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Original Article

Preemptive and Upfront Plerixafor: Safe and Effective Strategy for Patients Undergoing Autologous Stem Cell Transplant and at High Risk for Mobilization Failure

Abstract

Introduction: Approximately 10%–30% of patients are unable to collect the minimum number of stem cells to support high-dose chemotherapy and autologous stem cell transplant (hematopoietic stem cell transplantation). Plerixafor alone or in combination with granulocyte colony-stimulating factor (G-CSF) has been shown to significantly increase the CD34 cell collection, especially in patients who failed their initial harvest strategy. This is a retrospective study of 17 preselected patients (relapsed lymphoma and myeloma), who were considered to have high risk of mobilization failure and who had undergone upfront and preemptive plerixafor mobilization. **Patients and Methods:** The mobilization protocol consisted of G-CSF (10–15 μg/kg) subcutaneously daily for 4 days before the initiation of plerixafor on evening of day 4. The patients then underwent apheresis on day 5. **Results:** Among 17 patients who underwent apheresis, 16 (93%) yielded the minimum required cell collection of ≥2 × 106 CD34+ cells/kg in a single apheresis session (2 days). Out of these 16 patients, 8 (53%) patients achieved the minimum target dose in a single day. Eight (50%) of all patients achieved the optimum target cell collection in a single apheresis session. Out of these eight patients, five (62%) patients collected optimum yield in a single day. **Conclusion:** Plerixafor is safe and effective if used upfront and preemptively for patients in whom mobilization of stem cells is considered to be a problem.

Keywords: *Autologous stem cell transplant, plerixafor, preemptive upfront*

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Introduction

Autologous hematopoietic stem cell transplantation (HSCT) after high-dose chemotherapy is the standard treatment for patients with relapsed non-Hodgkin's lymphoma (NHL) and myeloma.[1,2] The success of transplant depends on the number of hematopoietic stem cells collected.

Approximately 10%–30% of patients are unable to collect the minimum number of stem cells, defined as 2×10^6 CD34 cells/kg, to support high-dose chemotherapy and autologous HSCT.[3] Plerixafor (AMD3100) reversibly inhibits chemokine stromal cell-derived factor-1 binding to its cognate receptor CXC chemokine receptor 4. Plerixafor alone or in combination with granulocyte colony-stimulating factor (G-CSF) has been reported in various clinical studies (Phase 2), to significantly increase the number of peripheral blood (PB) CD34 cells and CD34 cell collection, especially in patients who failed their initial harvest strategy.[4]

Two subsequent large Phase III trials of upfront plerixafor plus G-CSF (P + G-CSF) mobilization confirmed that the combination was associated with higher CD34 cell yields, better achievement of collection targets, lower failure rates, and fewer apheresis sessions compared with G-CSF alone.[5-9]

This is a retrospective study of 17 preselected patients (relapsed lymphoma and myeloma after first best response), who were considered to have high risk of mobilization failure and who had undergone upfront and preemptive plerixafor.

Study Design and Patients and Methods

Eligibility and exclusion criteria

This is a retrospective study of 17 preselected patients (relapsed lymphoma

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and myeloma after initial best response) considered high risk for failed mobilization and who had undergone transplant postplerixafor mobilization at a single tertiary care center.

The mobilization protocol consisted of G-CSF (10–15 μg/kg) subcutaneously daily for 4 days before the initiation of plerixafor. Plerixafor (0.24 mg/kg, *Mozobil*) was then administered subcutaneously on the evening of day 4. Patients underwent apheresis on day 5 approximately 10–11 h after the dose of plerixafor. Plerixafor, G-CSF, and apheresis were continued for up to until ≥2 × 10^6 CD34+ (or whatever was considered to be optimal) cells had been collected.

The study was approved by the hospital ethical committee.

Study objectives

The primary study objective was to assess the efficacy of plerixafor and G-CSF as a mobilization regimen, as measured by the number of patients having minimum (≥2 × 10^6 CD34+ cells/kg) and optimum (≥5 × 10^6 CD34+ cells/kg for NHL and Hodgkin's disease or ≥6 × 10^6 CD34+ cells/kg for multiple myeloma [MM]), and the number of days required to do so. Secondary objectives were to assess the clinical effectiveness of plerixafor and G-CSF-mobilized stem cells by examining hematopoietic cell engraftment and graft durability and confirm the safety of mobilization and survival.

