Factors influencing engraftment in autologous peripheral stem cell transplantation

The experience of a local Kuwaiti transplantation center

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ABSTRACT

Objectives: To assess factors affecting engraftment among patients with lymphoproliferative disorders treated with high dose-chemotherapy and autologous peripheral blood stem cell transplantation.

Methods: Fifty-four patients with lymphoproliferative disorders were treated from March 2000 to April 2006, at the Hamid Al-Essa Multiorgan Transplant Center, Kuwait. There were 37 males and 17 females, with a median age of 43 years (range 12-60). The cohort included 13 Hodgkin's lymphoma, 31 non-Hodgkin's lymphoma, and 10 multiple myeloma cases.

Results: The median number of infused CD34+ cells was 1.7 x 10^6 per kg (0.38-15). The medians for absolute neutrophil count (ANC) and platelet (PLT) engraftment were 12 days (10-15) and 11 days (6-33). The CD34+ cell dose and timing of granulocyte-colony stimulating growth factor administration had no significant influence on ANC engraftment (p=0.3 and p=0.05).

Conclusion: The results imply that the CD34+ cell dose is the most important predictor of hematopoietic engraftment, namely PLT engraftment. The other factors studied had no clear influence on engraftment kinetics in this cohort.

Saudi Med J 2007; Vol. 28 (7): 1080-1085

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Received 20th November 2006. Accepted 12th March 2007.

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Hematopoietic stem cell transplantation (HSCT) plays an important role in restoring hematopoiesis after intensive myeloablative therapy in patients suffering from various malignancies. The ablated bone marrow (BM) is reconstituted via re-infusion of normal stem cells. These immature cells are capable of continuous differentiation and self-renewal and can provide sustained long-term production of all types of hematopoietic cells.[1] In addition, these primitive stem cells express a specific transmembrane glycoprotein antigen known as CD34. Based on this clinical marker, the number of infused stem cells can be quantified,[2] allowing assessment of engraftment potential after autologous hematopoietic stem cell transplantation. Autologous HSCT was first successfully employed to cure patients with leukemia and lymphoma in the late 1970s.[3,4] It involves the use of the patient's own cells to re-establish hematopoietic cell function after the administration of high-dose chemotherapy. In the early 1990s, there was a gradual switch from BM to peripheral blood stem cell (PBSC) transplantation. The use of the latter is advantageous because of an accelerated rate of hematological recovery. Several studies have examined the timing of absolute neutrophil count (ANC) and platelet (PLT) engraftment and the CD34+ cell dose in the setting of HSCT.[5-10] It has been postulated that the engraftment kinetic is associated with the number of CD34+ cells infused. A higher number of CD34+ cells are thus associated with rapid engraftment of ANC and PLT and a reduction of hospital stay. The reported minimum threshold of CD34+ cells that is necessary for the recovery of neutrophil and PLT ranges between 1-2.5 x 10^6/kg.[1,11] However, patients receiving CD34+ cells >2.5 x 10^6/kg showed a significantly faster engraftment for both ANC and PLT when compared with patients receiving <2.5 x 10^6 CD34+ cells/kg.[10,12] The administration of granulocyte-colony stimulating growth factor (G-CSF) following CD34+ cell infusion has also been shown to play a role in enhancing ANC engraftment.[13-16] However, the timing and dosage of G-CSF have been debated in the

literature.[17,18] Using post-transplant G-CSF following stem cell infusion enhances neutrophil recovery. The purpose of this study was to determine factors affecting ANC and PLT recovery. The factors assessed included age, diagnosis, number of previous chemotherapy lines, and infused cell dose/kg for all of the following: CD34+ cells, mononuclear cell count (MNC), and colony-forming unit-granulocyte-monocyte (CFU-GM). The impact of G-CSF initiation time on hematopoietic recovery and on the demand for red blood cell (RBC) and PLT transfusion and on hospitalization was also assessed.

