Original article:

Risk Factors for Poor Autologous Peripheral blood Stem Cell Mobilization among Lymphoproliferative Disease Patients

Mohd Nazri Hassan[1], Azlan Husin[2], Rapiaah Mustaffa[3], Rosline Hassan[4], Mohd Ismail Ibrahim[5], Abu Dzarr Abdullah[6], Noor Haslina Mohd Noor[7]

Abstract:

Objective: Autologous peripheral blood haemopoietic stem cell (PBSC) transplantation is a standard therapeutic option for eligible patients with lymphoproliferative disease (LPD). The prerequisite for autologous PBSC transplantation is the successful stem cell mobilization. This study is aimed to determine the factors associated with poor PBSC mobilization in LPD patient at our center. ***Materials and methods:*** This retrospective record review involved 39 multiple myeloma (MM) and 92 of lymphoma patients who had undergone PBSC mobilization from January 2009 until December 2016. Patients were mobilized with combination chemotherapy and granulocyte colony stimulating factor. Factors affecting mobilization including patient's, disease and treatment characteristics werestudied. ***Results:*** Majority of patients were Malay (93.9%) with the mean age at mobilization of 41.4 years. The mean of CD34+ cell dosage was $9.6x10^6$ cells/kg. Successful and poor mobilization was found to be 90.8% and 9.2% respectively. Multivariate analysis showed that the significant risk factors for poor mobilization were age of ≥ 60 years (adjusted OR=38.43, p=0.005) and PB CD34+ cell count, <20 cells/uL (adjusted OR=132.69, p<0.001). ***Conclusion:***PB CD34+ cell count and age ≥ 60 years were the main risk factors for poor PBSC mobilization. Thus, alternative strategies of mobilization is needed to reduce risk of poor mobilization in a such group of patient.

Keywords: autologous transplantation; stem cell mobilization; multiple myeloma; lymphoma

Bangladesh Journal of Medical Science Vol. 19 No. 03 July'20. Page :458-466
DOI: https://doi.org/10.3329/bjms.v19i3.45863

Introduction:

Salvage chemotherapy followed by autologous peripheral blood haematopoietic stem transplantation (APBSCT) is globally accepted as the standard of care for lymphoproliferative disorder (LPD) namely multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and relapsed Hodgkin lymphoma (HL) patients[1,2]. Hospital Universiti Sains Malaysia (USM)

1. Mohd Nazri Hassan, Department of Haematology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia & Hospital USM, Health Campus, USM, 16150 Kubang Kerian, Kelantan, Malaysia.
2. Azlan Husin, Hospital USM, Health Campus, USM, 16150 Kubang Kerian, Kelantan, Malaysia & Department of Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
3. Rapiaah Mustaffa, Department of Haematology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia & Hospital USM, Health Campus, USM, 16150 Kubang Kerian, Kelantan, Malaysia.
4. Rosline Hassan, Department of Haematology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia & Hospital USM, Health Campus, USM, 16150 Kubang Kerian, Kelantan, Malaysia.
5. Mohd Ismail Ibrahim, Department of Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
6. Abu Dzarr Abdullah, Hospital USM, Health Campus, USM, 16150 Kubang Kerian, Kelantan, Malaysia & Department of Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
7. Noor Haslina Mohd Noor, Department of Haematology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia & Hospital USM, Health Campus, USM, 16150 Kubang Kerian, Kelantan, Malaysia.

Correspondence to: Dr Mohd Nazri Hassan, Address: Department of Haematology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia; email: nazrihas@usm.my;

is a referral transplantation center for APBSCT treatment of MM and lymphoma patients for the East Coast states of Malaysia since 2009.

Peripheral blood stem cell (PBSC) is now the preferred source of haematopoietic stem cell (HSC) replacing bone marrow because of relative ease of collection, avoidance of hospital admission or general anaesthesia, faster haematopoietic engraftment and lesser transplant related morbidity[3]. Adequate stem cell mobilization is essential for a successful APBSCT. Poor mobilization leads to a stem cell collection failure and this result in increase resource utilization in terms of increase use of growth factors, mobilization reattempts using other mobilzer agent, hospitalizations, transfusions requirement, and antibiotics for neutropenic fever[4,5].

A minimum CD34+ cell dosage of $2x10^6$ cells/kg are required to achieve haematopoietic engraftment[6,7] while some studies suggest that higher dosage, more than $5x10^6$ cells/kg are associated with faster neutrophil and platelet engraftment[3,6]. Factors affecting PBSC mobilization had been studied, and beside the PB CD34+ cell count, no other factor has been shown to conclusively predict stem cell mobilizability[1,8]. Furthermore, factors unique to a particular population, may still be a significant determinant affecting stem cell mobilization, and should be studied.

