (14.8–19.2)	0.549
NHL-HL	35	31 (88.6)	20 (17.8–22.2)		30 (85.7)	16 (9.7–22.3)	
Conditioning				0.486			0.549
MEL-200	35	34 (97.1)	15 (11.6–18.4)		33 (94.3)	17 (14.8–19.2)	
BEAM	35	31 (88.6)	20 (17.8–22.2)		30 (85.7)	16 (9.7–22.3)	
Stage at diagnosis				0.001			0.245
Early	21	20 (95.2)	15 (10.6–19.4)		20 (95.2)	16 (10.0–22.0)	
Advanced	49	45 (91.8)	20 (17.9–22.1)		43 (87.8)	17 (14.2–19.8)	
Disease status at transplantation				0.281			0.779
CR	16	13 (81.3)	16 (14.4–17.6)		13 (81.3)	21 (11.2-30.8)	
< CR	54	52 (96.3)	20 (17.6–22.4)		50 (92.6)	16 (13.8-18.2)	
Number of previous chemotherapy cycle				0.014			0.161
< 8	33	29 (87.9)	22 (15.4–28.6)		28 (84.8)	18 (11.1–24.9)	
≥ 8	37	36 (97.3)	15 (11.6–18.4)		35 (94.6)	16 (13.0–19.0)	
Pre-transplant radiotherapy				0.008			0.035
Yes	12	12 (100)	14 (8.9–19.1)		12 (100)	12 (6.9–17.1)	
No	58	53 (91.4)	20 (17.6–22.4)		51 (87.9)	18 (15–21)	
Infused CD34+ dosage ($\times 10^6$/kg)							
< 2	8	8 (100)	24 (18.5–29.5)	0.143	8 (100)	21 (12.7–29.3)	0.403
≥ 2	62	57 (91.9)	17 (13.8–20.2)		55 (88.7)	16 (13.3–18.7)	
< 5	46	42 (91.3)	17 (13.9–20.1)	0.719	40 (87.0)	20 (16.5–23.5)	0.008
≥ 5	24	23 (95.8)	20 (17.6–22.4)		23 (95.8)	14 (11.1–16.9)	
< 7	56/14	51 (91.1)	18 (15.4–20.5)	0.559	49 (87.5)	18 (14.9–21.1)	0.002
≥ 7	14	14 (100)	13 (3.2–22.8)		14 (100)	12 (10.8–13.2)	
< 10	66	61/4 (92.4)	18 (14.6–21.4)	0.383	59 (89.4)	18 (15.7–20.3)	0.463
≥ 10	4	4 (100)	28 (-)		4 (100)	11 (9.0–13.0)	
Diagnosis-transplant interval, years				0.051			0.161
< 1	20	19 (95.0)	21 (13.7–28.3)		18 (90.0)	17 (10.4–23.6)	
≥ 1	50	46 (92.0)	17 (13.7–20.3		45 (90.0)	17 (14.6–19.4)	
Preservation, months				0.380			0.451
< 5	35	33 (94.3)	19 (13.4–24.6)		32 (91.4)	17 (13.8–20.2)	
/≥ 5	35	32 (91.4)	18 (15.6–20.4)		31 (88.6)	17 (13.7–20.3)	

Table 4: Differences of median neutrophil and platelet engraftment time after APBSCT among patients with LPDs using Kaplan-Meier analysis (n = 70).