Methods. Between March 2000 and April 2006, in the Hamid Al-Essa Multiorgan Transplant Centre, a total of 54 patients (37 males and 17 females) with hematologic malignancies (31 non-Hodgkin's lymphoma, 13 Hodgkin's lymphoma, and 10 multiple myeloma) were enrolled in this study with a median age of 43 years (range, 12-60) and weight of 76.5 kg (range, 44-124). Patients were pretreated with a median of 2 lines of different chemotherapy regimens (range, 1-3) based on disease type. All patients received high-dose chemotherapy regimens without total body irradiation: 27 patients received carmustine, etoposide, cytosine arabinoside, and melphalan (BEAM); 10 patients received high-dose melphalan 200 mg/m^2; only 3 patients received Cytoxan, etoposide, cytosine arabinoside, and melphalan (CEAM); and 14 patients had carmustine, etoposide, cytosine arabinoside, and Cytoxan (BEAC). All patients underwent autologous peripheral blood stem cell transplantation with a median infusion of CD34+ cells equal to 1.7 x 10^6 cells/kg (range, 0.38-15.0 x 10^6). Patients also received a median of 9.49 x 10^9 cells/kg (range, 2.88-38.09 x 10^9) of TNC, 4.64 x 10^8 cells/kg (1.27-16.86 x 10^8) of MNC, 26.3 x 10^4 cells/kg (range, 21.6-112.5 x 10^4) of CFU-GM, and 95.0 x 10^4 cells/kg (65.0-288 x 104) of CFU. Following the infusion of stem cells (day 0), patients were given a fixed dose of 5 µg/kg/day of G-CSF. The growth factor was administered after the infusion at either day +1 (n=28) or day +5 (n=26). This choice of protocol was not a randomization but administered according to physician preference (**Table 1**). Leukapheresis were performed with a continuous-flow separator COBE Spectra (COBE Laboratories, Heimstetten, Germany). A total blood volume between 2 and 3 blood mass volumes at a flow rate of 40 to 60 ml/min was processed through double-lumen leukapheresis catheters for up to 4 consecutive days. For cryopreservation, the apheresis product was centrifuged and adjusted with autologous plasma to a calculated volume. Then, the product was divided into a number of cryo bags, making a maximum volume of 60 ml per bag. A cryoprotectant, dimethylsulfoxide (Impfstoffwerk Dessau-Tornau GmbH, Germany), was added to achieve a final concentration of 10% of the total suspension. The suspension of cells was frozen in a cryopreservation controlled-rate freezer (Kryo 10 series, Planar product LTD, Sunbury-on-Thames, England and Forma Scientific, Inc, USA). The frozen cells were stored at -196°C in liquid nitrogen until infusion. For CD34+ stem cell, enumeration was performed on aliquots of apheresis samples using a single-platform flow cytometric method based on the ISHAGE gating strategy as previously described.[19] Briefly, 10-20 µl of phycoerythrin (PRE) conjugated anti-CD34 monoclonal antibody (moAb) and fluorescein isothiocyanate (FITC)-conjugated anti-CD45 (Beckman Coulter, Inc, Miami, Florida, and Dako Cytomation, Denmark) were added to 100 µl of each patient's sample. As negative control, 10-20 µl of PRE-conjugated IgG-I antibody was added to samples. Then, the samples and controls were incubated for 15-20 minutes in the dark at room temperature. After the incubation period, lysing, re-incubation, and washing were performed. Finally, the samples and the controls were acquired, and both percentage and absolute CD34+ cell counts were obtained. The CD34+ cells were analyzed on a FACS calibur flow cytometer (BD Biosciences, USA) with a 488-nm argon laser and Cell Quest 3.1 software (BD Biosciences, USA).

The percentage of MNCs was determined, using an electronic cell analyzer (Coulter MD II series analyzer, Coulter Corporation, Miami, Florida). Leukocytes, such as monocytes, and lymphocytes, were defined as MNCs. According to a semisolid clonogenic culture technique, total colony-forming units (CFU) were assessed from frozen samples. Approximately 200 µl of 0.5 x 10^6/ml of white blood cells were added to 2 ml of methyl cellulose medium (Stem Cell Technologies, Inc, Vancouver, BC). The culture dishes were incubated at 37°C in a humid chamber with 5% CO_2 (Forma Scientific, Inc, USA) for 2 weeks to enhance the growth of the cells. After 14 days of incubation, the colonies were counted with the aid of a phase-contrast microscope (Zeiss, Oberkochen, Germany).[15] Cell viability was analyzed using Trypan-Blue exclusion or 7-aminoactinomycin D dye (7-AAD; ImmunoTech, Beckman Coulter, Marseille, France) that was used in combination with the CD34+ cell enumeration. Pre-analyzed cryopreserved units were thawed rapidly in a 37°C water bath and infused immediately through the central venous catheter. After the CD34+ stem cell infusion, all patients received post-transplant G-CSF (Neupogen; Filgrastim, F. Hoffman-la Roche Ltd, Basel, Switzerland) with a fixed dose of 5 µg/kg. Along with G-CSF, patients received antiviral, antibacterial, and antifungal chemoprophylaxis. Platelet and red blood cell units were transfused as needed to

maintain HB levels above 80 g per L. Prophylactic PTLs transfusions were given in order to maintain PLTs count >20 x 10^9 per L. Hematologic recovery was defined from the day of stem cell infusion (day 0). Neutrophil recovery was defined as a neutrophil count above 500/ul for 3 consecutive days from the day of autograft. Platelet recovery was also characterized as the first day of a PLT count of >20,000/µl, independent of PLT transfusion.