Thus, the aim of this study was to determine the risk factors affecting poor PBSC mobilization in LPD patient at our center. Hopefully, the results obtained may provide a useful guidance to predict which patient is at risk for unsuccessful PBSC mobilization. Hence additional intervention can be incorporated early on to reduce of collection failure.

Materials and Methods:

Study design and characteristic of patients

This was a retrospective record review involved of all lymphoma and MM patients who had undergone APBSC mobilization from January 2009 until December 2016 in Stem Cell Transplantation Unit, Department of Internal Medicine, Hospital USM. A total of 132 LPD patients underwent PBSC mobilization during 8 years of period. One lymphoma patient was excluded from this study because of procedural failure resulting from equipment failure. The factors that might affect PBSC mobilization including patient's characteristics, disease and treatment status and haematological parameters during collection from 131 patients had been investigated. The patients who were enrolled in this study include 39 with MM, 55 with non-Hodgkin lymphoma (NHL) and 37 with Hodgkin lymphoma (HL). For the purpose of the analysis, the disease was categorized into early stage (stage I and II for MM and lymphoma) and advanced stage (stage III for MM and stage III/IV for lymphoma). The disease staging for MM was done based on International staging system (stage I, II, III)[9]. While for lymphoma, Lugano classification was applied (stage I, II, III, IV)[10].

A standard approach in our institution is that, patients with lymphoma that achieved partial response (PR) following anthracycline based chemotherapy; cyclophosphamide-doxorubicin-vincristine-prednisone with or without rituximab (CHOP, R-CHOP) for NHL; or adriamycin-bleomycin-vinblastine-dacarbazine (ABVD) for HL will undergo stem cell collection. The decision regarding APBSCT will be decided later on case to case basis. On the other hand, for MM a minimum achievement of PR with marrow plasma cells less than 5% following at least four cycles of thalidomide with or without velcade based chemotherapy regime was a prerequisite for stem cell collection. In addition, there were circumstances where stem cell collections were performed not confined to the above criteria.

PBSC mobilization and collection

All 39 MM patients were mobilized with the combination of cyclophosphamide (CPM) and GSCF at 10 µg/kg/day (600 µg/daily), while NHL and HL patients were mobilized with combination of GSCF at 10 µg/kg/day and etoposide (VP-16) (17 patients) or salvage chemotherapy regime (75 patients) (ifosfamide-carboplatin-etoposide with or without rituximab, ICE/RICE or dexamathasone-doxorubicin-cytarabine-carboplatin, DHAC or etoposide-solumedrole-cytarabine-cisplatin, ESHAP or gemcitabine-docetaxel-carboplatin, GDC). SubcutaneusGCSF was started 24 hours post completion of chemotherapy.

Full blood count was evaluated daily with Sysmex XE-5000 haematology analyzer and daily peripheral blood (PB) CD34+ cells counts enumeration was started when total white blood cell count (WBC) had risen from nadir to more than $1.0x10^9$/L. Leukapheresis for PBSC collection was carried out when PB CD34+ cell counts were at least 20 cells/uL. Since patients were enrolled over an extended period and different apheresis machines models were used at different period, collection protocol varied

between one patient from another in accordance to model used. Leukapheresis procedures were performed by using Spectra Optia (Terumo BCT, Lakewood, CO USA) or Com.Tec (Fresenius, Lake Zurich, III) blood cell separator. A total of 2.5 to 3 times of the calculated patient's total blood volume was processed daily until targeted CD34+ dose of at least $3x10^6$ cell/kg or $6x10^6$ cell/kg were collected for lymphoma or MM respectively. Venous access was obtained via a double lumen catheter placed in the femoral vein.

CD34+ cell enumeration

Peripheral blood CD34+ cells count and leukapheresis product CD34+ dose was determined by using single-platform flow cytometric method using BD TruCOUNT™ Stem Cell Enumeration kit with CellQuest™ Pro program in Becton Dickson FACSCalibur™ flow cytometry and based on International Society of Haematotherapy and Graft Engineering (ISHAGE) gating strategy[11].

Definition of outcome of mobilization

Successful mobilization is defined based on the collection of CD34+ dose of $\geq 2x10^6$ cells/kg by leukapheresis after a single mobilization procedure[12,13].

Poor or unsuccessful mobilization is defined based on peak PB CD34+ cells count of <20 cells/uL[14] or collection of CD34+ dose of $<2x10^6$cells/kg by leukapheresis after a single mobilization procedure[12,13].

