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Research Article

Stem Cell Mobilization with and without Plerixafor: A Comparative Analysis

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Abstract

Patients scheduled for high-dose chemotherapy who fail to mobilize a sufficient number of hematopoietic stem cells have a poor prognosis. Since 2008 the CXCR4-inhibitor plerixafor is available to improve stem cell collection and to reduce the number of failed mobilizers.

The primary mobilization success of 47 patients with Non-Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HD) and Multiple Myeloma (MM) was evaluated (group A). All patients received G-CSF with or without chemotherapy for mobilization. This group was matched by age, sex and diagnosis to 47 proven poor mobilizers receiving plerixafor (group B).

In group A, 92.9% diagnosed with NHL and all patients diagnosed with MM and HD gathered more than 2.0 × 10^6 CD34+ cells/kg BW. In group B, 64.3% of the NHL patients, 88.2% of the patients diagnosed with MM and all patients with HD were able to collect the defined minimum of CD34+ cells. In total, 74.5% of poor mobilizing patients who received plerixafor gathered more than 2.0 × 10^6/kg BW CD34+ cells. Transplanted cells engrafted in both cohorts; however, in NHL and MM patients, engraftment of white blood cells and platelets were significant earlier in group A than in group B.

In conclusion, only 4.3% of patients failed first mobilization attempt. For these limited number of patients plerixafor is a valuable additive.

Keywords: Plerixafor; Poor mobilization

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Abbreviations

NHL: Non-Hodgkin Lymphoma
MM: Multiple Myeloma
HD: Hodgkin Lymphoma
Group A: Patients in first mobilization
Group B: Proven poor mobilizers
BW: Body weight
PB: Peripheral blood

Introduction

High-dose chemotherapy followed by autologous stem cell transplantation is an approved therapeutic intervention in numerous malignant as well as non-malignant diseases [1]. Since more than one decade, the possibility of collecting Peripheral Blood Stem Cells (PBSC) as primary source for stem cell transplantation has largely replaced the use of bone marrow cells [2,3]. Hematopoietic Stem Cells (HSC) and progenitor cells, identifiable by the expression of CD34 [4], reside in a special environment of the bone marrow, the stem cell niche. Because of their physiologically low presence in peripheral blood, HSC have to be mobilized from the bone marrow into circulation prior to collection by apheresis. For mobilization, most investigators use hematopoietic growth factors like Granulocyte Stimulating Factor (G-CSF) without or with chemotherapy ("chemomobilization").

The success of autologous stem cell transplantation relies on multiple factors, with the dose of reinfused HSC being a key factor [5]. Most investigators define the minimum dose of HSC necessary to allow a prompt and durable engraftment as 2 × 10^6 CD34+ cells/kg Body Weight (BW) or 4 × 10^6 CD34+ cells/kg BW for patients with multiple myeloma scheduled for tandem transplantation [6-8]. Unfortunately, some patients undergoing mobilization attempts are unable to reach the required minimum, being considered as "poor mobilizers". In literature, the rate of poor mobilizers differs between 5% and 46% [9-12]. If patients fail an initial mobilization, they often undergo additional mobilization attempts, which increases the risk associated with treatment [13]. Since December 2008 the bicyclam plerixafor is available to increase mobilization success. Plerixafor was found to interrupt the interaction between chemokine Stromal-Cell Derived Factor-1 alpha (SDF-1a) [14], which is constitutively expressed

on bone marrow stromal cells, and its cognate receptor CXCR4 on CD34+ HSC [15], resulting in a rapid increase of PBSC [16]. In a phase I study, a single dose of 240µg/kg BW SC was as affective as a five-day mobilization regimen with G-CSF [17]. Before approval plerixafor was applied in two major registration trials in patients with Non-Hodgkin Lymphoma (NHL) [18] and Multiple Myeloma (MM) [19] undergoing first mobilization as well as in Compassionate-Use-Programs (CUP) around the world for patients who failed as least one conventional mobilization regimen.

In this work we analyzed patients receiving their first mobilization to evaluate the number requiring a second mobilization attempt. In a matched pair process, these patients were compared to a group of second mobilizers receiving plerixafor. This analysis will allow us to describe the actual need for plerixafor and the re-mobilization success in comparable patients.

