Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

Enhancing CD34$^+$ Cell Mobilization and Engraftment after Autologous Hematopoietic Stem Cell Transplantation via Adjustment of Granulocyte Colony-Stimulating Factor Dose and Period, a Single Center Experience

Mohammad Rafiee[1], Hossein Bonakchi[2], Sajjad Rahimi Pordanjani[3], Seyedeh Zahra Shahrokhi[4], Sina Mohagheghi[5], Mehdi Allahbakhshian Farsani[6], Mohammad Hossein Mohammadi[6*]

1. *Dept. of Medical Laboratory Sciences, School of Paramedical Sciences, Zanjan University of Medical Sciences, Zanjan, Iran*
2. *Dept. of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
3. *Dept. of Epidemiology and Biostatistics, Semnan University of Medical Sciences, Semnan, Iran*
4. *Dept. of Biochemistry, School of Medicine, AJA University of Medical Sciences, Tehran, Iran*
5. *Dept. of Clinical Biochemistry, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*
6. *Dept. of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Article Info

10.30699/jambs.31.148.488

Received: 2023/03/23;
Accepted: 2023/06/26;
Published Online: 29 Oct 2023;

Use your device to scan and read the article online

Corresponding Information:
Mohammad Hossein Mohammadi, Dept. of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

E-Mail: Drmohammadi@sbmu.ac.ir

ABSTRACT

Background & Objective: Insufficient mobilization of hematopoietic stem cells and delayed engraftment are reported in autologous hematopoietic stem cell transplantation (AHSCT). The aim if this study was to identify and introduce predictive factors for mobilization and engraftment.

Materials & Methods: The participants include AHSCT candidates. Pre-apheresis CD34$^+$ cells and CD34$^+$ count per kilogram (CD34$^+$ CPK) in the apheresis products were assessed by flow cytometry. There were other parameters connected to platelet and neutrophil engraftment as well as mobilization by granulocyte-stimulating growth factor (G-CSF). Univariate, multivariate, and receiver operating characteristic (ROC) analyses were used in the statistical study.

Results: The predictive value of CD34$^+$ CPK for platelet engraftment was fair (AUC: 76.9%) with the cut-off of 3.5×10^6, while it was poor for neutrophil engraftment (AUC: 64.4%) with the cut-off of 3.4×10^6. The multiple-variate analysis demonstrated that age and CD34$^+$ CPK were positively correlated with platelet engraftment (p-values less than 0.01 and 0.005, respectively), while CD34$^+$ CPK and total dose of infused G-CSF (TDIG) were associated with neutrophil engraftment (p-values: 0.03). In high rates, the TDIG correlated negatively with CD34$^+$ CPK, CD34$^+$ cell counts in pre-apheresis peripheral blood samples, and total engraftment, indicating negative effects of high and long-term doses of G-CSF on mobilization and engraftment.

Conclusion: The management of AHSCT will be more efficient by considering the age, CD34$^+$ CPK, and TDIG. For enhanced engraftment, adjusting the G-CSF injection days for <4 days and total dose of G-CSF on <4000 micrograms are suggested.

Keywords: Engraftment, Granulocyte Colony-stimulating Factor, Hematopoietic Stem Cell Transplantation, Mobilization

Copyright © 2023, This is an original open-access article distributed under the terms of the Creative Commons Attribution-noncommercial 4.0 International License which permits copy and redistribution of the material just in noncommercial usages with proper citation.

Introduction

High dose chemotherapy, along with the autologous hematopoietic stem cell transplantation (AHSCT), was applied for over 50 years as a beneficial treatment for a wide range of malignancies (1, 2). AHSCT is a conventional and standard therapy for the management of multiple myeloma (MM) and lymphoma (3). Due to their many benefits, mobilized peripheral blood hematopoietic stem cells are used as a preferred source of hematopoietic stem cells (HSCs) (4). Granulocyte-colony stimulating factor (G-CSF), the primary mobilizer agent, is a desirable medication for mobilization because it facilitates affordable and predictable apheresis scheduling (5). A sufficient number of CD34$^+$ HSCs or CD34$^+$ count per kilogram (CD34$^+$CPK) is a critical factor for engraftment, and successful transplantation; however, in 5–40% of patients, CD34$^+$ cells don't reach desired number (6). Despite the lack of correlation among age, gender, bone marrow involvement, and mobilization efficiency (7),

stress, tissue injury, exercise, and sterile inflammation result in higher rates of $CD34^+$ HSC mobilization in the peripheral blood (8). Several risk factors, such as senescence, being affected by non-Hodgkin's lymphoma (NHL), the history of radiation therapy, lenalidomide consumption, having a low number of $CD34^+$ cells in pre-apheresis peripheral blood samples (PAPBS), diabetes, and smoking, are involved in mobilization failure (5). However, the prediction of mobilization would be difficult and sufficient $CD34^+$ CPK may mobilize in the individuals with risk factors while it may fail in individuals with no risk factors (5). Overall, mobilization-related parameters, particularly engraftment, may affect the results of HSCT (6, 9). It was shown that the 3-year survival rate is lower in poor mobilizers (patients having $CD34^+$ CPK $<2\times10^6$) than in those with sufficient mobilizers (33% vs. 71%, respectively) (10). The enhancement of mobilization protocols, and the prediction of poor mobilizers can reduce the costs of additional health care. Hence, the effects of G-CSF mobilization-related factors, and other AHSCT and patient's related factors on the quality and quantity of harvested grafts and engraftment after AHSCT are studied.

