Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Research Article

Method of Mobilization: Implications on Graft Composition and Immune Reconstitution Post Autologous Hematopoietic Cell Transplantation

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Received: June 01, 2016; **Accepted:** July 06, 2016; **Published:** July 08, 2016

Abstract

Background: Plerixafor, a reversible CXCR4 antagonist, is used in conjunction with G-CSF for stem cell mobilization prior to autologous hematopoietic cell transplantation (AHCT). The effect of adding plerixafor to growth factors during mobilization on graft composition and early myeloid and immune recovery has not been widely described.

Methods: 49 adult AHCT recipients were enrolled on a single arm prospective trial where blood samples were freshly collected from the pheresis product and from patients' peripheral blood on days 30 and 60 post AHCT. Flow cytometric analysis was done to quantify CD3+ T cells, CD3+ CD56+ NK-like T cells, CD56+ CD16+ and CD56+ CD16- NK cells as well as CD19+ B cells.

Results: Compared to patients mobilized with G-CSF, patients mobilized with Plerixafor plus G-CSF (G+P) required less number of collection days (1.9 vs 1.4 days; p=0.05) to reach the target CD34+ cell dose. Both groups had similar median times to neutrophil and platelet engraftment. G+P group had a higher percentage of CD4 (12.9% vs 9.2%), similar CD3+, NK and B cells in the graft compared to G-CSF mobilization. Both G+P and G-CSF groups had similar peripheral hematologic and immune recovery at days 30 and 60 post AHCT.

Conclusion: Our study shows that patients mobilized with G+P have similar immune and hematologic recovery to G-CSF mobilization post AHCT.

Keywords: Plerixafor; Mobilization; G-CSF; Autologous; Immune

Introduction

Autologous Hematopoietic Cell Transplantation (AHCT) is an established treatment for patients with multiple myeloma and chemo sensitive, relapsed or refractory lymphomas [1]. As more than 98% of AHCTs in adults are performed using peripheral blood stem cell grafts, the success of this procedure depends largely on the ability to collect enough hematopoietic stem cells for adequate engraftment [2]. The quantity of CD34+ cells has traditionally been used as a surrogate for the number of hematopoietic stem cells, and the infused CD34+ dose is correlated with successful neutrophil and platelet engraftment, progression free survival and overall survival post high dose chemotherapy and AHCT [3-5]. The International Myeloma working Group Suggested collection of at least $4x10^6$ CD34+ cells/kg for a single AHCT and $8x10^6$ CD34+ cells/kg to allow for two transplants if feasible [6]. In many centers, a minimum dose of $2x10^6$ CD34+ cells/kg is considered acceptable to proceed with AHCT for myeloma or lymphoma patients.

The optimal mobilization method for either myeloma or lymphoma patients is still debatable and strategies for graft collection vary between different centers. The mobilization strategy may affect the stem cell graft that can be associated with overall patient outcomes [1,7]. Chemotherapy followed by granulocyte-colony-stimulating factor (G-CSF) or G-CSF alone has been the standard for CD34+ cells mobilization into the peripheral blood. Myeloma patients were traditionally mobilized with high dose cyclophosphamide (4-7g/m^2) followed by G-CSF [8]. Inadequate mobilization using traditional strategies among myeloma and lymphoma patients can be seen in 5-30% of the cases [9]. Lately, alternative strategies for CD34+ cells mobilization include lower dosages of cyclophosphamide followed by G-CSF, G-CSF alone or G-CSF combined with Plerixafor with or without chemotherapy [10,11].

Plerixafor (AMD3100), a reversible and selective antagonist of the CXCR4 chemokine receptor that blockes CXCR4 and stromal-cell derived factor 1-α interactions, was originally synthesized for activity against human immune deficiency virus. In initial studies, plerixafor was found to cause an increase in peripheral blood counts and mobilization of CD34+ from the bone marrow to the peripheral blood [12]. Addition of Plerixafor to G-CSF has been shown to be superior to G-CSF alone in myeloma and lymphoma patients in terms of mobilization as measured by CD34+ counts, collection yield and number of collection days to achieve the target yield [10,13]. The effect of Plerixafor on graft composition was assessed in cryopreserved grafts of NHL patients and it was found to mobilize more CD3+ cells, Helper CD4+ cells and CD8+ cells [14]. This study was conducted to evaluate the effect of plerixafor on graft composition of freshly collected stem cell aphaeresis product and to further delineate the implication of adding plerixafor on count recovery and immune reconstitution markers in the first 60 days post AHCT.