Statistical analysis. Data were analyzed using the Statistical Package for Social Sciences 13.0 software (SPSS Inc, Chicago, IL, USA). Correlations between quantitative single variables were calculated using Spearman's correlation coefficient test. The Mann-Whitney U test was used for comparisons of continuous variables between the 2 groups. Rates of granulocyte and PLT recovery were estimated using the product-time method of Kaplan-Meier and compared using the log-rank test. The multivariate regression model was used for the analysis of the potential factors influencing ANC and PLTs engraftment, namely, CD34+ cell dose, infused MNC and CFU-GM, age, diagnosis, and previous chemotherapy treatment. The corresponding p value was calculated so that any difference less than 0.05 was considered statistically significant. All reported p values are the result of 2-sided tests.

Results. All patients involved in the study exhibited an ANC recovery to ≥0.5 x 10^9/L at a median of 12 days (range 10-15); PLT recovery to ≥20 x 10^9/L occurred at a median of 11 days (range 6-33). Univariate analysis showed that the infused dose of CD34+ cells x 10^6/kg correlated significantly with PLT engraftment (p=0.045) (**Figure 1**). However, no significant association was observed with ANC engraftment (p=0.3) (**Figure 2**). Further, none of the other variables such as age, diagnosis, number of previous chemotherapy lines, number of infused MNCs, or CFU-GM showed an influence on the engraftment rate, based on univariate analysis (**Table 2**). These findings were further supported by the use of multivariate regression analysis, which was used to determine which of the previously described factors were associated with the hematopoietic recovery, adjusting for the effect of a CD34+ cell dose ≥2 x 10^6/kg versus <2 x 10^6/kg. Multivariate logistic regression was performed by assigning PLTs and ANC engraftment as dependent variables, while the infused dose of CD34+ cells, and other factors were independent variables. The results show that the overall model was significant for CD34+ cell dose, namely, patients who received a CD34+ cell dose ≥2 x 10^6/kg exhibited better PLT engraftment compared to those who received <2 x 10^6/kg, with a median of 10 and 12 days (p≤0.0001). However, ANC engraftment was not significantly associated with the CD34+ cell dose, with a median of 12 and 12.5 days, (p=0.3). Age, diagnosis, number of previous chemotherapy lines, dose of infused MNC, and dose of infused CFU-GM cells had no influence on ANC and PLT recovery. To assess the effect of G-CSF administration time on the duration of neutropenia after autologous stem cell rescue, 54 patients were divided into 2 groups; group I (n=28) received G-CSF (5 µg/kg /day) at day+1 and group II (n=26) received it on day+5. The results show that there was not a significantly different effect on ANC and PLT engraftment for patients who received G-CSF at day+1 versus day+5 (p=0.08 and p=0.5) (**Figures 3 & 4**). Furthermore, the impact of G-CSF initiation time on the demand for RBC and PLT transfusion and on hospitalization was also assessed.

Table 1 - The characteristics of all 54 patients studied.

Characteristic	Patient population (range)
Number of patients	54
Gender (male/female)	37/17
Median age, years	43.0 (12.0-60.0)
Median weight, kg	76.5 (44.0-124.0)
Diagnosis	
Hodgkin's disease	13
Non-Hodgkin's lymphoma	31
Multiple myeloma	10
Median previous chemotherapy lines	2 (1-3)
Myeloablative (conditioning) therapy	
BEAM	27
High-dose melphalan (200 mg per m^2)	10
CEAM	3
BEAC	14
Median of infused $CD34^+$ x 10^6 cells/kg	1.7 (0.38-15.0)
Median of infused MNC x 10^8 cells/kg	4.64 (1.27-16.86)
Median of infused CFU-GM x 10^4 cells/kg	26.3 (21.6-112.0)

BEAM - Carmustine, etoposide, aracytabin.
CEAM - Cytoxan, etoposide, aracytabin, and melphalan.
BEAC - Carmustine, etoposide, aracytabin, and cytoxan.