Materials and Methods

Participants

Between October 2019 and May 2020, patients who were AHSCT candidates at the Taleghani Hospital's Bone Marrow Transplantation Department in Tehran, Iran, were included in the study. The following diseases were present in the patients: NHL, Hodgkin's diseases (HD), and MM. The exclusion criteria had infectious diseases, bleeding, splenomegaly, and using myelo-suppressive agents. All patients had received a myeloablative conditioning regimen, including Melphalan/Velcade for the patients with MM in a 1-day course and CEAM (Lomustine, Etoposide, Cytarabine, and Melphalan) for the patients with lymphoma in a 4-day course. The study is approved by the ethics committee with code IR.SBMU.REC.1398.157.

Participant's data collecting

Data on procedures, medication dosages, regimens, periods of engraftment, and other topics were gathered from information in medical records, test data, and other sources. The patients had all been receiving G-CSF daily up to leukapheresis. Recorded total dose of infused G-CSF (TDIG), and the number of days of G-CSF infusion (NDGI) were collected. $CD34^+$ cells per microliter of PAPBS that were analyzed by flow cytometry, were collected. Leukapheresis was performed by Spectra Optia (Terumo BCT, Lakewood, CO). Pre-apheresis white blood cell (WBC) count, time, and duration of apheresis, as well as the volume of processed blood and collected cells were collected. Moreover, $CD34^+$ CPK, the number of $CD45^{dim}$, WBC, and mononucleated cells (MNCs) in the apheresis products were collected. In the hospital, evaluation of $CD34^+$ CPK was conducted based on the protocols established by the International Society of Hematotherapy and Graft Engineering (ISHAGE) (11). Hospitalization days, the time interval between the last injection of G-CSF and apheresis, neutrophil, and platelet (PLT) engraftment days were collected from medical records. Engraftment day was defined as the first day of three consecutive days with neutrophil and PLT counts of 500 cells/µl and 20×10^3 cells/µl, respectively that were collected (12).

Statistical analysis

The recorded outcomes of AHSCT were time of neutrophil and PLT engraftments. The predictive value of $CD34^+$ CPK was evaluated for neutrophil and PLT engraftments using receiver-operating characteristic (ROC) analysis. The cut-off value for $CD34^+$ CPK was determined by ROC analysis. The univariate and multiple variate analyses of time to event data were conducted using Cox proportional hazards model. Using the score process plot and the Kolmogorov-type supremum test (the significance threshold was 0.05), the assumption of proportional hazards was tested. The backward technique was used in this model's multiple variate analysis to identify the traits with the greatest predictive values. The significance level was set at 5% to eliminate variables from the model. A logarithmic transformation was used for non-normal variables and variables with large scales. For the univariate analysis of risk factor effects on WBC, MNC, $CD34^+$ CPK, and $CD34^+$ cell counts in PAPBS, generalized additive model was used. The significance level for the univariate analysis of Cox and generalized additive regression models was set at 10%. For a more detailed assessment, the patients were divided into two groups based on TDIG, and the correlation of TDIG with $CD34^+$ CPK, $CD34^+$ cell count in PAPBS, WBC counts at apheresis day, and the day of total engraftment was analyzed. SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and R (version 3.5.2) were used to analysis the data.

Results

In general, 50 candidates for AHSCT were included, and the clinical characteristics of patients are shown in Table 1. The median time of neutrophils, PLTs, and the total engraftment (the engraftment of neutrophil and PLT), was 11 days, with the following ranges: 7-20, 9-19, and 9-21 days, respectively. The median numbers of $CD34^+$ CPK and MNCs in the apheresis product were 3.5×10^6/kg (1-15.4) and 6.2×10^8/kg (3.3-17.5), respectively.

Table 1. **Characteristics of patients (N=50)**

Features	Mean±SD /Median (Rang) / Frequency (%)
Age (year)	42.40±14.61
Gender	
Male	25(50)
Female	25(50)
Diagnosis	
MM	24(48)
HD	15(30)
NHL	11(22)
BMI Before transplantation	26.94±5.46
BMI after transplantation	26.72±5.41
NDGI (day)	6 (5-9)
TDIG (µg)	4002±1147.75
WBC count at day of start of mobilization ($\times10^3$/µl)	6.05(2.4-22.1)
Last injection of G-CSF to apheresis (h)	6.5±4.83
WBC count at apheresis day ($\times10^3$/µl)	39.42±14.59
Neutrophil count on apheresis day ($\times10^3$/µl)	34.82±14.28
Platelet count on apheresis day ($\times10^3$/µl)	171.64±53.35
Apheresis duration (min)	386.81±50.28
ACD volume for apheresis (ml)	1507(950-3000)
Total processed blood in apheresis (l)	18.43±3.76
Apheresis bag volume (ml)	406.14±84.11
WBC count in apheresis product ($\times10^8$/kg)	11.38±4.39
MNC count in apheresis product ($\times10^8$/kg)	6.20(3.3-17.5)
$CD45^+$ in apheresis product (%)	98.05(95-99.5)
$CD45^{+dim}$ in apheresis product (%)	1.20(0.2-9.2)
$CD34^+$ CPK ($\times10^6$/kg)	3.5(1-15.4)
$CD34^+$ in PAPBS (/µl)	45.85±29.73

Predictive values of $CD34^+$ CPK for neutrophil and PLT engraftment

ROC analysis and the assessment of the area under the curve (AUC) were carried out to evaluate the predictive values of $CD34^+$ CPK for neutrophil and PLT engraftment. AUC was 76.9% (62-92%) with a cut-off value of 3.5×10^6 (Figure 1A) for PLT. Therefore, it seems $CD34^+$ CPK could be used as a fair predictive factor for PLT engraftment. AUC was 64.4% (44-84%) with a cut-off value of 3.4×10^6 (Figure 1B) for neutrophils. So, it appears that $CD34^+$ CPK is a poor predictive factor for neutrophil engraftment.