Materials and Methods

In a first step we evaluated retrospectively the mobilization success of a group of 47 patients treated at the university hospital of cologne between 2007 and 2010 (group A). Twenty-eight patients were diagnosed with NHL, 17 with MM and 2 with Hodgkin Lymphoma (HD). Prior to mobilization patients had received a median of 1 (range 0-5) line of treatment. The ratio between chemomobilization and cytokine only was 24/4 for NHL, 14/3 for MM and 2/0 for HD, respectively.

Patients included in group A were matched by age, sex and diagnosis to a group of proven poor mobilizers enrolled in the German plerixafor Compassionate Use Program (CUP) between May 2008 and August 2009 [20] (group B). In the CUP 60 patients were enrolled; however, 13 patients with other diagnoses than NHL, MM and HD and also minors were excluded from the analysis. Patients included in group B had received a median of 3 (range 1-5) prior lines of treatment. All patients received plerixafor and G-CSF with or without chemotherapy for a second mobilization attempt.

Mobilization without chemotherapy started with a four-day treatment of non-pegylated G-CSF. In general, a subcutaneous dosage of 10µg/kg daily was administered in the morning. Patients in group B received plerixafor (240µg/kg; Mozobil™, Genzyme Inc., Naarden, NL) in the evening of the fourth day subcutaneously 11 hours prior to apheresis. G-CSF was given on day five 1 hour before apheresis. If multiple days of collection were required, the schedule of plerixafor and G-CSF was repeated until a maximum of seven days of plerixafor injections. Patients in group B were also allowed to receive a combination of chemotherapy with G-CSF and plerixafor for mobilization. In this case, G-CSF was started at the neutrophil nadir after chemotherapy.

Patients were considered as poor mobilizers if at least one mobilization regimen was unable to increase the peripheral blood count of CD34+ cells above 10 cells/µl in multiple measurements or if patients were unable to collect the required minimum of at least 2,0 × 10^6 CD34+ cells/kg BW within five apheresis sessions. Measurement of CD34+ cells was started on the day of leukocyte recovery or at last beginning on day five after application of G-CSF. Apheresis procedure was started if CD34+ cell counts exceeded 10 cells/µl in peripheral blood. Flow cytometry was used for detection of CD34+ cells. Volume, processing, and storage of apheresis product were done according to the standardized procedures (approximately 3 times blood volume). Aphereses were performed using continuous-flow blood cell separators on consecutive days for a maximum of 7 collections. Pooling of collected CD34+ cells was allowed. The trial was conducted according to the standards of ethical principles. Patients had to sign an informed consent prior to administration of plerixafor.

Results

A total of 47 patients were enrolled in group A. Characteristics of the patients are shown in table 1. Of 28 patients diagnosed with NHL, 24 (85.7%) were mobilized with a combination of chemotherapy and G-CSF and yielded a median of 5.08 × 10^6 CD34+ cells/kg BW (range 1.1-41.4). Twenty-two (91.7%) reached the defined minimum and proceeded to high-dose chemotherapy followed by autologous stem cell transplantation. A median of one (range 1-3) apheresis procedure was needed. Four NHL patients (14.3%) received G-CSF only for mobilization purpose and had a median of 6.67 × 10^6 CD34+ cells/kg BW (range 3.6-11.2) collected, allowing all patients to undergo transplantation. All four patients yielded enough CD34+ cells in one single apheresis.

Fourteen of 17 patients (82.4%) diagnosed with MM received chemomobilization and gathered a median of 6.15 ×10^6 CD34+ cells/kg BW (range 2.6-13.0) in a median of 2 (range 1-4) aphereses, whereas three patients (17.6%) mobilized with G-CSF only yielded a median of 5.71 × 10^6 CD34+ cells/kg BW (range 4.9-8.6) in a median of 2 apheresis sessions (range 1-3). All patients with MM were able to collect a sufficient amount of cells to undergo transplantation.

Two patients diagnosed with HD received a combination of chemotherapy and G-CSF for mobilization and yielded a median of 6.44 × 10^6 CD34+ cells/kg BW (range 5.6-7.3). Both patients proceeded to transplantation after undergoing one single apheresis.

In total 95.7% (45/47) of patients in group A were able to collect a median of 5.71 × 10^6 CD34+ cells/kg BW (range 1.1-41.4) to proceed to high dose chemotherapy followed by autologous stem cell transplantation. A median of 2 apheresis procedures (range 1-4) were necessary for yielding the required minimum of CD34+ cells.