Statistical analysis

The data was analysed using SPSS (statistical package for the social) software version 22.0. The descriptive results were expressed as percentage, mean and standard deviation. Pearson Chi square (categorical variable) and independent T-test (numerical variable) were used to compare the independent variables between two groups, MM and lymphoma. The bivariate Pearson Correlation was used to evaluate correlation between PB CD34+ cell count and harvested CD34+ cell dosage. Simple (SLR) and multiple (MLR) logistic regression analysis were used for statistical analysis of potential risk factors that might influence poor PBSCs mobilization. From the result of SLR, clinically important independent variables with p value of <0.25 were included in the MLR analysis. The p value of <0.05 was considered significant.

Ethical clearance: The written consent to participate for APBSCT was obtained from all patients prior to initiation of PBSC mobilization treatment. This study was approved by Human Research Ethics Committee, Universiti Sains Malaysia with protocol number of USM/JEPeM/140362.

Results:

Majority of patients were Malay (93.9%) ethnic reflecting population distribution. Disease wise, lymphoma (70.2%) was the main diagnosisandthe mean age of all patients at mobilization, 41.4 years. Lymphoma patient underwent PBSC mobilization at younger age compare to MM patient and was statistically significant (p<0.001). The mean of collected CD34+ dosage for all patients was $9.6x10^6$ cells/kg and MM patients had significant higher CD34+ dosage compare to lymphoma patients(p=0.003). The details of all patients characteristics and comparison between MM and lymphoma patients are shown in Table 1 and Table 2 respectively.

Poor mobilizer

Majority of patients (90.8%) had successful mobilization (CD34+ $\geq 2x10^6$ cells/kg) and only 12 (9.2%) of patients was documented to have poor mobilization where half of them did not qualify for leukapheresis since PB CD34+ cell count was very low, <10cells/μL at the peak of GCSF stimulation. Nine of poor mobilizer were NHL (majority were diffuse large B cell lymphoma), and only two of them with HL and 1 with MM. The details of poor mobilizer patients are shown in Table 3.

Risk factors of poor mobilization

We found that there was significant strong positive correlation between PB CD34+ cell count and harvested CD34+ cell dosage (r = 0.774, p<0.001) (Figure 1). Univariate analysis documented that there were significant differences betweenpoor mobilization and age at mobilization (>60/≤60 years; p=0.029), PB CD34+ cells count (<20/≥20 cells/uL; p<0.001), previous chemotherapy regime and cycle(≥3/<3 line; p=0.010 ans ≥8/<8 cycles; p=0.047 respectively) and premobilization platelet count (p=0.049) by. However from the multivariate analysis, the only factors that were mantained significantly associated with poor PBSC mobilization was age at mobilization (adjusted OR=38.43, p=0.005) and PB CD34+ cell count (adjusted OR=132.69, p<0.001). Patients who underwent PBSC mobilization at the age ≥ 60 years have increased odds of having poor

mobilization by 38.4 times than patients who are <60 years. Meanwhile patients with PB CD34+ of <20 cells/uL have increased odds of having poor mobilization by 132.7 times than patients with PB CD34+ of ≥20 cells/uL.

Factors such as gender, weight, blood group, type of diagnosis, stage and status of disease, bone marrow infiltration, haematological parameter, duration of GCSF given, number of chemotherapy cycles and regimes, history of radiotherapy and duration of diagnosis to mobilization were not significant as risk factors of poor mobilization (Table 4).

Table (1) Patient characteristics and descriptive data on mobilization (n=131)