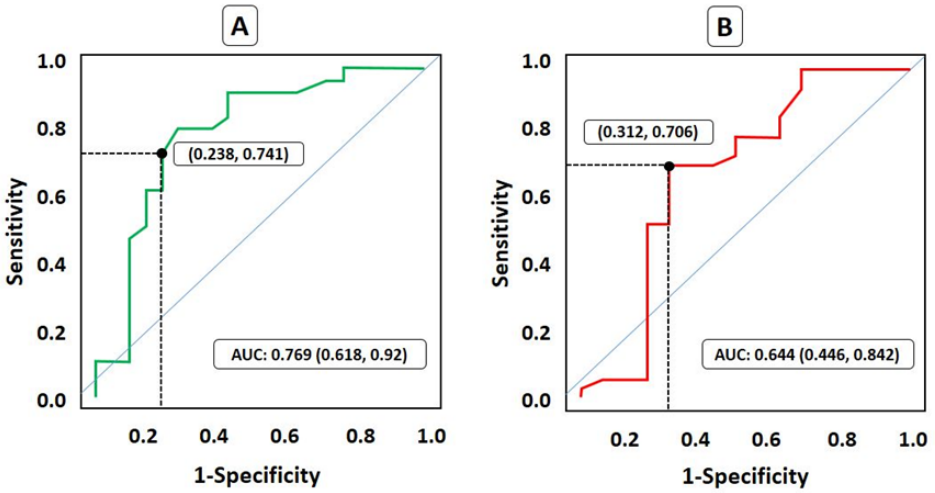


Figure 1. ROC assessment for the predictive value of CD34⁺ CPK for engraftment. Cut off points are shown. A. Platelet engraftment, B. Neutrophil engraftment

Risk factors of PLT and neutrophil engraftment

PLT engraftment

The factors in Table 2 that are associated with PLT engraftment. Using the backward method to incorporate significant risk factors from the univariate model into the multivariate model, age and CD34+ CPK were found to be associated with PLT engraftment. Assuming the number of $CD34^+$ CPK cells was fixed, a one-year increase in the age of patient's results in an improvement of PLT engraftment by 5%. Assuming age does not affect the engraftment outcomes, the number of $CD34^+$ CPK cells $\geq 3.5\times10^6$/kg led to the enhancement of PLT engraftment compared with those with $CD34^+$ CPK $<3.5\times10^6$. Regarding Figure 2, the patients with an age of over 42 years old and $CD34^+$ CPK $\geq 3.5\times 10^6$ have better PLT engraftment outcomes than those with an age of ≤42 and $CD34^+$ CPK $<3.5\times 10^6$ (p-value: 0.02).

Table 2. The influence of risk factors on platelet engraftment

	Univariate		Multiple[2]	
Variables	HR (90% CI)	P-Value	AHR[3] (95% CI)	P-Value
Age	1.02(1.003-1.04)	0.06*	1.05(1.01-1.08)	0.003**
Gender		0.56		
Male	1.25(0.66-2.36)	0.56		
Female (RL[1])	1	-		
Diagnosis		0.06*		NS
MM	5.33(2.25-12.61)	0.02		
HD	3.35(1.35-8.34)	0.12		
NHL (RL[1])	1	-		
BMI Before transplantation	1.06(1.001-1.13)	0.09*		NS
BMI after transplantation	1.06(1.004-1.13)	0.08*		NS
NDGI	0.72(0.52-1.007)	0.10		NS
TDIG[4]	0.11(0.03-.35)	0.001*		NS
WBC count in day of start of Mobilization	1.06(0.99-1.13)	0.11		
Last injection of G-CSF to apheresis	0.97(0.89-1.05)	0.54		

	Univariate		Multiple[2]	
WBC count at apheresis day	0.98(0.95-1.004)	0.16		
Neutrophil count at apheresis day[4]	0.47(0.22 - 0.99)	0.09*		NS
Apheresis duration	1.004(0.99-1.01)	0.33		
ACD volume for apheresis[4]	1.89(0.31-11.51)	0.56		
Total processed blood in apheresis[4]	4.97(0.90-27.47)	0.12		
Apheresis bag volume	1.001(0.99-1.005)	0.52		
WBC count in apheresis product	0.93(0.86-1.01)	0.17		
MNC count in apheresis product	0.92(0.82-1.04)	0.28		
CD45^{+} % in apheresis product	1.09(0.77-1.53)	0.67		
CD45^{+dim} % in apheresis product	0.97(0.84-1.12)	0.77		
CD34^{+} CPK ($\times 10^6$)		0.002*		0.0003**
=>3.5	3.78(1.82-7.85)	0.002	6.27(2.29-17.41)	0.0003
<3.5(RL[1])	1	-	1	-
CD34^{+} in PAPBS	1.005(0.99-1.01)	0.52		

1: Reference Level, 2: Backward Selection, 3: Adjusted Hazard Ratio, 4: Logarithm scale, Underline: Borderline significant
***. Significant at 0.1**
****. Significant at 0.05**