In the matching group B, 85.7% (24/28) of the NHL-patients, who received chemomobilization combined with plerixafor yielded a median of 2.29 × 10^6 CD34+ cells/kg BW (range 0-8.77) in a median of 2 aphereses (range 0-3), allowing 13 patients (54.2%) to undergo high dose chemotherapy. Four patients diagnosed with NHL treated with G-CSF and plerixafor collected a median of 2.1 × 10^6 CD34+ cells/kg BW (range 1.6-3.7). Three of them (75%) underwent transplantation after undergoing a median of 2.5 apheresis procedures (range 1 -3). Patients diagnosed with NHL in group B received a median of 2 (range 1-4) doses of plerixafor.

A median of 4.94 × 10^6 CD34+ cells/kg BW (range 0-10.98) were collected in 82.4% (14/17) of the MM patients mobilized by a combination of chemotherapy, G-CSF and plerixafor, allowing 12 patients (85.7%) to undergo transplantation. Those patients had to undergo a median of 2 apheresis days (range 0 -5) and received a median of 2 (range 1-3) doses of plerixafor. Three MM patients who underwent "steady state" mobilization with plerixafor and G-CSF gathered a median of 5.43 × 10^6 CD34+ cells/kg BW (range 4.4-8.7). All three patients received plerixafor for two consecutive days and proceeded to high dose chemotherapy.

N (%)	NHL		MM		HD		Total	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
	28 (59.6)	28 (59.6)	17 (36.2)	17 (36.2)	2 (4.3)	2 (4.3)	47 (100.0)	47 (100.0)
Age (years)								
Mean (s)	54.5 (12.2)	57.46 (9.64)	60.94 (8.31)	60.88 (7.70)	28 (7.07)	20.0 (1.41)	55.7 (12.52)	57.11 (11.85)
Median	57.5	57	63	60	28	20	59	59
Min, Max	21, 71	38, 75	44, 74	46, 70	23, 33	19, 21	21, 74	19, 75
Sex (%)								
Female	14 (50.0)	14 (50.0)	7 (41.2)	7 (41.2)	2 (100.0)	2 (100.0)	23 (48,9)	23 (48,9)
Male	14 (50.0)	14 (50.0)	10 (58.8)	10 (58.8)	0 (0.0)	0 (0.0)	24 (51,1)	24 (51,1)
Prior lines of treatment								
Median (range)	1 (0, 5)	3 (1, 4)	1 (1, 4)	3 (1, 5)	1.5 (1, 2)	3.5 (3, 4)	1 (0, 5)	3 (1, 5)
Radiation pretreatment (%)	4 (8.5)	5 (10.6)	3 (6.4)	5 (10.6)	1 (2.1)	0 (0.0)	8 (17.0)	10 (21.3)

Table 1: Patients characteristics.

Two patients diagnosed with HD were treated with chemomobilization and plerixafor and collected a median of 2.41 × 10^6 CD34+ cells/kg BW (range 2.01-2.8). Although both patients reached the defined minimum in two aphereses after receiving 2 doses of plerixafor, one patient declined to receive high-dose therapy and transplantation.

In total, 74.47% (35/47) of proven poor mobilizers in group B reached the defined minimum of CD34+ cells after a mobilization regimen containing plerixafor. Thirty-two of them (91.4%) underwent transplantation. Two patients with a poor performance status declined high-dose chemotherapy and transplantation and received best supportive care; one patient died from high dose chemotherapy.

In the CUP, engraftment of White Blood Cells (WBC) was defined as a WBC count of > 1.0 × 10^9/l following autologous stem cell transplantation. Measurement of more than 20 × 10^9/l platelets without transfusions was defined as platelet engraftment. In group A of NHL patients WBC engraftment could be observed after a median of 9 days (range 7-15 days) and in group B after a median of 12 days (range 7-14) (P = 0.042). Platelets recovered after a median of 10 days (range 7-15) in group A and after a median of 13 days (range 8-36) in group B (P = 0.023), respectively. WBC of patients diagnosed with MM recovered after a median of 11 days (range 6-13) in group A and after a median 13.5 days (range 10-27) in group B (P = 0.02). Platelet recovery in group A occurred after a median of 10 days (range 6-11) and in group B after a median of 18 days (13- 24) (P < 0.0001).

The most common side effects in patients receiving plerixafor were gastro-intestinal disorders and exhaustion observed in three patients, followed by dyspnea, sweating and injection side pain observed in one patient. All adverse events were mild and manageable.