Citation: Solh M, Rathmann K, Chang-Fong S, Lamontagne D, Oyer J, Copik A, et al. Method of Mobilization: Implications on Graft Composition and Immune Reconstitution Post Autologous Hematopoietic Cell Transplantation. Ann Hematol Oncol. 2016; 3(4): 1089.

Table 1: Demographics for the total population and by collection group.

Treatment Group	Total Population N (%)	G-CSF	Plerixafor +G-CSF	P – value[1]
Number of Patients	49	16 (33%)	33 (67%)	
Median Age at Infusion	58 years	53 years	61 years	0.11
Gender Female Male	 20(41%) 29 (59%)	 6(37.5%) 10(62.5%)	 14(42.4%) 19(57.6%)	0.74
Histology MM NHL	 35 (71%) 14 (29%)	 10(62.5%) 6 (37.5%)	 25(75.8%) 8(24.2%)	0.33
Disease Status CR PR Progression	 10(20%) 36(73%) 3(7%)	 1(6.3%) 14(87.5%) 1(6.3%)	 9(27.3%) 22(66.7%) 2(6.1%)	0.23
RFI disease risk High Intermediate Low	 7(14%) 9(18%) 33(67%)	 2(12.5%) 4(25.0%) 10(62.5%)	 5(15.2%) 5(15.2%) 23(69.7%)	0.70
Conditioning regimen Melphalan R-BEAM	 35(71%) 14(29%)	 10(62.5%) 6(37.5%)	 25(75.8%) 8(24.2%)	0.34

[1]P-value compares patients in G-CSF group versus Plerixafor +G-CSF
MM: Multiple Myeloma; NHL: Non-Hodgkins Lymphoma; CR: Complete Remission; PR: Partial Response; RFI: Risk; R-BEAM: Rituxan BCNU Eetoposide Ara-c Melphalan.

Methods

Patients

A total of fifty one patients eligible for AHCT and stem cell mobilization at our center were enrolled on a prospective trial to evaluate graft composition and immune reconstitution markers at day 30 and day 60 post AHCT. Only patients with multiple myeloma or non Hodgkin's lymphoma were included in this analysis and 2 patients with Hodgkin's disease were excluded. This study was conducted according to the declaration of Helsinki and was approved by our institutional IRB. All subjects included in this study signed an IRB approved informed consent prior to participation. Thirty three patients received plerixafor + G-CSF (G+P) and 16 patients received G-CSF alone. A small portion (2.5mL) of the autologous peripheral blood stem cell product was collected prior to transplant and peripheral blood (~10 mL) was collected on days +30, and +60 post transplantation.

Mobilization and Collection for Stem Cells

The mobilization regimen consisted of filgrastim 10 µg/kg/day for 4 consecutive days. Daily measurements of blood CD34+ and total white counts were started on day 4. CD34+ levels were determined using flow cytometry (BD FACS Canto II) using a single platform assay (Beckman-Coulter stem Kit) based on recommendations by the international society of hematopathology and graft engineering (ISHAGE). Patients who had a peripheral blood CD34+ level ≤ 20/µl on day 4, received plerixafor 0.24 mg/Kg at 10 pm of that day in addition to the scheduled filgrastim dose. Peripheral blood aphaeresis was started in the morning of day 5 and continued till the target cell dose or patient failed to collect. The minimum acceptable cell dose was ≥ 2 x10^6 CD34+cell/Kg and patients who did not reach this cell dose after 3 days of collection, were considered mobilization failures. Patients who had received plerixafor on the night of day 4, continued to receive plerixafor through the mobilization period. Collection was performed with a COBE Spectra auto PBSC machine. The daily blood volume processed during the aphaeresis was 20 liters.