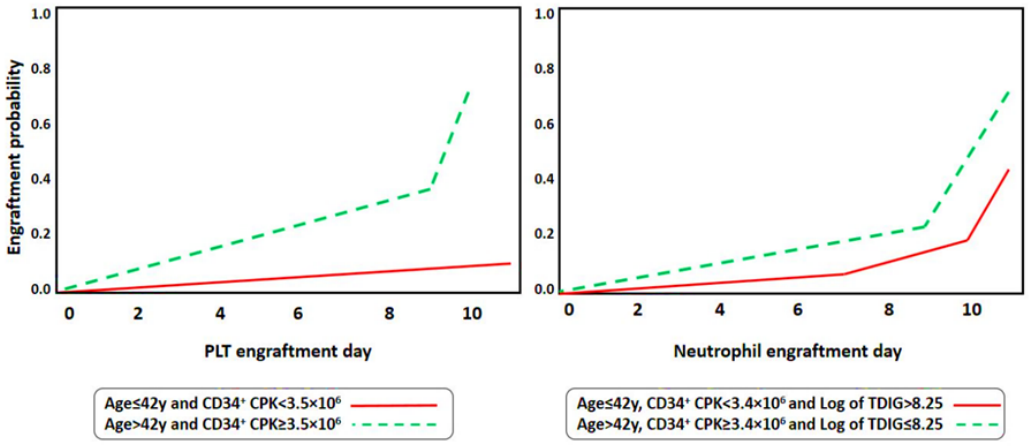


Figure 2. Cumolative incidence of PLT and Neutrophil engraftment based on Age, CD34^{+} CPK and TDIG

Neutrophil engraftment

Table 3 is showing risk factors for neutrophil engraftment. The significant risk factors in the univariate model were integrated with multiple-model using the backward method. The findings revealed that neutrophil engraftment was correlated with patient age, TDIG, and CD34+CPK. While the effect of other variables was fixed, a one-year increase in the age of patients improved the rate of neutrophil engraftment by 4%. Moreover, a one-unit increase in the logarithmic scale of TDIG declined the rate of neutrophil engraftment by 76%. Finally, CD34^{+} CPK $\geq 3.4\times10^6$/kg was associated with an improved time of neutrophil engraftment compared with the patients with CD34^{+} CPK $<3.4\times10^6$. Regarding Figure 2, patients with an age >42, CD34^{+} CPK $\geq 3.4\times 10^6$, and TDIG ≤ 8.25 on the logarithmic scale have a higher rate of neutrophil engraftment compared with those with an age ≤ 42, CD34^{+} CPK $<3.4\times 10^6$ and TDIG >8.25 (p-value: 0.032).

Table 3. The influence of risk factors on neutrophil engraftment

	Univariate		Multiple[2]	
Variables	HR (90% CI)	P-Value	AHR[3] (95% CI)	P-Value
Age	1.02(1.008-1.05)	0.02*	1.04(1.01-1.07)	0.002**
Gender		0.71		
Male	1.13(0.64-1.99)	0.71		
Female (RL[1])	1	-		
Diagnosis		0.01*		NS
MM	3.92(1.59-9.68)	0.01	-	
HD	1.78(0.66-4.79)	0.33	-	
NHL (RL[1])	1	-		
BMI Before transplantation	1.04(0.98-1.10)	0.20		
BMI after transplantation	1.05(0.99-1.11)	0.16		
NDGI	0.74(0.55-0.99)	0.09*	-	NS
TDIG[4]	0.20(0.06-0.58)	0.01*	0.24(0.06-0.89)	0.03*
WBC count at day of start of Mobilization	1.04(0.97-1.11)	0.31		
Last injection of G-CSF to apheresis	0.98(0.92-1.04)	0.63		
WBC count at apheresis day	0.97(0.95-0.99)	0.08*	-	NS
Neutrophil count at apheresis day[4]	0.47(0.23-0.95)	0.07*	-	NS
Apheresis duration	1.002(0.99-1.008)	0.59		
ACD volume for apheresis[4]	2.99(0.60-14.69)	0.25		
Total processed blood in apheresis[4]	2.55(0.61-10.55)	0.27		
Apheresis bag volume	1 (0.99-1.003)	0.94		
WBC count in apheresis product	0.93(0.87-1.002)	0.10	-	NS
MNC count in apheresis product	0.86(0.77-0.97)	0.05*	-	NS
$CD45^+$ % in apheresis product	1.02(0.77-1.36)	0.88		
$CD45^{+dim}$ % in apheresis product	0.93(0.81-1.07)	0.42		
$CD34^+$ CPK ($\times 10^6$)		0.01*		0.03**
=>3.4	2.48(1.33-4.65)	0.01	2.50(1.07-5.79)	0.03
<3.4(RL[1])	1	-	1	-
$CD34^+$ in PAPBS	1.005(0.99-1.01)	0.45		

1: Reference Level, 2: Backward Selection, 3: Adjusted Hazard Ratio, 4: Logarithm scale, Underline: Borderline significant
***. Significant at 0.10**
****. Significant at 0.05**

Risk factors of mobilization

Table 4 lists the mobilization risk variables. The findings showed that NDGI and TDIG were the most prevalent and significant risk variables for $CD34^+$ CPK and $CD34^+$ cell count in PAPBS. The $CD34^+$ CPK and $CD34^+$ cell count in PAPBS decreased by 22% and 7.46%, respectively, in response to an increase in NDGI over one day.The results showed that the counts of $CD34^+$ CPK and $CD34^+$ cells in PAPBS were decreased (by 63% and 36.62%, respectively) in response to a one-unit increase in the logarithmic scale of TDIG.