Characteristic	All patients n (%)	Poor mobilization (n=12) (<2x10^6 cells/kg), n (%)	Successful mobilization (n=119) (≥2x10^6 cells/kg), n (%)
Diagnosis			
MM	39 (29.8)	1 (2.6)	38 (97.4)
NHL	55 (42.0)	9 (16.4)	46 (83.6)
HL	37 (28.2)	2 (5.4)	35 (94.6)
Gender (male/female)	68/63 (51.9/48.1)	8/4	60/59
Race (Malay/non-Malay)	123/8 (93.9/6.1)	11/1	112/7
Age (years) *			
at diagnosis	40.2 (16.2)	44.2 (17.3)	39.3 (16.3)
at mobilization	41.5 (16.3)	45.7 (17.9)	40.5 (16.3)
Age at mobilization (<60/≥60 years)	115/16 (87.8/12.2)	8/4 (66.7/33.3)	107/12 (89.9/10.1)
Weight (kg) *	58.9 (15.4)	64.1 (13.1)	58.7 (15.6)
Blood group (O/non-O)	56/75 (42.7/57.3)	4/8 (33.3/66.7)	52/67 (43.7/56.3)
Disease stage at diagnosis (Early/Advanced)	36/95 (27.5/72.5)	2/10 (16.7/83.3)	34/85 (28.6/71.4)
BM infiltration (yes/no) #	9/83 (9.8/90.2)	1/10	8/73
Number of prior chemotherapy (cycles) *	7.9 (2.4)	9.7 (1.2)	7.7 (2.4)
Prior radiotherapy (yes/no)	11/120 (8.4/91.6)	1/11	10/109
Disease status at mobilization (CR/<CR)	20/111 (15.3/84.7)	1/11	19/98
Premobilization WBC (x10^9/L) *	6.4 (2.7)	5.2 (2.1)	6.4 (2.8)
Premobilization Hb (g/dL) *	11.1 (1.7)	10.9 (2.0)	11.1 (1.7)
Premobilization platelet (x10^9/L) *	265.5 (118.3)	223.7 (87.2)	270.9 (120.7)
Mobilization regime			
CPM + GSCF	39 (29.8)	1 (2.6)	38 (97.4)
VP-16 + GCSF	17 (13.0)	5 (29.4)	12 (70.6)
ICE + GCSF	66 (50.4)	4 (6.1)	62 (93.9)
Others chemotherapy + GCSF	9 (6.9)	2 (22.2)	7 (77.8)
Duration of GCSF (days) *	11.3 (2.6)	12.0 (2.8)	11.1 (2.5)
Precollection WBC (x10^9/L) *	30.3 (19.2)	33.9 (8.2)	30.3 (19.8)
PB CD34+ cell count (cells/μL) *	110.8 (142.6)	24.7 (18.3)	120.7 (146.2)
Harvest CD34+ dosage (x10^6 cells/kg) *	9.6 (8.2)	1.6 (1.0)	10.0 (8.2)
Duration of diagnosis-mobilization (year)*	1.3 (1.3)	1.9 (2.3)	1.2 (1.2)

MM: multiple myeloma, NHL: non-Hodgkin lymphoma, HL: Hodgkin lymphoma; BM: bone marrow; CR: complete response; GCSF: Granulocyte colony stimulating factor; CPM:cyclophosphamide; VP16:etoposide; ICE: ifosfamide-carboplatin-etoposide; PB: peripheral blood; #: except MM; *: mean (SD)

Table (2) Comparison of mobilization characteristic between MM and lymphoma

Variables	MM (n=39)	Lymphoma (n=92)	p value
Age at mobilization (years)*	54.3 (8.3)	36.0 (15.8)	**<0.001**[a]
Age at mobilization (years)**			
<60	30 (76.9)	85 (92.4)	**0.041**[b]
>60	9 (23.1)	7 (7.6)	
Duration of diagnosis-mobilization (year)	0.9 (0.6)	1.5 (1.5)	**0.020**[a]
PB CD34+ counts (cells/μL)*	146.7 (150.2)	96.4 (137.7)	0.070 [a]
CD34+ dosage (x10^6 cells/kg)*	13.0 (9.0)	8.2 (7.4)	**0.003**[a]
Outcome of mobilization			
Successful (≥2x10^6 cells/kg)**	38 (97.4)	81 (88.0)	0.088[b]
Poor (<2x10^6 cells/kg)**	1 (2.6)	11 (12.0)	

PB: peripheral blood; *: Mean (SD); **: Frequency (%);
[a]: Independent T-Test; [b]: Pearson Chi-Square

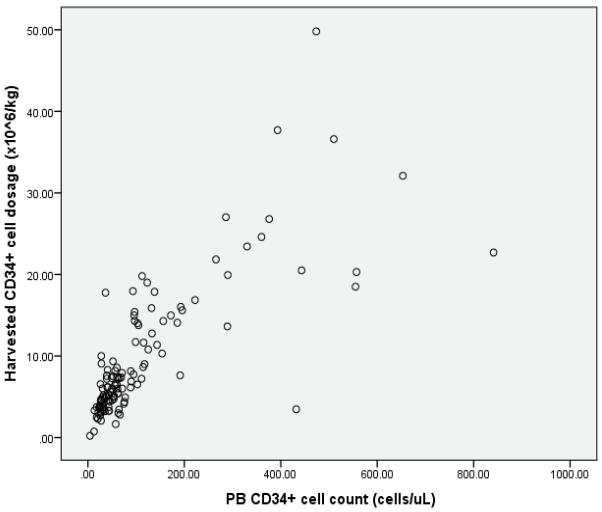

Figure (1) Pearson Correlation showed statistically significant strong positive correlation between harvested CD34+ dosage and PB CD34+ cell count (r = 0.774, p <0.001)

Table (3) Details data on patients with poor mobilization (n=12)