High Dose Chemotherapy and Transplant course

All patients who had a successful collection were admitted to the inpatient unit for high dose chemotherapy and autologous stem cell infusion. Non-Hodgkin's lymphoma patients received a conditioning regimen consisting of R-BEAM (Rituximab 375 mg/m^2 on day -7, Carmustine 300 mg/m^2 on Day -6, etoposide 200 mg/m^2 days -5 to -2, cytarabine 300 mg/m^2 days -5 to -2 and melphalan 140 mg/m^2 on day -2). Multiple myeloma patients received conditioning regimen with high dose melphalan (melphalan 200 mg/m^2 on day -2). CD34+ cells were infused on day 0. All patients received G-CSF at 5 µg/kg/day starting day +5 after AHCT till neutrophil engraftment or until the first day with absolute neutrophil count (ANC) >2500x10^9/l. All patients received antibacterial, antiviral and antifungal prophylaxis and blood product and nutritional support per institutional guidelines.

Neutrophil engraftment was defined as ANC ≥0.5x10^9/l for 3 consecutive days. Platelet engraftment was defined as platelet level of ≥20x10^9/l without transfusion. All patients remained in the bone marrow transplant unit till neutrophil engraftment and were followed in the clinic until at least 100 days post transplantation.

Graft and Post Transplant Peripheral blood Cell subset Analysis

Samples were drawn from the aphaeresis product (2.5 ml) and from transplant recipients' peripheral blood (10 ml) on days +30 and +60 post AHCT. The CD34+ content of the graft was analyzed by flow cytometry (BD FACS Canto II). A single platform assay was used (Beckman-Coulter Stem kit) via ISHAGE protocol. This kit contains CD34 and CD45 monoclonal antibodies, 7- aminoactinomycin D (7-ADD), NH_4CL, and stem-kit fluorospheres. The data was analyzed using FACS Diva software (BD biosciences).

Samples drawn on collection day, and days +30 and +60 post AHCT were immediately processed, stained with antibodies and analyzed for lymphocyte content. Peripheral blood cells were depleted of red blood cells using a red blood cell lysis solution, washed twice in PBS and re-suspended in staining buffer (PBS + 2mM EDTA + 0.5% BSA). Next, cells (0.5 x 10^6) were stained with antibody cocktail (30 min at 4°C), washed and analyzed by flow cytometry. The antibody cocktail contained the following pre-conjugated monoclonal antibodies: CD56-PE (Miltenyi Biotech, Auburn, CA), CD3-APC, CD16-FITC, (Beckman Coulter, Brea, CA), CD19-PE-CY7 (BD Biosciences, San Jose, CA). Data were acquired using BD FACS Canto II (BD Biosciences) and analyzed with the FACSDiva software (BD Biosciences) to quantify CD3+ T cells, CD3+ CD56+ NK-like T cells, CD56+ CD16+ and CD56+ CD16- NK cells as well as CD19+ B cells.

Statistical Analysis and Data collection

Cell subset data were prospectively collected as per the study protocol. The clinical and demographic data was collected from the clinical program database and was subsequently merged into the cell subsets data for analysis. All calculations and statistical analysis were conducted using SPSS statistics 21.0 for windows. Continuous numerical variables were described with their medians and ranges. The Mann-Whitneu U test was used to analyze differences between quantitative variables and where the variables were not normally

distributed. This test was also used due to low number of observations. The Chi-square test was used to compare categorical variables. A p-value of less than 0.05 was considered significant.

Results

A total of 51 patients were enrolled on this study. Two patients with Hodgkin's disease were excluded from the analysis. Of 49 eligible patients, 16 were mobilized with G-CSF alone (G-CSF group) and 33 with G-CSF plus plerixafor (G+P). The median age for the study group was 58 years (range 21-75 years).Thirty five patients (71%) had multiple myeloma (MM) and all received high dose melphalan conditioning before stem cell infusion. 14 patients (29%) had non-hodgkins lymphoma (NHL) and all received R-BEAM conditioning. There was no difference between the two groups (G-CSF versus G+P) in any of the basic demographic and disease parameters (Table 1).