-continued

Variables	Frequency	Neutrophil engraftment time, days			Platelet engraftment time, days		
		Engraftment (%)	Median (95% CI)	*p*-value*	Engraftment (%)	Median (95% CI)	*p*-value*
Blood group				0.751			0.864
O	26	25 (96.2)	17 (13.8–20.2)		25 (96.2)	15 (12.6–17.4)	
Other	44	40 (90.9)	20 (17.7–22.3)		38 (86.4)	18 (16–20)	
Percentage of plasma cells at diagnosis, (except lymphoma)				0.403			0.462
< 40	15	15 (100)	15 (4.9–25.1)		15 (100)	18 (11.7–24.3)	
≥ 40	16	16 (100)	12 (10.7–13.3)		15 (93.8)	14 (11.1–16.9	
Marrow infiltration, (except MM)				0.642			0.342
Yes	2	2 (100)	22 (-)		1 (50.0)	11 (-)	
No	33	29 (87.9)	20 (17.9–22.1)		29 (87.9)	16 (9.9–22.1)	
Number of leukapheresis				0.966			0.337
1	45	40 (88.9)	18 (15.2–20.8)		39 (86.7)	16 (12.5–19.1)	
> 1	25	25 (100)	19 (10.9–27.1)		24 (96.0)	18 (16.4–19.6)	
Infection post-transplant				0.519			0.114
Yes	45	40 (100)	20 (16.3–23.7)		38 (84.4)	18 (15.4–20.6)	
No	25	25 (88.9)	16 (12.1–19.9)		25 (100)	16 (11.1–20.9)	

CI: confidence interval; APBSCT: autologous peripheral blood stem cell transplantation; LPDs: lymphoproliferative diseases; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; MEL-200: melphalan-200mg; BEAM: carmustine-etoposide-cytarabine-melphalan; CR: complete response.

period between diagnosis-transplant, preservation time of harvest product, amount of leukapheresis, conditioning regime, a number of previous chemotherapy cycle, pre-transplant radiotherapy, stage of disease during diagnosis, disease status at transplant, marrow infiltration, the number of plasma cells in bone marrow and post-transplant infection on neutrophil and platelet engraftment time were summarized in Table 4.

In patients with MM (n = 35), the median neutrophil engraftment time was faster than in patients with lymphoma (n = 35) at 15 and 20 days, respectively. On the other hand, there was not much difference in platelet engraftment time (17 and 16 days, respectively). Statistically, there were no significant differences between the type of disease with both neutrophil and platelet engraftment time.

In univariate analysis, we found significant differences between neutrophil engraftment and patient weight (< 60/≥ 60 kg, $p = 0.047$), stage of disease at diagnosis ($p = 0.001$), the number of previous chemotherapy cycles (< 8/≥ 8, $p = 0.014$), and pre-transplant radiotherapy ($p = 0.008$). For platelet engraftment, we found significant differences with gender ($p = 0.016$), patient weight (< 60/≥ 60 kg, $p = 0.047$), pre-transplant radiotherapy ($p = 0.035$), and infused CD34+ dosage (< 5.0/≥ 5.0, $p = 0.008$ and < 7.0/≥ 7.0 × 10^6/kg, $p = 0.002$). There were no significant differences between platelet engraftment time and the other factors analyzed.

There was a significant difference between gender and platelet engraftment time and no significant difference with neutrophil engraftment time. Males (n = 32) showed faster platelet engraftment time compared to females (n = 38), 15 and 20 days ($p = 0.016$), respectively. There was statistically significant difference between patient's weight with both neutrophil and platelet engraftment time. Patients weighing ≥ 60 kg (n = 26) had faster neutrophil and platelet engraftment times compared to patients < 60 kg (n = 43), 16 and 20 ($p = 0.047$), and 15 and 18 ($p = 0.047$) days, respectively. There was a significant difference between the infused CD34+ dosage and platelet engraftment time, but no significant difference with neutrophil engraftment time. CD34+ dosage ≥ 5.0 × 10^6/kg (n = 24) and ≥ 7.0 × 10^6/kg (n = 14) showed faster platelet engraftment time at 14 and 20 days ($p = 0.008$) compared to < 5.0 × 10^6/kg (n = 46) and < 7.0 × 10^6/kg (n = 56) at 12 and 18 days ($p = 0.002$), respectively.

Table 5: Factors influencing neutrophil and platelet engraftment after APBSCT among patients with LPD using Cox proportional hazard regression (n = 70).