Statistical methods

Categorical variables were summarized as frequency counts and continuous variables as mean or median. Survival was calculated using the Kaplan–Meier Survival method. IBM statistical package for windows version 24, Armonk, New York, USA was used for all the analyses.

Results

Demographic characteristics

A total of 17 patients were given plerixafor. The demographics of patients included in the study are shown in Table 1. The risk factors predicting failed mobilization are given in Table 2. Eight (50%) patients had myeloma and nine patients (50%) had lymphoma.

Mobilization

Among 17 patients who underwent apheresis, 16 (93%) yielded the minimum required cell collection of ≥2 × 10^6 CD34+ cells/kg in a single apheresis session (2 days). According to the disease status, eight (87%) patients within the NHL group and eight (100%) patients within the MM group yielded the minimum target cell collection. Out of these 16 patients, 8 (53%) patients achieved the minimum target dose in a single day.

Eight (50%) of all patients achieved the optimum target cell collection (i.e., ≥5 × 10^6 CD34+ cells/kg for lymphoma or ≥6 × 10^6 CD34+ cells/kg for MM) in a single apheresis session. According to disease status, two (25%) patients within the lymphoma group and six (75%) patients within the MM group achieved the optimum target cell collection. Out of these eight patients, five (62%) patients collected optimum yield in a single day. The median total number of all CD34+ cells collected over 2 days was 3.4 × 10^6 CD34+ cells/kg (range: 1.5–16 cells/kg), [Table 3].

Table 1: Demographic characteristics of patients (*n*=17)

Demographic profile	Number (%)
Age	
Myeloma	57 (42-63)
Lymphoma	36 (14-58)
Gender: Male, *n* (%)	
Myeloma	4 (50)
Lymphoma	5 (62)
Diagnosis, *n* (%)	
Myeloma	8 (50)
Lymphoma	9 (50)
Conditioning regime, *n* (%)	
BACE	3 (25)
LACE	5 (62)
BEAM	1 (12)
Melphalan (myeloma)	8 (100)

B – Carmustine; A – Cytosine arabinoside; E – Etoposide; C – Cyclophosphamide; M – Melphalan; L – Lomustine

Only one patient did not yield adequate number of cells in one session of apheresis. He was a case of heavily pretreated transformed lymphoma. However, we could get optimal yield in second session which was carried out after 10 days. The median number of days of apheresis for minimal collection (2 × 10^6 cells/kg) was 2 days for lymphoma 1.5 days for myeloma.

Transplantation and engraftment

Thirteen (86%) of the 17 patients who underwent transplantation achieved neutrophil engraftment and 9 (60%) of 17 patients achieved platelet engraftment within 15 days of transplantation. The median times to neutrophil and platelet engraftment were 11 days (range: 8–15, one patient did not engraft and expired) and 12 days (range: 10–29, four patients did not engraft till the day + 15, and one patient expired), respectively.

One hundred percent of patients received G-CSF posttransplantation. Six patients had completed 100-day follow-up in myeloma, and the progression-free and overall survivals were 100% for myeloma. Seven patients (one expired) had completed 100-day follow-up in lymphoma, and progression-free survival was 75% and overall survival was 87%.

Discussion

PB stem cell collection is the standard of care at present. Factors predicting mobilization practices take into

Table 2: Poor mobilizing factors for the patients undergoing mobilization with plerixafor

	Myeloma (*n*=8)	Lymphoma (*n*=9)
Age (years), median (range)	57 (47-63)	36 (14-58)
Prior chemotherapy regimen >2, *n* (%)	2 (25)	2 (25)
Number of cumulative prior chemotherapy cycles >10, *n* (%)	3 (37)	8 (100)
Number of patients with prior lenalidomide treatment, *n* (%)	4 (50)	0
Number of patients with prior radiotherapy, *n* (%)	2 (25)	2 (25)
Number of patients who had undergone prior auto-HSCT, *n* (%)	1 (12)	0