Table 4. Univariate analysis for Risk factors of mobilization

	WBC count in apheresis product		MNC count in apheresis product[2]		$CD34^+$ CPK[2]		$CD34^+$ cell count in PAPBS	
Variables	Beta	P-Value	Beta	P-Value	Beta	P-Value	Beta	P-Value
Age	0.03	0.42	-0.001	0.64	-0.003	0.60	0.45	0.21
Weight before transplantation	-0.06	0.12	-0.007	0.04*	0.005	0.36	0.25	0.43
NDGI	0.41	0.46	0.03	0.47	-0.25	0.001*	-7.46	0.09*
TDIG[2]	0.74	0.72	-0.05	0.76	-1.0003	0.0006*	-36.62	0.03*
WBC count at day of start of Mobilization	-0.06	0.68	-0.004	0.76	0.02	0.27	0.74	0.50
Last injection of G-CSF to apheresis	-0.05	0.70	0.004	0.71	0.01	0.56	1.45	0.23
WBC count at apheresis day	0.15	0.0001*	0.009	0.008*	0.002	0.69	0.41	0.18
Neutrophil count at apheresis day[2]	5.43	0.0002*	0.29	0.02*	0.01	0.95	11.87	0.33
Platelet count at apheresis day[2]	2.01	0.20	0.15	0.26	0.64	0.01*	15.49	0.33
Apheresis Time, Morning		0.03		0.18		0.95		
Yes	-3.46	0.03	-0.18	0.18	-0.01	0.95		
No (RL[1])	-	-	-	-	-	-		
Afternoon		0.02		0.14		0.33		
Yes	3.34	0.02	0.17	0.14	-0.21	0.33		
No (RL[1])	-	-	-	-	-	-		
Evening		0.64		0.36		0.29		
Yes	-0.57	0.64	-0.09	0.36	0.19	0.29		
No (RL[1])	-	-	-	-	-	-		
Apheresis duration	0.002	0.85	0.0004	0.96	0.001	0.56		
ACD volume for apheresis[2]	-3.36	0.31	-0.34	0.19	1.29	0.008*		
Total processed blood in apheresis[2]	-1.76	0.55	-0.30	0.20	0.81	0.06*		

1: Reference Level, 2: Logarithm scale
***: Significant at 0.10**

Correlation of TDIG with the mobilization and engraftment results in experimental groups

Patients were divided into two groups based on the mean values of TDIG on the logarithmic scale (8.25), and then the correlations were analyzed. In a group with TDIG values of >8.25, an increase in TDIG was negatively significant and correlated with the number of $CD34^+$ CPK and $CD34^+$ cells in PAPBS (Figure 3). On the other hand, in both experimental groups, a rise in TDIG was positively correlated with WBC levels on the apheresis day. Additionally, a rise in TDIG

considerably slowed total engraftment in a group with TDIG > 8.25 (Figure 3).

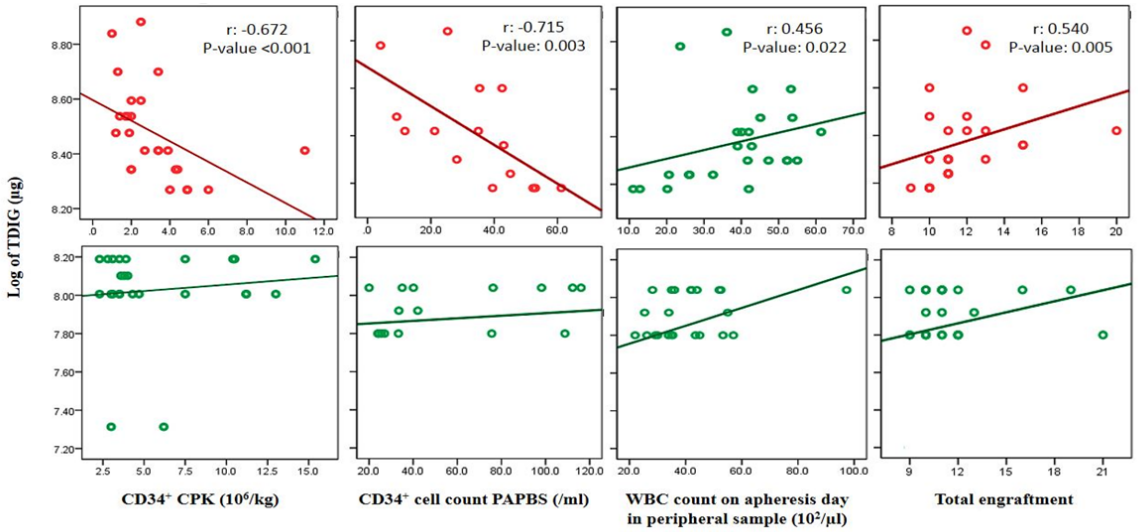


Figure 3. Correlation of TDIG in tow group (low and high) with CD34$^+$ CPK, CD34$^+$ cell count in PAPBS, WBC count at apheresis day and total engraftment

Discussion

Methods and strategies to increase mobilization efficiency are being evaluated to prevent mobilization failure, delayed recovery following transplantation, and additional costs (5). Insufficient mobilization may occur in the individuals without any risk factors (5, 13), and a total of 10-30% of AHSCT candidates are unable to mobilize a sufficient number of CD34$^+$ cells (14). Therefore, a comprehensive assessment of all involved parameters seems to be necessary. Cellular engraftment, including neutrophils and platelets, affected by a group of factors, from chemotherapy (15) to transfusion-related iron overload mobilization (16), is considered the first and most significant outcome of AHSCT (17), and its precise prediction can be useful in the management and treatment process to prevent complications and high costs (18). The effect of medication administration on mobilization may be assessed by counting the cells in peripheral blood after mobilization and using apheresis products. The predictive value and impact of several parameters on the outcomes of apheresis and engraftment at our facility were examined in the current research.

Numerous studies showed that 3-5×10^6/kg of CD34$^+$ CPK can largely guarantee rapid neutrophil, and platelet engraftment (5). The number of CD34$^+$ CPK cells in the range of 1.5×10^6 to 2.5×10^6/kg cells may result in delayed platelet engraftment, and values above 1×10^6 may necessitate erythrocyte injection and even permanent engraftment failure (5). Based on to our results, CD34$^+$ CPK is a poor predictor of neutrophil engraftment and a fair predictor of platelet engraftment. According to a study conducted by Demirer et al., CD34$^+$ CPK >5×10^6/kg has no effect on improving the kinetics of neutrophil engraftment but could result in faster platelet recovery (19), while Weavwe et al. reported that CD34$^+$ CPK >5×10^6/kg is a threshold to ensure rapid platelet and neutrophil engraftment (20). CD34$^+$ CPK >10×10^6/kg is associated with faster neutrophil and platelet engraftment by 1-2 and 2-4 days, respectively (20, 21). Further research is needed to see if more CD34$^+$ cells improve engraftment (5).