Diagnosis	Gender	Age at mobilization	Disease stage	Premobilization disease status	prior chemotherapy (line/cycle)	Prior radiotherapy	Mobilization agent	Highest PB CD34+ (cells/μL)	No. of mobilization	No. of harvest	Total CD34+ dose (x10^6 cells/kg)
MM	M	62	III	VGPR	1/4	No	CPM-GCSF	6.10	2	0	-
DLBCL	M	63	IV	PR	3/12	No	VP16-GCSF	20.60	2	2	1.14
DLBCL	F	32	IV	CR	3/9	No	VP16-GCSF	27.20	2	2	1.18
DLBCL	M	55	IV	PR	3/9	No	VP16-GCSF	14.33	3	1	0.21
DLBCL	M	63	III	PR	2/10	No	ICE-GCSF	57.70	2	2	1.65
DLBCL	M	69	II	SD	2/9	No	ICE-GCSF	7.99	1	0	-
DLBCL	M	58	IV	PR	2/12	No	VP16-GCSF	1.78	1	0	-
PMBL	M	34	IV	PR	1/8	No	VP16-GCSF	5.11	1	0	-
MCL	F	42	III	VGPR	2/9	No	ICE-GCSF	25.2	2	3	2.71
MCL	F	56	III	CR	2/10	No	ICE-GCSF	3.80	2	0	-
HL	F	19	II	PR	2/9	No	ICE-GCSF	12.75	2	1	0.74
HL	M	36	IV	PR	3/8	Yes	GDC-GCSF	7.88	2	0	-

MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma; PMBL: primary mediastinal B-cell lymphoma; MCL: mantle cell lymphoma; HL: Hodgkin lymphoma; CPM: cyclophosphamide; GCSF: granulocyte colony stimulating factor; VP16: etoposide; ICE: ifosfamide-carboplatin-etoposide; GDC: gemcitabine-docetaxel-carboplatin; VGPR: very good partial response; PR: partial response; CR: complete response; SD: stable disease

Table (4) Risk factors for poor APBSC mobilization, CD34+ dosage <2.0x10⁶ cells/kg (n=131)

Variables	Crude OR[a] (95% CI)	*p* value[a]	Adjusted OR[b] (95% CI)	*p* value[b]
Age at mobilization (≥60/<60 years)	**4.46 (1.17, 17.03)**	**0.029**	**38.43 (3.10, 476.98)**	**0.005**
Gender (male/female)	1.97 (0.56, 6.88)	0.290		
Race (non-Malay/Malay)	1.56 (0.16, 12.93)	0.737		
Diagnosis (lymphoma/MM)	5.16 (0.64, 41.43)	0.123	19.92 (0.62, 643.45)	0.092
Blood group (non-O/O)	1.55 (0.44, 5.44)	0.492		
Stage of disease (advanced/early)	2.00 (0.42, 9.61)	0.387		
Premobilization disease status (<CR/CR)	1.01 (0.25, 4.97)	0.990		
BM infiltration (yes/no)*	0.91 (0.10, 8.08)	0.934		
Percentage of PC in BM (%)**	1.10 (0.90, 1.33)	0.359		
PB CD34+ cells count (<20/≥20 cells/uL)	**76.00 (14.45, 399.60)**	**<0.001**	**132.69 (13.33, 1321.19)**	**<0.001**
Number of prior chemotherapy cycle (≥8/<8 cycles)	**8.25 (1.03, 65.98)**	**0.047**	9.54 (0.51, 178.70)	0.132
Number of prior chemotherapy regime (≥3/<3 lines)	**6.11 (1.54, 24.27)**	**0.010**	4.14 (0.31, 54.51)	0.281
Weight (>60/≤60 kg)	2.13 (0.46, 9.98)	0.336		
Prior Radiotherapy (no/yes)	1.01 (0.12, 8.64)	0.993		
Premobilization WBC (x10⁹/L)	0.87 (0.65, 1.15)	0.313		
Premobilization platelet (x10⁹/L)	**1.01 (1.00, 1.01)**	**0.049**	0.99 (0.98, 1.00)	0.125
Premobilization Hb (g/dL)	0.88 (0.61, 1.26)	0.478		
Preharvesting WBC (≥30/30x10⁶/L)	2.33 (0.67, 8.18)	0.185	0.20 (0.02, 1.89)	0.159
Duration of GCSF (≥11/<11 days)	2.71 (0.70, 10.51)	0.150	2.06 (0.15, 28.20)	0.588
Duration of diagnosis-mobilization (≥1/<1 year)	3.06 (0.87, 10.8)	0.080	2.12 (0.16, 30.56)	0.560

[a]: Simple logistic regression; [b]: Multiple logistic regression (by backward variable selection); OR: odd ratio; MM: multiple myeloma; CR: complete response; BM: bone marrow; PC: plasma cell; PB: peripheral blood; WBC: white blood cell; Hb: haemoglobin; *: except MM; **: except lymphoma; GCSF :granulocyte colony stimulating factor

The model reasonably fits well. Model assumption are met. There are no interaction and multicollinearity problems.