Variables	Neutrophil engraftment time, days				Platelet engraftment time, days			
	Crude HR (95% CI)	*p*-value[a]	Adjusted HR (95% CI)	*p*-value[b]	Crude HR (95% CI)	*p*-value[a]	Adjusted HR (95% CI)	*p*-value[b]
Age at transplantation, years								
≥ 50	1.00		-	-	1.00		1.00	
< 50	1.43 (0.85–2.41)	0.175			1.46 (0.89–2.40)	0.135	1.71 (1.03–2.85)	0.038
Weight, kg								
< 60	1.00		-	-	1.00		1.00	
≥ 60	1.65 (0.98–2.79)	0.059			1.68 (0.98–2.86)	0.057	1.93 (1.12–3.31)	0.017
Infused CD34+ cell dose ($\times 10^6$/kg)								
< 7.0	1.00		-	-	1.00		1.00	
≥ 7.0	1.19 (0.65–2.16)	0.574			2.45 (1.32–4.53)	0.005	2.79 (1.45–5.36)	0.002
Stage of disease at diagnosis								
Advanced	1.00		1.00		1.00		-	-
Early	2.51 (1.41–4.44)	0.002	2.71 (1.49–4.94)	0.012	1.37 (0.79–2.38)	0.263		
Pre-transplant radiotherapy								
No	1.00		1.00		1.00		-	-
Yes	2.33 (1.19–4.53)	0.013	2.20 (1.1–4.38)	0.025	1.93 (1.01–3.66)	0.045		

APBSCT: autologous peripheral blood stem cell transplantation; LPDs: lymphoproliferative diseases; HR: hazard ratio; CI: confidence interval.
[a]*Simple Cox proportional hazard regression.*
[b]*Multiple Cox proportional hazard regression.*

Between patients with early (n = 21) and advanced (n = 49) stage at diagnosis, we observed significant differences regarding neutrophil engraftment only. Patients with early stage disease had a faster neutrophil engraftment time compared to advanced stages, 15 and 20 (p = 0.001) days, respectively. We also found significant differences regarding neutrophil engraftment in patients with ≥ 8 cycles (n = 37) of chemotherapy who showed a faster neutrophil engraftment time compared to patients with < 8 cycles (n = 33), 15 and 22 (p = 0.014) days, respectively. Between patients with (n = 12) or without (n = 58) a history of pre-transplant radiotherapy, there were significant differences regarding both neutrophil engraftment time (14 and 20 days, p = 0.008) and platelet engraftment time (12 and 18 days, p = 0.035), respectively.

In multivariate analysis, stage of disease at diagnosis (adjusted hazard ratio (HR) = 2.71, p = 0.012) and pre-transplant radiotherapy (adjusted HR = 2.20, p = 0.025) were found to be independent factors for neutrophil engraftment whereas patient's weight (adjusted HR = 1.93, p = 0.017), age at transplantation (adjusted HR = 1.71, p = 0.038), and infused CD34+ dosage (adjusted HR = 2.79, p = 0.002) were independent factors for platelet engraftment [Table 5].

DISCUSSION

There are many studies evaluating the factors affecting neutrophil and platelet engraftment after APBSCT. Most studies found that only infused CD34+ dosage correlated with faster neutrophil and platelet engraftment. Our study evaluated the data from 70 patients with MM and lymphoma who had undergone APBSCT between January 2008 and December 2016 in our center. Beside the infused CD34+ cell dose, we found that the age at transplantation and patient's weight were also predictive factors for platelet engraftment while the stage of disease at diagnosis and pre-transplant radiotherapy were the predictive factors for neutrophil engraftment.

The engraftment kinetic has been postulated as being associated with the infused CD34+ dosage where the higher CD34+ dosage are associated with rapid neutrophil and platelet engraftment.[12,13,19] However, in this study we found that CD34+ dosage was only a predictive factor for platelet engraftment and this result was consistent with other studies.[10,11] In addition, we failed to demonstrate an association between CD34+ dosage and neutrophil engraftment, which implies differences in engraftment kinetics between platelets and neutrophils.[20] It is widely accepted that the minimum number of CD34+ cells count is at least 2.0×10^6/kg for successful neutrophil and platelet engraftment.[7–9,21] In other studies, they proposed that the CD34+ dosage of 2.5×10^6/kg was the threshold for optimum engraftment.[22,23]