HSCT – Hematopoietic stem cell transplantation

Table 3: Efficacy of plerixafor as mobilization agent

	MM (*n*=8)	Lymphoma (*n*=9)
CD34+ cells/kg $\times 10^6$ collected, median (range)	5.5 (1.5-8.8)	2.4 (2-16)
Number of patients yielding minimal cell dose ($\geq 2 \times 10^6$ CD34+ cells/kg), *n* (%)	8 (100)	7 (87)
Days to collect minimal cell dose, median (range)	1.5 (1-3)	2 (1-4)
Number of patients that obtained minimum target in a single day, *n* (%)		8 (53)
Number of patients yielding optimal cell dose ($\geq 5\times 10^6$ NHL and $\geq 6\times 10^6$, MM CD34+ cells/kg), *n* (%)	6 (75)	2 (25)
Number of patients who yielded optimum yield in a single day, *n* (%)		5 (62)

NHL – Non-Hodgkin's lymphoma; MM – Multiple myeloma

consideration the number of chemotherapy cycles given earlier, agents used and type of disease (stage and remission status), age of patient, prior radiation, and lenalidomide pretreatment.[10-12]

The optimal target of 5×10^6 CD34 cells/kg was selected because transplantation with this cell dose is associated with prompt and durable engraftment.[13-15] Increasing the G-CSF does improve on this, but it is still associated with some failure rates.[16] Chemotherapy-based mobilization regimens may further improve mobilization rates further but with added toxicities.[17,18]

Plerixafor is usually used in subgroup of patients having failed mobilization with conventional agents such as chemomobilization or G-CSF mobilization.[19] These data were analyzed to study the effect of upfront preemptive plerixafor mobilization in a cohort of patients having high chances of mobilization failure.

The number of patients who yielded the optimum target cell collection of $\geq 5 \times 10^6$ CD34+ cells/kg for NHL or $\geq 6 \times 10^6$ CD34+ cells/kg for MM in a median of 2 days of apheresis (one session) by disease group was 2 (25%) for patients with NHL and 6 (75%) for patients with MM. The optimum yield of 5×10^6 CD34 cells in PREDICT study (115 patients, 90 patients with myeloma and 25 with lymphoma) was 80 (89%) in myeloma and 12 (48%) in lymphoma. The optimum yield obtained in our study was lesser than other groups probably because we did our stem cell collection at the end of salvage treatment as compared to earlier collection in other groups.[20]

Peripheral CD34 has been the most important factor in predicting outcomes of mobilization as per other studies.[21] Costa *et al*.[22] used center-specific cost simulation to develop preestablished PB CD34 thresholds at which plerixafor would be added to improve collection efficiency and reduce the cost of mobilization attempts. In future studies, algorithms, using PB CD34 on day 4 of G-CSF, daily yield, and risk factors predicting mobilization failure could be taken into account for deciding on days of plerixafor needed for optimal yield. We could not involve PB CD34 in addition to risk factors for poor mobilization in our approach to preemptive plerixafor, as we do not have in-house CD34 testing (but this is the problem with majority of centers across the country). This along with a small sample size (relatively new strategy) remains a major drawback to the study.

It is worth mentioning that four patients had received prior lenalidomide treatment. All of them achieved minimal yield of 2 × 106 CD34 cells/kg. Three out of four patients (75%) achieved optimal yield of 6 × 106 CD34/kg in a single apheresis session. Overall, prior lenalidomide treatment made no difference to final product yield. Furthermore, at the time of this study, generic plerixafor was not available. There is indeed a huge cost difference between generic (25,000–30,000) and *Mozobil*. (55,000–60,000) Implementing generics in future will certainly further bring down further upon the cost of this approach, which would be significantly lower than an additional apheresis session. Furthermore, the yield reduces with every passing apheresis session (especially in high-risk patients), and this strategy can significantly reduce the chances of mobilization failure, as well as bring down the burden of extra costings and time of an additional apheresis.

Conclusion

Plerixafor is safe and effective if used upfront and preemptively for patients in whom mobilization of stem

cells is considered to be a problem. There is a need to study this strategy in a prospective manner in future.

Authorship contribution: VS, AG and RJ contributed equally, wrote the manuscript, analyzed the data, and designed the study; AG treated patients; RJ mentored paper and treated patients, TS mentored paper and treated patients.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflicts of interest

There are no conflicts of interest.

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