Discussion:

The incidence of poor mobilization in MM and/or lymphoma patients who were mobilized with combination of GCSF and chemotherapy varied between 4% and 47%[4,14-19] Our result showed only 9.2% of patients were poor mobilizer keeping within the reported range. Disease characteristic alone cannot predict mobilization outcome, as within high risk group there will be a group of patients who will successfully mobilize with standard approaches and there are patients within low risk group who mobilized poorly[6]. There are many reports on patients who failed to mobilized sufficient numbers of PBSC, however because of the retrospective nature of the study, heterogeneity of studied population, low numbers of patients, use of different mobilization regimes and lack of uniform criteria of poor mobilization led to difficulty in deriving a conclusion[8,20].

Thus, there are no specific well accepted factors to identify potential poor mobilized patient.The most consistent findings for the predictive factors of stem cell mobilization is the PB CD34+ cell count[8,21,22]. Few study had proposed the predicted poor mobilizer included patient who failed a previous mobilization[1,22,23], diagnosis of NHL[1,15,24], increasing age[12,20,23], advanced disease at the time of mobilization[18,23], BM involvement[23,25,26], thrombocytopenia before mobilization[12,26-28], history of radiotherapy[23,25,27], multiple chemotherapy regime[18,24,27] and increased weight[15,20,26]. Our study only demostrated that low PB CD34+ cell count and advanced age were the most important risk factor for poor PBSC mobilization.

Our findings showed agreement with the all the previous study that PB CD34+ cell count is the main important factors for predicting of CD34+ cell dosage[8,20,21]. There was significant strong positive correlation between PB CD34+ cell count

and CD34+ cell dosage. The level of PB CD34+ lower than 20 cells/uL shown to be the risk factor for poor mobilization. Thus, identification of patient with low PB CD34+ cell counts may allow for the initial mobilization attemps with the alternative mobilize agent, thereby reducing the high failure rate and resource utilization. Alternative strategies of mobilization such as using other mobilizer agent like plerixafor (mozobil), may be considered, which had been reported to be very efficient for mobilization of poorly mobilized patients[6,25,29]. The possible defects of low PB CD34+ mobilization is due insufficient number of HSC in the bone marrow due to HSC intrinsic factors, low number or defective niches or inadequate number or response of BM effector/ supporter cells[30].

Beside CD34+ dosage, we also found that advanced age (≥60 year old) was shown to be most important risk factor for poor mobilization as reported by previous study in which younger patients had better CD34+ cell dosage[13,20] and increasing age adversely affected CD34+ cell dosage[1,12,15]. However, some of the study have failed to show independent effect of patient age on mobilization[21,31]. The influence of patient age on autologous stem cell mobilization is unclear. However it is reasonable hypothesis that as people age, the functional capacity of the early stem cell compartment may decrease and furthermore, chemotherapy may have differential effects on stem cell compartment and its functional capacity[31]. Thus, transplant team should be aware of the increased risk of a poor mobilization in advanced age patients and alternative remobilization methods should be considered from the beginning.

Our result showed that number of previous chemotherapy and premobilization platelet level had significant association with poor mobilization at univariate analysis, but it was not significant at multivariate analysis and it is concordance to previous study that demostrated there was no significant impact between CD34+ dosage with number of previous chemotherapy[15,26] or platelet level[21,32]. However, many studies reported that premobilization platelet counts and numbers of chemotherapy have been significantly associated with the total CD34+ cell dosage where thrombocytopenia[20,27,28] and increased number of previous chemotherapy were risk factor for poor mobilization[1,18,24,27]. Theoritically, repetitives cycles of chemotherapy lead to rapid exhaustion of HSC self renewal and reconstitution potential and may also damage niches for HSC and BM macrophages effector cells[30] and resulted to poor PBSC mobilization. However, our result did not support this theory.

Although some studies had reported that the diagnosis of lymphoma and advanced disease as risk factor for poor mobilization, but there are a few studies did not demonstrate significant result[4,21] which is consistent with our finding. Although our result showed that the diagnosis and stage of disease were not a risk factor for poor mobilization, but we found that 11 out of 12 poor mobilized patients were lymphoma and majority were NHL (9 patients). Majority of them also presented with advanced stage (stage III or IV).

Our study also did not show that the history of previous radiotherapy and increased weight as risk factor for poor mobilization although a few studies had reported their significant impact on the ability to mobilize and associated with poor CD34+ yield in APBSC collection[18,20,27]. A lot of other factors that had been investigated by previous studies such as gender, stage of disease, premobilization haemoglobin level and premobilization WBC count and similar results had been demonstrated with our results[14,15,21]. We demonstrated that those factors was not a risk factor for poor APBSC mobilization.