Our findings indicated that people over 42 years old, afflicted with MM, having CD34$^+$ CPK >3.5×10^6/kg, are correlated with improved platelet engraftment. High neutrophil counts on the apheresis day and increased values of TDIG lead to delayed platelet engraftment. Other studies have shown that NDGI ≥3 days, CD34$^+$ CPK <2×10^6/kg, low platelet counts (<150×10^3), and low hemoglobin concentrations in PAPBS lead to delayed platelet engraftment while having MM and being over the age of 28 results in enhanced platelet engraftment (22-24). Furthermore, based on the results of our study, age over 42 years, being afflicted with MM, and CD34$^+$ CPK >3.4×10^6/kg lead to faster neutrophil engraftment, while the elevated number of MNCs in the apheresis product results in prolonged neutrophil engraftment. In contrast to our findings, Grubovic et al. (25), found that an increase in MNC counts in the apheresis product is associated with faster neutrophil engraftment, whereas one study found that an increase in MNC counts is not associated with the kinetics of neutrophil engraftment in the apheresis product (19). The quantity of WBCs (including MNCs) is suggested to rise in tandem with an extension of the mobilization time; however, as the

cells mature, fewer immature HSCs may need to be injected into patients (26). Additionally, it has been shown that age and long-term mobilization have a negative connection with neutrophil engraftment (25).

Some factors are effective on apheresis products, as Gambell et al. reported a linear association among $CD34^+$ cell counts in PAPBS and $CD34^+$ CPK, so that as the number of $CD34^+$ cells in PAPBS is increased by two folds, the count of $CD34^+$ CPK is doubled (27). PAPBS contains more than 50/µl of $CD34^+$ cells, results in $CD34^+$ CPK > 2.5×10^6/kg (19). When the number of $CD34^+$ in PAPBS is <20/µl, it is commonly considered poor mobilization, which may vary depending on different centers, patient types, treatment regimens, and mobilization protocols (28). It has been reported that the number of white blood cells (WBCs) and micronucleated cells (MNCs) in the pre-apheresis blood sample (PAPBS) can be used to predict the optimal time to perform apheresis (29). Our study showed that although the count of MNCs in apheresis products is decreased with high weight before transplantation, the number of WBCs, and neutrophils on apheresis day is directly related to the number of MNCs. In a study carried out by Moreb et al., being overweight and having a male gender increased the risk of poor mobilization (30).

It was found in our study that with an increase in the values of NDGI and TDIG, the number of $CD34^+$ CPK and $CD34^+$ cells in PAPBS decreased. The maximum number of CD34+ cells are seen in the peripheral blood when G-CSF is used for mobilization within 4-6 days after the time of injection; however, using G-CSF for more than 7 days has been shown to decrease the amount of progenitor cells (19). At doses greater than 5µg/kg/day, and 10µg/kg/day, the number of $CD34^+$ cells in peripheral blood increases 7- and 28-fold, respectively (19). However, as shown in Figure 3, at high injection doses of G-CSF (TDIG >8.25, approximately 4000 µg), the number of $CD34^+$ CPK and $CD34^+$ cells in PAPBS are decreased. Zheng et al. showed that NDGI >5 days could be regarded as one of the negative factors of mobilization (31). It is possible that at high concentrations of G-CSF for a long time, the bone marrow undergoes hyperplasia, and mature WBCs are released into the bloodstream, reducing the number of HSCs (26). As shown in Figure 3, the number of WBCs increases in the peripheral blood on the day after apheresis with a logarithmic rise in TDIG >8.25. These cells are probably mature cells, and a possible reduction in the number of HSCs might ultimately result in a longer duration of engraftment at high TDIG levels. Therefore, based on previous studies, it is recommended to mobilize with G-CSF within 4-5 days (32). It was shown that the injection of 2.5×10^6/kg of $CD34^+$ CPK with a short mobilization period will have a better transplantation outcome than the injection of 5×10^6/kg with a longer mobilization period (5). The standard dose of G-CSF is 5-16µg/kg/day, which is associated with a 38% failure in mobilization (5, 33). Increasing the dose of injectable G-CSF up to 40µg/kg/day is correlated with improved mobilization (34). The number of HSCs ($CD34^+$) in the PAPBS sample should be evaluated, and G-CSF injection should be sustained for up to 4 days, according to the algorithms of various research. If the appropriate number of cells is not obtained, Plerixafor is injected for one day (5). Beartsch et al. identified platelet counts before mobilization as a predictor of the need for Plerixafor (35). Our study found a positive correlation among platelet counts on the day of apheresis and $CD34^+$ CPK counts. Therefore, platelet count before apheresis can be suggested as a predictor of mobilization outcome.

Besides, larger-volume leukapheresis (LVL) can provide a useful yield for $CD34^+$ CPK cells (36). In the patients with poor mobilization and $CD34^+$ CPK<2×10^6/kg, the use of LVL may improve the count of $CD34^+$ cells by 40-100 % (37). In our study, in parallel with an increase in the volume of blood processed during apheresis, the number of $CD34^+$ CPK was increased; however, such an increment was not statistically significant.

Conclusion

The results of this study showed that the parameters of age, $CD34^+$ CPK, and total dose of G-CSF are involved in the platelet and neutrophil engraftment, and they should be considered in the management of AHSCT process. For enhanced engraftment and AHSCT outcomes, decreasing the G-CSF injection days to <4 days and total dose of G-CSF on <4000 micrograms are suggested.