We studied different cut-off values of infused CD34+ dosage (2.0, 5.0, 7.0, and 10.0×10^6/kg) since a few studies have reported different CD34+ dosage cut-off values associated with faster engraftment. We found that only the infusion of $\geq 7.0 \times 10^6$ CD34+ cells/kg showed significant faster platelet engraftment. In contrast to previous studies,[6–9,21–23] our study did not demonstrate that lower threshold than 7.0×10^6 cells/kg of infused CD34+ cells showed significant difference with neither neutrophil nor platelet engraftment time. Our result was in agreement with another study which showed that the infusion of CD34+ cells > 7.0×10^6/kg had significant faster platelet engraftment time among patients with LPDs who underwent APBSCT.[11] The significant association of infused CD34+ dosage and platelet engraftment rather than neutrophil engraftment does support that the quality of stem cells function is better reflected by megakaryopoiesis rather than granulopoiesis.[8] Granulopoiesis seems not to be so much affected since all patients were given granulocyte colony-stimulating growth factor as it has been shown to enhance neutrophil engraftment.[6,24]

Age is one factor considered when patients opted for transplantation. Many transplant centers in European countries decide those patients who are less than 65 years old and have no comorbidities are primarily eligible candidates for APBSCT.[25] A majority of studies showed that patient's age was not associated with neither neutrophil nor platelet engraftment.[12,13,19,26–28] However, this study found that patient's age at transplantation was a predictive factor for platelet engraftment. Younger patients aged < 50 years old had 1.71-times faster platelet engraftment than patients ≥ 50 years old. This finding was only agreed by a few studies. Tricot et al,[8] showed that only patients with MM ≤ 50 years old showed only significant for faster platelet engraftment in MM patients. Grubovic et al,[29] concluded that age was one of the potentially important variables for both neutrophil and platelet engraftment among lymphoma patients and Goncalves et al,[2] showed that patients with hematological malignancies aged 50–59 years demonstrated significant faster engraftment.

Body weight is very important for CD34+ cell dose calculation. We also found that body weight was the significant factor that affected platelet engraftment where patients ≥ 60 kg were 1.93-times more likely to have faster platelet engraftment compared to those weighing < 60 kg. This finding was consistent with our previous result in which dosage of infused CD34+ cell only affected platelet engraftment time since CD34+ cell dosage was calculated based on actual body weight. However, a few studies are suggesting that ideal body weight correlates better with engraftment after APBSCT than actual body weight.[30,31]

We found that early stage of the disease has a significant contribution towards faster neutrophil engraftment, but does not influence platelet engraftment. However, there are no other studies related to APBSCT that support our finding.[8,17,19] A possible reason is that patients with early-stage disease received fewer cycles of chemotherapy than those with advanced disease and thus less damage to the marrow stroma and microenvironment providing better conditions for neutrophil engraftment.

We also found the history of pre-transplant radiotherapy was significantly associated with delayed neutrophil engraftment time but not affected by platelet engraftment. A few other studies also showed pre-transplant radiotherapy which was significantly affected and delayed both neutrophil and platelet engraftment. This may be associated with distorted marrow microenvironment due to radiotherapy.[2,6]

Our study has some limitations. Some of the required independent variables might not be available due to the use of a record review method. This study only involved a small number of subjects due to a limited number of cases available within the study period. Thus, the findings need to be

inferred with caution since they might not be representative of the reference population.

CONCLUSIONS

Our study revealed that predictive factors for faster neutrophil engraftment were early/intermediate stage of the disease and no pre-transplant radiotherapy history while for faster platelet engraftment were infused CD34+ dosage ≥ 7.0 × 10^6/kg, body weight ≥ 60 kg, and younger age at transplantation (< 50 years). Other factors such as race, gender, diagnosis, conditioning regime, number of prior chemotherapy sessions, duration of the diagnosis-transplant interval, post-transplantation infection, disease status before transplant, and preservation time were not found to influence neutrophil or platelet engraftment.

Disclosure

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