This study has limitations. Some of the independent variable could not be studied due to retrospective record review method. Furthermore, our result showed wide range of of 95% confidential interval value in MLR analysis indicates a poor distribution between the two comparing groups due to small sample size. Thus the findings need to be inferred with cautious since it might not be representative of the reference population.

Conclusions:

Patients for stem cell collection should be carefully screened for the presence of risk factors so that poor mobilizers can be identified early and suitable interventions can be incorporated to reduce rate of mobilization failure. Although various factors had been reported, we found that PB CD34+ count less than 20 cell/μL and age more than 60 years old were associated with poor mobilization outcome in patients with LPD planned for APBSCT.

Conflict of interest:

All the authors declare that there is no conflict of interest exists.

Acknowledgements:

We thanked the Universiti Sains Malaysia (USM) for financially support by providing Short Term Grant (304/PPSP/61313042) for this study and to the staff of the Transfusion Medicine Unit and Transplantation unit, Hospital USM for their support and help

Authors' contributions:

Type of contribution	Contributors
Data gathering and idea owner of this study	Mohd Nazri Hassan
Study design	Mohd Nazri Hassan Rapiaah Mustaffa
Data gathering	Mohd Nazri Hassan Rapiaah Mustaffa Noor Haslina Mohd Noor
Writing and submitting manuscript	Mohd Nazri Hassan Azlan Husin
Editing and approval of final draft	Mohd Ismail Ibrahim Abu Dzarr Abdullah Rosline Hassan

References:

1. Olivieri J, Attolico I, Nuccorini R, Pascale SP, Chiarucci M, Poiani M, et al. Predicting failure of haematopoietic stem cell mobilization before it starts: the predicted poor mobilizer (pPM) score. *Bone Marrow Transplant.* 2018; **53**(4): 461-73.
2. Sureda A, Barder P, Cesaro S, Dreger P, Duarte RF, Dufour C, et al. Indication for allo- and auto-SCT for haematological diseases, solid tumour and immune disorder: current practice in Europe, 2015. *Bone Marrow Transplant.* 2015; **50**(8): 1037-56.
3. Lee HS, Park LC, Lee EM, Shin SH, Kim YS, Moon JH, et al. Predictive factors for rapid neutrophil and platelet engraftment after allogenic peripheral blood stem cell transplantation in patients with acute leukaemia. *Ann Hematol*. 2013; **92**(12): 1685-93.
4. Gertz MA and Dingli D. How we manage autologous stem cell transplantation for patients with multiple myeloma. *Blood.* 2014; **124**(6): 882-90.
5. Sinha S, Gastineau D, Micallef I, Hogan W, Ansell S, Buadi F, et al. Predicting peripheral blood stem cell harvest failure using circulating CD34 levels: developing target-based cut points for early intervention. *Bone Marrow Transplant.* 2011; **46**(7): 943-49.
6. Giralt S, Costa l, Schriber J, Dipersio J, Maziarz R, McCarty J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transplant.* 2014; **20**(3): 295-308.
7. DiPersio JF. Can every patient be mobilized*? Best Pract Res Clin Haematol*. 2010; **23**(4): 519–23.
8. Duarte FB, Prado BP, Vieira GM and Costa LJ. Mobilization of haematopoietic progenitor cells for autologous transportation: consensus recommendation. *Rev Assoc med Bras (1992).* 2016; **62**(suppl 1): 10-15.
9. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC, 2008.
10. Freedman AS and Freiedberg JW. Evaluation, staging, and response assessment of non-Hodgkin lymphoma. In: UpToDate [online]. Available at: www.uptodate.com/contents/evaluation-staging-and-response-assessment-of-non-hodgkin-lymphoma. Accessed August 9, 2018.
11. Gratama JW, Sutherland DR and Keeney M. Flow Cytometric Enumeration and Immunophenotyping of Hematopoietic Stem and Progenitor Cells. *Semin Hematol.* 2001; **38**(2): 139-147.
12. Musto P, Simeon V, Grossi A, Gay F, Bringhen S, Larocca A, et al. Predicting poor peripheral blood stem cell collection in patients with multiple myeloma receiving pre-transplant induction therapy with novel agents and mobilized with cyclophosphamide plus granulocyte-colony stimulating factor: results from a

Gruppo Italiano Malattie E Matologiche dell' Adulto Multiple Myeloma Working Party study. *Stem Cell Res Ther.* 2015; **6**(64): 1-7.