Overall, the rate of mobilization failure in patients of group A (first mobilization without plerixafor) was 4.25% (2/47). Poor mobilizers receiving plerixafor (group B) had a mobilization success of 74.47% (35/47). Results are shown in table 2.

Discussion

Several major findings emerge from this analysis: 1) In Hodgkin lymphoma and multiple myeloma patients, the rate of failed mobilization is rare; 2) Patients with non-Hodgkin lymphoma have a higher rate of failed mobilization; 3) In those patients mobilizing poorly, plerixafor is effective in three-fourth of patients for rescue mobilization; 4) The second mobilization attempt is less effective in non-Hodgkin lymphoma patients 5) Recovery of WBC and platelets takes significantly longer in patients being considered as poor-mobilizers.

High-dose chemotherapy followed by autologous stem cell transplantation represents the standard of care for patients suffering from relapsed lymphoma and newly diagnosed multiple myeloma. Successful mobilization of hematopoietic stem cells is the essential precondition for this procedure. Therefore, most patients who mobilize poorly cannot benefit from it and are likely to have an inferior prognosis.

In 1998, Desikan et al., compared the mobilization success of 44 patients diagnosed with multiple myeloma in a randomized fashion. One group received a mobilization regimen with cytokines and cyclophosphamide, the other group received G-CSF alone. Failure rates were 18% in the chemomobilization group and 23% in the cytokines group, respectively. Although patients receiving cyclophosphamide yielded greater CD34 cell quantities, median recovery times following transplantation were similar in both groups [21].

In a large, retrospective evaluation, Pusic et al., compared the records of 1040 patients (502 NHL, 137 HD, 401 MM) of which 976 received G-CSF and 64 a combination of chemotherapy and G-CSF. Although the median CD34+ cell yield was higher in the group of chemomobilized patients than in the cytokine-mobilized group, the failure rates were comparable: 18.6% versus 18.8%. Two-hundred-sixty-nine patients received a remobilization attempt with G-CSF or GM-CSF alone or combined with chemotherapy and/or plerixafor. Failure rates in remobilization showed a significant difference between the remobilization regimens: G-CSF and/or GM-CSF 81.6%, chemomobilization 73.5% and G-CSF with plerixafor 27.8% (P < 0.001), respectively [7].

NHL	Cytokines		Chemomobilization		Total	
	Group A	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
N (%)	4 (8.51)	4 (8.51)	24 (51.06)	24 (51.06)	28 (59.57)	28 (59.57)
No of apheresis sessions						
Median (range)	1 (1, 1)	2,5 (1, 3)	1 (1, 3)	2 (0, 3)	1 (1, 3)	2 (0, 3)
CD34+ prior to apheresis in PB (/µl)						
Median	85.1	22.75	54.93	13.95	58	14.5
Min, Max	40.9, 224	22.5, 23	9.8, 442	3, 47	9.8, 442	3, 47
CD34+ cell yield (× 10^6/kg BW)						
Median	6.67	2.09	5.08	2.29	5.08	2.21
Min, Max	3.6, 11.2	1.6, 3.7	1.1, 41.4	0, 8.77	1.1, 41.4	0, 8.77
Transplanted (%)	4 (8.51)	3 (6.38)	22 (46.81)	13 (21.67)	26 (55.32)	16 (26.67)
Engraftmet of leucocytes (days) > 1,0 × 10^9/l						
Median (range)	8.5 (8, 15)	12 (12, 12)	9 (7, 13)	11 (7, 14)	9 (7, 15)	12 (7, 14)
Engraftment of thrombcytes (days) > 20 × 10^9/l						
Median (range)	9.5 (9, 15)	13 (13, 14)	10 (7, 14)	13 (8, 36)	10 (7, 15)	13 (8, 36)
MM	**Cytokines**		**Chemomobilization**		**Total**	
	Group A	Group B	Group A	Group B	Group A	Group B
N (%)	3 (6.38)	3 (6.38)	14 (29.79)	14 (29.79)	17 (36.17)	17 (36.17)
No of apheresis sessions						
Median (range)	2 (1, 3)	2 (2, 2)	2 (1, 4)	2 (0, 5)	2 (1, 4)	2 (0, 5)
CD34+ prior to apheresis in PB (/µl)						
Median	89	50.2	28.35	16	33.39	26.5
Min, Max	26.6, 179.8	50.2 , 50.2	11.8, 274.5	4, 68.85	11.84, 274.48	4, 68.85
CD34+ cell yield (× 10^6/kg BW)						
Median	5.71	5.43	6.15	4.94	5.96	5.38
Min, Max	4.9, 8.6	4.4, 8.7	2.6, 13.0	0, 10.98	2.6, 13.0	0, 10.98
Transplanted (%)	3 (6.38)	3 (6.38)	14 (29.79)	12 (25.53)	17 (36.17)	15 (31.91)
Engraftmet of leucocytes (days) > 1,0 × 10^9/l						
Median (range)	11 (10, 12)	14 (12, 17)	11 (6, 13)	13,5 (10, 27)	11 (6, 13)	13 (10, 27)
Engraftment of thrombcytes (days) > 20 × 10^9/l						
Median (range)	10 (10, 11)	18 (15, 22)	10 (6, 11)	18 (13, 24)	10 (6, 11)	18 (13, 24)
Hodgkin Lymphoma	**Cytokines**		**Chemomobilization**		**Total**	
	Group A	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
N (%)	0 (0.0)	0 (0.0)	2 (4.26)	2 (4.26)	2 (4.26)	2 (4.26)
No of apheresis sessions	0	0				
Median (range)	0, 0	0, 0	1 (1, 1)	2 (2, 2)	1 (1, 1)	2 (2, 2)
CD34+ prior to apheresis in PB (/µl)						
Median	0	0	115	8.6	115	8.6
Min, Max	0	0	106, 124	8.6, 8.6	106, 124	8.6, 8.6
CD34+ cell yield (× 10^6/kg BW)						
Median	0	0	6.44	2.41	6.44	2.41
Min, Max	0	0	5.6, 7.3	2.01, 2.8	5.6, 7.3	2.01, 2.8
Transplanted (%)	0 (0.0)	0 (0.0)	2 (4.26)	1 (2.13)	2 (4.26)	1 (2.13)
Engraftmet of leucocytes (days) > 1,0 × 10^9/l						
Median (range)	0 (0.0)	0 (0.0)	9.5 (9, 10)	0 (0, 0)	9.5 (9, 10)	0 (0, 0)
Engraftment of thrombcytes (days) > 20 × 10^9/l						
Median (range)	0 (0.0)	0 (0.0)	9.5 (9, 10)	0 (0, 0)	9.5 (9, 10)	0 (0, 0)