Acknowledgments

There is no financial support for this study; however, the authors would like to thank the staff of the BMT department of Taleghani Hospital, Tehran, for their general support.

Funding

None.

Authors' contributions

Mohammad Rafiee & Seyedeh Zahra Shahrokhi: Conceptualization, Data curation; Investigation; Writing and Project administration, Hossein Bonakchi: Formal analysis; Software, Sajjad Rahimi Pordanjani, Mehdi Allahbakhshian Farsani, Sina Mohagheghi: Review & editing, Mohammad Hossein Mohammadi: Conceptualization; Supervision and Validation.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Hübel K, Ostermann H, Glaß B, et al. Plerixafor in non-Hodgkin's lymphoma patients: a German analysis of time, effort and costs. Bone Marrow Transplant. 2019;54(1):123-9. [PMID][PMCID] [DOI:10.1038/s41409-018-0228-z]
2. Rafiee M, Farsani M.A, Amiri V, et al. Circulatory miR-155 correlation with platelet and neutrophil recovery after autologous hematopoietic stem cell transplantation, a multivariate analysis. Int J Hematol 2021;114, 235-45. [DOI:10.1007/s12185-021-03154-2] [PMID]
3. Ali N, Adil SN, Shaikh MU. Autologous hematopoietic stem cell transplantation-10 years of data from a developing country. Stem Cell Transl Med. 2015;4(8):873-7. [PMID] [PMCID] [DOI:10.5966/sctm.2015-0015]
4. Grubovic R, Georgievski B, Cevreska L, Genadieva-Stavric S, Grubovic MR. Factors associated with successful mobilization and collection of peripheral blood hematopoietic stem cells in autologous and allogeneic donors. South East Europ J Immunol. 2017;2017:1-6. [DOI:10.3889/seejim.2017.20012]
5. Giralt S, Costa L, Schriber 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. [DOI:10.1016/j.bbmt.2013.10.013] [PMID]
6. Kim JS. Hematopoietic stem cell mobilization: current status and future perspective. Blood Res. 2017;52(2):79-81. [DOI:10.5045/br.2017.52.2.79] [PMID] [PMCID]
7. Alexeev S, Babenko E, Estrina M, Mikhailova N, Zubarovskaya L, Afanasyev B. Factors influencing stem cell mobilization in patients with hematologic malignancies and solid tumors. Cell Ther Transplant. 2009;1(3).
8. Ratajczak MZ, Adamiak M, Plonka M, Abdel-Latif A, Ratajczak J. Mobilization of hematopoietic stem cells as a result of innate immunity-mediated sterile inflammation in the bone marrow microenvironment-the involvement of extracellular nucleotides and purinergic signaling. Leukemia. 2018;32(5):1116-23. [PMID] [PMCID] [DOI:10.1038/s41375-018-0087-z]
9. Song GY, Jung SH, Ahn SY, et al. Optimal chemo-mobilization for the collection of peripheral blood stem cells in patients with multiple myeloma. BMC Cancer. 2019;19(1):59. [PMID] [PMCID] [DOI:10.1186/s12885-019-5285-1]
10. Pavone V, Gaudio F, Console G, et al. Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell transplantation. Bone Marrow Transplantat. 2006;37(8):719-24. [DOI:10.1038/sj.bmt.1705298] [PMID]
11. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. J Hematother. 1996;5(3):213-26. [DOI:10.1089/scd.1.1996.5.213] [PMID]
12. Bejanyan N, Brunstein CG, Cao Q, et al. Delayed immune reconstitution after allogeneic transplantation increases the risks of mortality and chronic GVHD. Blood Adv. 2018;2(8):909-22. [DOI:10.1182/bloodadvances.2017014464] [PMID] [PMCID]
13. Jantunen E, Kuittinen T, Nousiainen T. Is chemotherapy scoring useful to predict progenitor cell mobilisation in patients with non-Hodgkin's lymphoma? Bone Marrow Transplant. 2003;32(6): 569-73. [DOI:10.1038/sj.bmt.1704184] [PMID]
14. Gutierrez Aguirre CH, Gomez-Almaguer D, Alvarado Navarro DM, et al. Low-dose plerixafor and granulocyte colony-stimulating factor for first-line autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma. Blood. 2017;130(Supplement 1):5459.
15. Costa L, Abbas J, Hogan K, et al. Growth factor plus preemptive ('just-in-time') plerixafor successfully mobilizes hematopoietic stem cells in multiple myeloma patients despite prior lenalidomide exposure. Bone Marrow Transplant. 2012;47(11): 1403-8. [DOI:10.1038/bmt.2012.60] [PMID]
16. Alva LC, Bacher U, Seipel K, et al. Iron overload is correlated with impaired autologous stem cell mobilization and survival in acute myeloid leukemia. Transfusion. 2018;58(10):2365-73. [DOI:10.1111/trf.14895] [PMID]
17. Cluzeau T, Lambert J, Raus N, et al. Risk factors and outcome of graft failure after HLA matched and mismatched unrelated donor hematopoietic stem cell transplantation: a study on behalf of SFGM-TC and SFHI. Bone Marrow Transplant. 2016;51(5): 687-91. [DOI:10.1038/bmt.2015.351] [PMID]
18. Locatelli F, Lucarelli B, Merli P. Current and future approaches to treat graft failure after allogeneic hematopoietic stem cell transplantation. Exp Opin Pharmacother. 2014;15(1):23-36. [DOI:10.1517/14656566.2014.852537] [PMID]
19. Demirer T, Buckner CD, Bensinger WI. Optimization of peripheral blood stem cell mobilization. Stem Cell. 1996;14(1):106-16. [DOI:10.1002/stem.140106] [PMID]
20. Weaver CH, Hazelton B, Birch R, et al. An analysis of engraftment kinetics as a function of the CD34 content of peripheral blood progenitor cell collections in 692 patients after the administration of myeloablative chemotherapy. Blood.1995; 86(10):3961-9. [DOI:10.1182/blood.V86.10.3961.bloodjournal86103961] [PMID]
21. Ketterer N, Salles G, Raba M, et al. High CD34+ cell counts decrease hematologic toxicity of autologous peripheral blood progenitor cell transplantation. Blood. 1998;91(9):3148-55. [DOI:10.1182/blood.V91.9.3148] [PMID]
22. Lutfi F, Skelton IV WP, Wang Y, et al. Clinical predictors of delayed engraftment in autologous