Table 2 - Correlations between sex, age, diagnosis, and previous chemotherapy lines with the recovery rate of both ANC and platelets.

Factors	Significant *P*-value	
	ANC recovery	Platelet recovery
Age	0.9	0.97
Diagnosis	0.9	0.23
Previous chemotherapy lines	0.7	0.9
CD34+ cells × 10^6/kg	0.3	0.045
MNC × 10^8/kg	0.3	0.9
CFU-GM × 10^4/kg	0.6	0.3

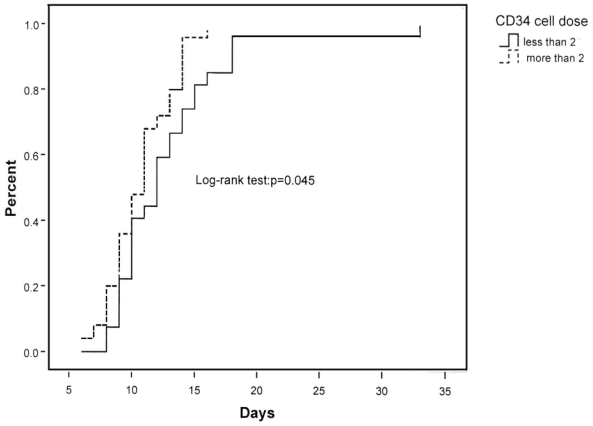

Figure 1 - The Kaplan-Meier analysis of achieving a platelet count ≥20 x 10^9/L in patients receiving a CD34+ cell dose of<2 x 10^6/kg versus ≥2 x 10^6/kg.

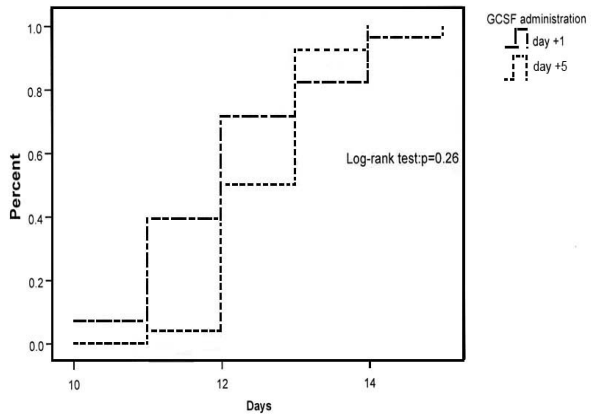

Figure 3 - The number of days to reach an absolute neutrophil count engraftment of 0.5 x 10^9/L in patients receiving granulocyte-colony stimulating growth factor starting on day+1 versus day+5 following autologous peripheral blood stem cell.

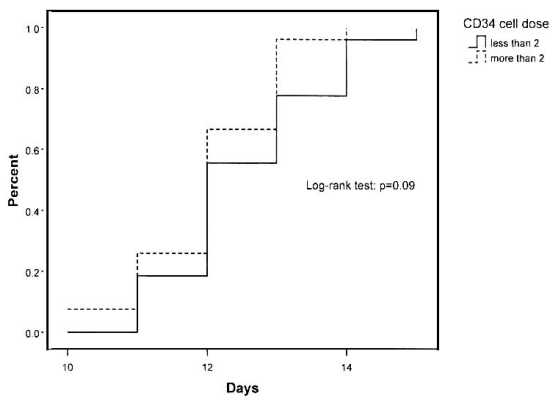

Figure 2 - Number of days to reach absolute neutrophil count 0.5 x 10^9/L in patients receiving a CD34+ cell dose of <2 x 10^6/kg versus ≥2 x 10^6/kg.

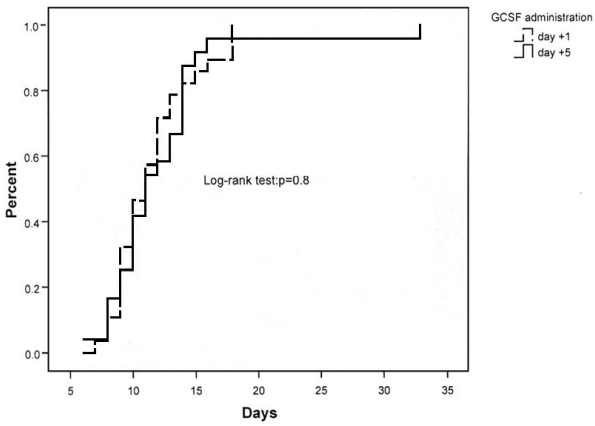

Figure 4 - Kaplan-Meier analysis of achieving a platelet count ≥20 × 10^9/L in patients receiving granulocyte-colony stimulating growth factor starting on day +1 versus day +5 following autologous peripheral blood stem cell transplantation.