Aphaeresis and Engraftment

The target cell dose was $6x10^6$ CD34+cells/Kg for multiple myeloma patients (sufficient for two autologous HCTs) and $5x10^6$ CD34+ cells/Kg for the NHL group. The minimum acceptable cell dose to proceed with auto HCT for both disease subtypes was $2x10^6$CD34+ cells/Kg. All patients enrolled on this study had a successful mobilization. Five out of the 35 MM patients and 6 out of the 14 NHL patients did not achieve the target cell dose but were able to collect more than the minimal acceptable CD34+ cell dose. The median number of collection days was 1.42 in the G+P group and 1.91 days in the G-CSF group (p=0.05) (Table 2). The CD34+ yield per day of collection was 8.28 CD34+$x10^6$/kg in the G+P and 5.24 CD34+$x10^6$/kg in the G-CSF group (p=0.22). Time to neutrophil and platelet engraftment was similar in both groups (11.69 versus 11.70 days for Neutrophils and 20.6 versus 21.3 days for platelet engraftment in G-CSF and G+P groups respectively).

Graft Composition

The median white blood count (WBC) concentration in the grafts was $262x10^9$/l in the G-CSF and $309x10^9$/l in the G+P group (p=0.38). The median CD34+ cell percentage from the total WBC in the graft was 0.73% and 0.75% in the G-CSF and G+P groups respectively (p=0.81). The median T cell percentage from the total WBC in the graft was 24.2% versus 26.7% in the G-CSF and G+P groups (P=0.56). There was no difference in the graft content as analyzed for the proportions of CD3+, CD4+,CD8+, NK, NKT and iNKT cells (Table 3). The CD4/CD8 ratio was 1.06 in the G-CSF group and 1.74 in the G+P group (p=0.10).

A subgroup analysis for graft composition was run separately for the MM patients and the NHL patients. There was no statistical difference in the graft composition for each histologic subgroup.

Day +30 Count Recovery and Immune Reconstitution.

The median WBC at day +30 post HCT was $5.08x10^9$/l and 5.01 $x10^9$/l in G-CSF and G+P groups (p=0.73). The absolute neutrophil count was also similar between both groups at 2.99 $x10^9$/l and 2.64 $x10^9$/l for G-CSF and G+P respectively (Table 4). The absolute Lymphocyte counts and absolute T cell counts were 1.09 $x10^9$/l and 0.72 $x10^9$/l for the G-CSF group versus 1.44 $x10^9$/l and 0.96 $x10^9$/l for the G+P group. Both groups were similar for the peripheral blood percentages of NK cells, NKT cells and B cells.

Table 2: Pheresis and engraftment outcomes.

Treatment Group	GCSF alone (N=16)	GCSF + Plerixafor (N=33)	P-value
Number of collection days	1.91	1.42	0.05
CD34 x 10^6/kg total collected	7.77	7.62	0.76
CD34 x 10^6/kg collected per day	5.84	8.28	0.22
CD34 x 10^6/kg infused	4.88	4.57	0.87
Time to platelet recovery (days)	20.63	21.39	0.70
Time to neutrophil recovery (days)	11.69	11.70	0.41

Table 3: Cell composition of the pheresis product.

	G-CSF (N=16)	Plerixafor +G-CSF (N=33)	P-value
WBC count	262.8	309.0	0.38
CD34%	0.73	0.75	0.81
% T cell	24.27	26.68	0.56
% NK cell	3.88	2.37	0.43
% NKT	2.75	1.81	0.61
% INKT	0.216	0.302	1.00
% B cell	0.799	1.37	0.25
%CD3	22.08	25.65	0.64
%CD4	9.26	12.90	0.09
%CD8	11.62	11.11	0.63
%CD4/%CD8 Ratio	1.06	1.74	0.10

NK: Natural Killer; INKT: Invariant Natural Killer Cells

NK, T, NKT and B cells are percentages of total nucleated cells. INKT reported as percentage of CD3+.