hematopoietic cell transplant recipients. Hematol Oncol Stem Cell Ther. 2020;13(1):23-31. [DOI:10.1016/j.hemonc.2019.08.003] [PMID]
23. Nagayama T, Ashizawa M, Ikeda T, et al. Factors that predict delayed platelet recovery after autologous stem cell transplantation for lymphoma or myeloma. Ann Hematol. 2020:1-9.
24. Yamaguchi J, Chinen Y, Takimoto-Shimomura T, et al. Prediction of delayed platelet engraftment after autologous stem cell transplantation for B-cell non-Hodgkin lymphoma. Leukemia Lymphoma. 2019; 60(14):3434-41. [DOI:10.1080/10428194.2019.1636982] [PMID]
25. Grubovic RM, Georgievski B, Cevreska L, Genadieva-Stavric S, Grubovic MR. Analysis of factors that influence hematopoietic recovery in autologous transplanted patients with hematopoietic stem cells from peripheral blood. Open Access Maced J Med Sci. 2017;5(3):324. [PMID] [PMCID] [DOI:10.3889/oamjms.2017.039]
26. Lee K, Jung S, Kim S, et al. Incidence and risk factors of poor mobilization in adult autologous peripheral blood stem cell transplantation: a single-centre experience. Vox Sang. 2014;107(4):407-15. [DOI:10.1111/vox.12183] [PMID]
27. Gambell P, Herbert K, Dickinson M, et al. Peripheral blood CD34+ cell enumeration as a predictor of apheresis yield: an analysis of more than 1,000 collections. Biol Blood Marrow Transplant. 2012;18(5):763-72. [DOI:10.1016/j.bbmt.2011.10.002] [PMID]
28. Mohty M, Azar N, Chabannon C, et al. Plerixafor in poor mobilizers with non-Hodgkin's lymphoma: a multi-center time-motion analysis. Bone Marrow Transplant. 2018;53(3):246-54. [DOI:10.1038/s41409-017-0033-0] [PMID]
29. Bao W, Liu R, Wang F, et al. Clinical analysis of autologous peripheral blood hematopoietic stem cell mobilization regimen in patients with malignant hematological diseases. Zhongguo shi yan xue ye xue za zhi. 2020;28(2):663-8.
30. Moreb JS, Byrne M, Shugarman I, et al. Poor peripheral blood stem cell mobilization affects long-term outcomes in multiple myeloma patients undergoing autologous stem cell transplantation. J Clin Apher. 2018;33(1):29-37. [DOI:10.1002/jca.21556] [PMID]
31. Zheng G, He J, Cai Z, et al. A retrospective study of autologous stem cell mobilization by G CSF in combination with chemotherapy in patients with multiple myeloma and lymphoma. Oncol Lett. 2020;19(1):1051-9. [DOI:10.3892/ol.2019.11177]
32. Yuan S, Wang S. How do we mobilize and collect autologous peripheral blood stem cells? Transfusion. 2017;57(1):13-23. [DOI:10.1111/trf.13868] [PMID]
33. Pusic I, Jiang SY, Landua S, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant. 2008;14(9):1045-56. [DOI:10.1016/j.bbmt.2008.07.004] [PMID]
34. Weaver C, Birch R, Greco F, et al. Mobilization and harvesting of peripheral blood stem cells: randomized evaluations of different doses of filgrastim. Br J Haematol. 1998;100(2):338-47. [DOI:10.1046/j.1365-2141.1998.00573.x] [PMID]
35. Baertsch MA, Kriegsmann K, Pavel P, et al. Platelet count before peripheral blood stem cell mobilization is associated with the need for plerixafor but not with the collection result. Transfus Med Hemother. 2018;45(1):24-31. [DOI:10.1159/000478911] [PMID] [PMCID]
36. Accorsi P, Dell'Isola M, Bonfini T, et al. Large volume leukapheresis with Amicus cell separator in peripheral blood stem cell autologous transplant. Transfus Apher Sci. 2001;24(1):79-83. [DOI:10.1016/S0955-3886(00)00130-2] [PMID]
37. Gašová Z, Marinov I, Vodvářková Š, Böhmová M, Bhuyian-Ludvíková Z. PBPC collection techniques: standard versus large volume leukapheresis (LVL) in donors and in patients. Transfus Apher Sci. 2005; 32(2):167-76. [DOI:10.1016/j.transci.2004.10.018] [PMID]

How to Cite This Article:

Rafiee M, Bonakchi H, Rahimi Pordanjani S, Shahrokhi S Z, Mohagheghi S, Allahbakhshian Farsani M, et al. Enhancing CD34+ Cell Mobilization and Engraftment after Autologous Hematopoietic Stem Cell Transplantation via Adjustment of Granulocyte Colony-Stimulating Factor Dose and Period, a Single Center Experience. J Adv Med Biomed Res. 2023; 31(138):488-98.

Download citation:
BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks

Send citation to:
Mendeley Zotero RefWorks