Patients in group I were transfused with a median of 4 PLT units (range, 1-16) and a median of 4 RBC units (range, 0-7). Patients in group II were transfused with a median of 3 PLT units (range, 0-7) and 4 RBC units (range, 0-8) (p=0.8). The median hospitalization was 23 days (range, 18-37) and 24 days (range, 20-40) for groups I and II, (p=0.6).

Discussion. Several studies have established the relationship between the number of CD34+ cells re-infused and hematopoietic recovery after high-dose chemotherapy and autologous stem cell transplantation.[5-7] It has been reported that the minimal CD34+ cell count required to accelerate both PLTs, and ANC engraftment should be ≥2 x 10^6 CD34+ cells/kg.[7-9] In this study, there was a significant relationship between the number of infused CD34+ cells and PLT recovery rate. However, there was no correlation observed between the number of infused CD34+ cells and ANC engraftment. The reason for the absence of this relationship is not known but could be the result of the fact that PLT recovery rate is more likely to be associated with the number of CD34+ cells/kg than ANC recovery is. Other investigators have also observed that the most significant variable influencing PLT engraftment was CD34+ cells content infused after the administration of myeloablative therapy.[10] Furthermore, patients involved in this study who were infused with <2 x 10^6 CD34+ cells/kg have engrafted successfully. However, there was a delay in PLT engraftment, suggesting that PLT recovery might be used as a predictive value for the appropriate dose of CD34+ cells content. Other

factors such as age, diagnosis, number of previous chemotherapy lines, or infused cell dose/kg of MNC and CFU-GM did not influence either granulocyte or PLT engraftments, a finding that is also in agreement with other published reports.[10,12] It has been suggested by several authors that the routine use of post-transplant myeloid growth factors is recommended to accelerate hematopoietic engraftment.[20,21] However, timing and dosing administration schedule are still a controversial issue.[22] The present study found no significant impact of G-CSF administration time on PLTs or ANC recovery. Other investigators have also reported similar observations. In a randomized, multi-centre study, initiating G-CSF on day+1 had no effect on PLTs and ANC engraftment rate compared to initiating the supportive care on day 5+.[17] Others have reported that starting G-CSF at day 5+ post-transplant does not compromise hematopoietic reconstitution; however, it lowers the overall cost of treatment.[23] Although the results of this retrospective study showed no significant impact of G-CSF administration time on hematopoietic reconstitution, large randomized prospective studies are necessary to confirm this observation in this kind of patient population. Further, several published trials have shown that a G-CSF dose of 5 μg/kg/day is equivalent to higher doses in accelerating ANC engraftment after autologous PBSCT.[21,24] Bolwell et al,[24] published a prospective randomized trial addressing the issue of 3 commonly used doses of G-CSF (5, 10, and 105 μg/kg/day) post-transplant on ANC engraftment. The results, however, did not show an impact of the different doses on the neutrophil engraftment.[24] In the current retrospective study, the use of low dose G-CSF was employed, and the results were comparable with those of other published reports.[21,24]

Functional assays of stem cell activity that were based on *in vitro* growth of colonies have been assessed for correlation with ANC and PLT engraftment.[21,25-28] In the current study, there was no correlation between the CFU-GM/kg infused and engraftment kinetics. Some initial reports have suggested that infusing >50 x 10^4 CFU-GM/kg has resulted in rapid engraftment with PBSC transplant; however, other investigators have found no relationship between the rate of hematopoietic recovery and CFU-GM content.[25-28] This discrepancy is not surprising because standardization and comparison between laboratories are difficult; measurement of the colony assay is laboratory dependent. Further, the CFU assay requires 14 days for interpretation. Therefore, it is not an ideal method for clinical judgment and assessment of quality of CD34+ cells harvest prior to autologous transplant.

In conclusion, we found that the most significant variable affecting PLT engraftment was CD34+ cells content of the infused peripheral blood stem cells. Further, although lower doses of CD34 (<2 x 10^6 CD34+ cells/kg) engrafted successfully, these doses were associated with a lower rate of PLT engraftment. Other factors, such as age, diagnosis, previous chemotherapy lines, MNC and CFU-GM doses had no effect. A larger patient population is needed to clarify the exact correlation of each factor with the recovery rate, avoiding the occurrence of trends, which can lead to an incorrect interpretation of some relationships.

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