Table 2: Results of rate of mobilization.

Ozkurt et al., [22] evaluated the effectiveness of various mobilization regimens to determine risk factors for poor mobilization and reported an overall failure rate of 11.8% in a total of 118 patients including 21 diagnosed with NHL, 56 with MM and 35 with HD. Patients diagnosed with NHL and HD were analyzed together. Failure rates were higher in patients diagnosed with lymphoma (12/56) than in patients diagnosed with MM (1/56) ($P < 0.001$) and in patients receiving "steady-state" mobilization with G-CSF alone (5/15) ($P = 0.01$).

In 2008 Calandra et al., [23] evaluated plerixafor in 115 patients within the AMD3100 compassionate use program. The overall mobilization success was >66%; similar to our analysis, mobilization success of patients diagnosed with MM (75%) was higher than in NHL (65,5%). Median time to WBC engraftment post-transplant was 11 days and median time to PLT engraftment was 18 days. Although median time to WBC engraftment were similar in NHL and MM patients, PLT engraftment was observed earlier in patients diagnosed with NHL (median 18 days) than in patients diagnosed NHL (median 21 days).

Compassionate use data from the United Kingdom and Spain published by Duarte et al., in 2011 showed an overall mobilization success of 75% (42/56 patients). Thirty-five patients underwent autologous stem cell transplantation. In contrast to other publications, there were no differences in WBC or PLT engraftment between NHL and MM patients [24].

The results of our analysis emphasize that modern mobilization regimens using G-CSF alone or in combination with chemotherapy are effective in the vast majority of patients. Although some algorithms predicting poor mobilization in patients with delayed hematopoietic recovery after mobilization with chemotherapy and G-CSF or insufficient increase of CD34+ cells in peripheral blood encourage the preemptive use of plerixafor [25,26], the low rate of mobilization failure in our cohort as well as in other publications [6,27] do not support the use of plerixafor in first-line mobilization. However, plerixafor is a very valuable option for poor mobilizers, allowing the majority of these patients to proceed to autologous stem cell transplantation and thus benefit from high-dose chemotherapy. This is further supported by the lack of relevant toxicity of plerixafor and safe engraftment following transplantation.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to the manuscript.

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