The MM patients (n=35) and NHL patients (n=14) were also analyzed separately for peripheral blood immune and count recovery at day +30 post HCT. For MM patients, the median ANC at day 30 was 2.78 $x10^9$/l and the absolute total lymphocyte count (TLC) was 1.4 $x10^9$/l. Myeloma patients who were mobilized with G-CF (n=10) had no significant difference in their day +30 absolute NK, absolute T cell and percentage of B cells when compared to those mobilized with G+P (n=25). The median ANC and TLC for NHL patients at day +30 were 5.4 $x10^9$/l and 2.41 $x10^9$/l. Six NHL patients were mobilized with G-CSF and 7 with G+P. Both NHL groups (G-CSF versus G+P) had similar ALC (p=0.28) absolute NK cell values (p=0.49) and ANC (p=0.57).

Day +60 Count Recovery and Immune Reconstitution.

Table 4 shows the count recovery at day +60 for G-CSF and G+P groups. The median WBC and ANC counts were 4.94 $x10^9$/l and 2.85 $x10^9$/l versus 5.38 $x10^9$/l and 3.01 $x10^9$/l for G-CSF and G+P respectively. Both groups had similar ALC, absolute NK count and percentage of B cells. Among MM and NHL subgroups, the method of mobilization did not affect day +60 WBC, ANC, ALC, %NK cells, %T cells, %B cells, absolute NK cell and absolute T cell counts.

Discussion

A significant proportion of patients eligible for AHCT fail to mobilize with G-CSF or chemotherapy plus G-CSF with failure rates higher than 20% in some instances [15,16]. In 2008, Plerixafor was approved by the FDA in combination with G-CSF for stem

Table 4: Immune and hematologic reconstitution at day 30 and day 60 post autologous transplantation.

Treatment Group	G-CSF (N=16)	Plerixafor + G-CSF (N=33)	P-value	G-CSF (N=16)	Plerixafor + G-CSF (N=33)	P-value
	Day 30			**Day 60**		
WBC	5.08	5.41	0.873	4.94	5.38	0.654
HGB	10.86	11.19	0.353	11.22	11.17	0.757
HCT	32.35	33.66	0.321	33.36	33.53	0.565
PLT	119.88	161.42	0.068	166.94	173.73	0.949
ALC	1.09	1.44	0.296	1.41	1.50	0.974
% NK	26.14	30.38	0.277	11.53	20.09	0.095
Abs NK	0.31	0.35	0.186	0.17	0.21	0.470
% T cell	67	60	0.183	76.15	67.39	0.340
Abs T cell	0.72	0.96	0.717	1.35	0.82	0.095
NKT%*	5.28	3.33		8.25	3.38	
B cell %	2.38	1.52	0.922	2.63	5.58	0.424
ANC	2.99	2.64	0.488	2.85	3.01	0.848

WBC: White Blood Count; HGB: Hemoglobin; PLT: Platelet Count; ALC: Absolute Lymphocyte Count; NK: Natural Killer Cells; Abs: Absolute; ANC: Absolute Neutrophil Count

NK, T, NKT and B cells are percentages of total nucleated cells. INKT reported as percentage of CD3+.

cell mobilization in MM and NHL patients undergoing high dose chemotherapy and AHCT [17]. Plerixafor is a reversible CXCR4 antagonist that acts by disrupting the interaction of CXCR4 with SDF-1 and hence leading to release of stem cells. It has a peak effect at 4-9 hours after administration with sustained effects for hours later [18]. The administered cell dose post high dose chemotherapy is essential for timely engraftment and to minimize transfusion burden with doses < $1x10^6$/kg have been associated with loss of engraftment [19]. The minimum recommended stem cell dose is 2 x 10^6 CD34+cells/Kg [17]. Our data, like several other studies, show that adding pre-emptive plerixafor to patients predicted to have a low mobilization yield based on their peripheral CD34+ counts, can help mobilize sufficient cells to achieve successful engraftment [10,13,20,21].