13. Shi Y, Zhou P, Han X, He X, Zhaou S, Liu P, et al. Autologous peripheral blood stem cell mobilization following dose-adjusted cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy alone or in combination with rituximab in treating high-risk non-Hodgkin's lymphoma. *Chin J Cancer.* 2015; **34**(11): 522-30.
14. Wuchter P, Ran D, Bruckner T, Schmitt T, Witzens-Harig M, Neben K, et al. Poor Mobilization of Hematopoietic Stem Cells-Definitions, Incidence, Risk Factors, and Impact on Outcome of Autologous Transplantation. *Biol Blood Marrow Transplant*. 2010; **16**(4): 490-9.
15. Donmez A, Yilmaz F, Gokmen N and Tombuloglu M. Risk factors for a poor hematopoietic stem cell mobilization. *Transfus Apher Sci.* 2013; **49**(3): 485-8.
16. Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem yields for autologous transplantation. *Biol Blood Marrow Transplant.* 2008; **14**(9): 1045-56.
17. Wood WA, Whitley J, Goyal R, Brown PM, Sharf A, Irons R, et al. Effectiveness of etoposide chemomobilization in lymphoma patients undergoing auto-SCT. *Bone Marrow Transplant.* 2013; **48**(6): 771-6.
18. Pavone V, Gaudio F, Console G, Vitolo U, Iacopino P, Guarini A, et al. Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell transplantation. *Bone Marrow Transplant.* 2016; **37**(8): 719-24.
19. Chao NJ, Grima DT, Carrum G, Holmberg L, Fung HC, Brown S, et al. Chemo-mobilization provides superior mobilization and collection in autologous stem cell transplants but less predictability and at a higher cost. ASH Annual Meeting Abstract. *Blood.* 2011; **118**: 4048
20. Akhtar S, Weshi AE, Rahal M, Khafaga Y, Tbakhi A, Humaidan H, et al. Factors affecting autologous peripheral blood stem cells collection in patients with relapsed or refractory diffuse large cell lymphoma and Hodgkin lymphoma: a single institution result of 168 patients. *Leuk Lymphoma.* 2008; **49**(4): 769-78.
21. Sakashita AM, Kondo AT, Ribeiro AA, Cipolletta AN, Colesanti MV, Hamerschlak N, et al. Factors affecting autologous peripheral blood hematopoietic stem cell collections by large-volume leukapheresis: a single center experience. *Einstein (Sao Paulo).* 2011; **9**(2): 196-200.
22. Gambell P, Herbet K, Dickinson M, Stokes K, Bressel M, Wall D, et al. Peripheral blood CD34+ cell enumeration as a predictive of apheresis yield: an analysis of more than 1000 collections. *Biol Blood Marrow Transplant.* 2012; **18**(5): 763-72.
23. Olivieri A, Marchetti M, Lemoli R, Tarella C, Iacone A, Lanza F, et al. Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytical hierarchy process by ad hoc working group Gruppo Italiano Trapianto di Midollo Osseo. *Bone Marrow Transplant.* 2012; **47**: 342-51
24. Montgomery M and Cottler-Fox M. Mobilization and collection of autologous hematopoietic progenitor/stem cell. *Clin Adv Hematol Oncol.* 2007; **5**(2): 127-36.
25. Copelan EA, Malik S and Avalos BR. Peripheral blood hematopoietic stem-cell mobilization for autologous transplantation. *US Oncol Hematol.* 2011; **7**(1): 75–7.
26. Kuittinen T, Nousiainen T, Halonen P, Mahlamaki E and Jantunen E. Prediction of mobilization failure in patients with non-Hodgkin's lymphoma. *Bone Marrow Transplant.* 2004; **33**(9): 907-12.
27. Han X, Ma L, Zhao L, He X, Liu P, Zhou S, et al. Predictive factors for inadequate stem cell mobilization in Chinese patients with NHL and HL: 14-year experience of a single-center study. *J Clin Apher.* 2012; **27**(2): 67-74.
28. Grubovic RM, Georgievski B, Cevreska L, Genadieva-Stavric S and Grubovic MR. Factors associated with successful mobilization and collection of peripheral blood hematopoietic stem cells in autologous and allogenic donors. *SE Eur J Immunol.* 2017; 20012: 1-6.
29. Josefsen D, Rechnitzer C, Parto K and Kvalheim G. The use of plerixafor for peripheral blood stem cell mobilisation reduces the frequency of mobilisation failure in patients planned to undergo autologous transplantation. *Euro Haematol.* 2010; **4**: 24-9.
30. To LB, Levesque JP and Herbert KE. How I treat patients who mobilize heematopoietic syem cells poorly. *Blood*. 2011; **118**(17): 4530-40.
31. Morris CL, Siegel E, Barlogie B, Cottler-Fox M, Lin P, Fassas A, et al. Mobilization of CD34+ cells in elderly patients (>/= 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. *Br J haematol.* 2003; **120**(3): 413-23.
32. Garcia MP, Farias MG, de castro Junior CG. Analysis of predictive factors of complete blood count for a high-yield hematopoietic stem cell apheresis collection. *J Mol Pathophisiol.* 2014; **3**(4): 47-51.