The method of mobilization can affect the composition of the graft and this may affect outcomes of patients receiving AHCT [22]. The cell content of the mobilized graft has been linked to outcomes among MM and NHL patients. A higher number of lymphocytes infused was associated with less relapses in MM patients [23]. Holtan, et al. reported on 36 NHL patients who were mobilized with G-CSF or G-CSF plus plerixafor and showed that patients mobilized with plerixafor collected more lymphocytes and had a better progression free survival [24]. Dendritc cell content in the graft was also linked to improved survival among diffuse large B cell Lymphoma patients [25].

Several studies have assessed the impact of mobilization method on the cell content of the infused graft. Most of these studies have used cryopreserved grafts [14,26]. Varmavuo, et al. showed that when plerixafor was used preemptively in addition to chemomobilization in NHL patients poorly mobilizing with chemotherapy plus G-CSF, plerixafor significantly increased the proportion and the number of most primitive stem cells (CD34+ CD133+ CD38-) in the graft [14]. Another analysis by the same group showed that injection of plerixafor increases the number of CD3+ T cells, Helper CD4+ T cell subsets and suppressor CD8+ T cell subsets in the graft compared to the graft collected the day prior to administration of plerixafor in patients mobilizing poorly with chemotherapy and G-CSF alone. This study did not evaluate the impact of these graft changes on immune reconstitution and overall outcomes [26].

The impact of adding plerixafor (AMD3100) to G-CSF on the graft content has scarce data with variable results [26-29]. Frehauf, et al. showed that patients mobilized with plerixafor plus G-CSF had a significant increase in primitive CD34+ CD38 (-) cells in the graft when compared to those mobilized with G-CSF alone [29]. Plerixafor was also shown to induce a >2 fold increase in dendritic cells when added to G-CSF compared to G-CSF alone in non-Hodgkin's lymphoma patients [30]. Cells mobilized by the addition of plerixafor had different gene expression that helps promote cell adhesion, motility, cell cycle and anti apoptosis [27]. Lundgvist, et al. reported that T cells mobilized with plerixafor retain the same phenotype as non mobilized T cells in contrast to G-CSF mobilized T cells that had altered expression of 16 cytokine-associated genes in CD3+ cells [28].

Our study did not show a significant difference in the graft characteristics among P+G and G-CSF alone mobilization. The graft composition was not affected by the mobilization in either MM or NHL patients when analyzed separately. Moreover, the hematologic and immune recovery was not significantly affected in the first 60 days post AHCT. All graft and peripheral blood samples were analyzed on a single site using the same lab method and all procedures were carried by an experienced lab technician. Our study differs from most in that we analyzed fresh samples, did not use chemotherapy as part of mobilization and used a different cutoff peripheral CD34 level to implement plerixafor into the mobilization method. There are several limitations with this study including the small sample size. Power studies were not done prior to analysis, so it is difficult to know if the differences are really not there or if the small sample size restricted the findings. Analysis for relapse and survival was not reported as the numbers in each disease category were small to detect a significant difference. We did not perform functional assays to determine the

functional activation of T cell subsets or the presence of T helper dendritic versus plasmacytoid dendritic cells [10]. Other factors that might affect immune recovery among autologous HCT recipients and were not accounted for in our manuscript include the baseline immune parameters prior to mobilization and the use of immune modulators (such as lenalidomide) before and after transplantation as these medications can boost NK cell activity.

In conclusion, Plerixafor when added to G-CSF in either MM or NHL recipients' helps in achieving mobilization goals among patients predicted to have poor mobilization based on peripheral blood CD34+ levels. Moreover, plerixafor doesn't affect the lymphocyte and NK cell proportions in the graft and peripheral blood samples in the first 60 days post AHCT.

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Ann Hematol Oncol - Volume 3 Issue 4 - 2016
ISSN : 2375-7965 | www.austinpublishinggroup.com

Citation: Solh M, Rathmann K, Chang-Fong S, Lamontagne D, Oyer J, Copik A, et al. Method of Mobilization: Implications on Graft Composition and Immune Reconstitution Post Autologous Hematopoietic Cell Transplantation. Ann Hematol Oncol. 2016; 3(4): 1089.