Single Dose Preemptive Plerixafor for Stem Cell Mobilization for ASCT After Lenalidomide Based Therapy in Multiple Myeloma: Impact in Resource Limited Setting

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Abstract Peripheral blood stem cell mobilization with cytokines for autologous stem cell transplant in multiple myeloma is adversely affected by initial induction therapy consisting of either Lenalidomide or cytotoxic drugs, with failure rates of up to 45%. The use of Plerixafor with G-CSF for PBSC mobilisation significantly improves the chances of a successful mobilization. Plerixafor is a costly therapy and increases the overall costs of ASCT which can affect the number of patients being taken up for ASCT in resource limited settings. We prospectively studied the impact of single dose preemptive Plerixafor for PBSC mobilization in patients with prior Lenalidomide exposure. 26 patients who had received Lenalidomide based induction protocol underwent PBSC mobilisation during the study period with G-CSF 10 µg/kg/day SC for 4 days and single dose preemptive Plerixafor 240 µg/kg SC stat 11 h before the scheduled PB stem cell harvest on D5, based on a D4 PB CD34+ counts of <20/µL. A median of 07 cycles of Lenalidomide based combination therapy was used for induction therapy prior to ASCT. 84% patients underwent successful mobilization with one sitting of stem cell

harvest post a single dose of Inj Plerixafor. 7.6% patients failed to mobilise the predefined minimum cell dose of CD34 and could not be taken up for ASCT. The median CD34% of the harvest bag sample was 0.33% (0.1–0.97%). Injection site erythema (34%), paresthesia's (34%) and nausea (30%) were the commonest adverse events reported post Inj Plerixafor. We did a real-world cost analysis for a resource limited setting for PBSC mobilization and found significant cost savings for the preemptive Plerixafor group.

Keywords Myeloma · Autologous · Plerixafor · Stem cell mobilisation

Introduction

Lenalidomide based induction therapy is the preferred initial therapy in newly diagnosed patients of Multiple Myeloma (MM) due to the high activity of this drug. Autologous Stem cell transplant (ASCT) continues to be the standard of care in the management of young patients with Multiple Myeloma post induction with triple drug therapy [1]. Lenalidomide based induction therapy has been associated with decreased rates of stem cell mobilization with steady state G-CSF based mobilization protocols with various studies reporting failure rates from 7 to 45% [2, 3]. Lenalidomide is myelosuppressive and alters the stromal milieu thereby suppressing stem cell mobilization [3]. Plerixafor with G-CSF has been shown to improve successful stem cell mobilization rates in patients receiving Lenalidomide based induction therapy [1, 2]. The addition of Plerixafor after failure of stem cell mobilization with G-CSF alone and an increased number of Peripheral Blood (PB) stem cell harvest days are two factors which

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increase the in-hospital stay of the patients and increases the costs and morbidity related to the mobilization procedure. Also, it has been shown that the use of Plerixafor for remobilization in patients who have failed prior mobilization with steady state G-CSF or chemotherapy based G-CSF protocols is associated with lesser efficacy and more number of required doses of Plerixafor [1, 4]. High cost of the drug and its adverse effects preclude the upfront use of the drug in all patients undergoing peripheral blood stem cell mobilization for ASCT in MM, especially in the resource limited setting.

The American Society of Bone Marrow Transplantation (ASBMT) consensus guidelines recommends that the goals of mobilization should be to reduce the overall failure rates to <5% so as to minimize mobilization-related complications and to optimize resource utilization [5]. High risk of failure of mobilisation of minimum dose of stem cell ($2 \times 10^6/\text{Kg}$) can be predicted by the peripheral blood CD34 count of <20/uL on D4 of G-CSF mobilization, who have been considered as poor mobilisers. Preemptive Plerixafor in poor mobilizers with PB D4 CD34+ counts of <20/uL improves the likelihood of minimum and optimum stem cell collection [6]. Therefore, it is imperative to optimize the use of Plerixafor for maximum benefits in terms of success of stem cell mobilization, especially in our resource limited settings. However, the right cutoff value for intervention with Plerixafor remains controversial in studies and practice [7–10].

We prospectively studied the impact of single dose preemptive Plerixafor in patients undergoing Autologous Stem Cell Transplantation (ASCT) post Lenalidomide based induction therapy with high risk of mobilisation failure based on D4 PB CD34⁺ counts <20/ μL .

Patients and Methods

All patients undergoing ASCT for MM after a Lenalidomide based induction therapy were included in the study for the period from Jan 2014 to Jun 2016. A total of 26 patients underwent ASCT during the study period. Patients with previous mobilization failure with steady state G-CSF were excluded from the study. A minimum wash-out period of 4 weeks was mandatory from the last exposure to Lenalidomide or any cytotoxic therapy to stem cell mobilisation. All patients received a standardized protocol of peripheral blood stem cell mobilization with G-CSF with 10 $\mu\text{g}/\text{kg}/\text{day}$ SC for 4 days. On fourth day a PB CD34 count was done. All patients with a PB CD34 count of <20/ μL , which was predictive of a possible stem cell mobilization failure, received a single dose of Injection Plerixafor 240 $\mu\text{g}/\text{kg}$ SC stat 11 h before the scheduled PB stem cell harvest on D5. All patients also received Inj

G-CSF dose on D5 prior to the harvest. The stem cell harvest bag CD34 count was assessed by flow cytometry as per the ISHAGE protocol. Patients not achieving a CD34 count of $2 \times 10^6/\text{kg}$ underwent a harvest for the second time on D6 after a repeat dose of Inj Plerixafor on D5 while G-CSF was continued. The procedure was abandoned beyond D6 if there was unsuccessful mobilization of minimum CD34+ cell dose and no further dose of Plerixafor was given. All adverse reactions related to Inj Plerixafor were monitored for a period of 07 days post the SC dose. All patients achieving the minimum dose of CD34 count of $2 \times 10^6/\text{kg}$ were taken up for ASCT in our BMT unit with High dose Melphalan (HDM) dose of 200 mg/m^2 . Neutrophil and platelet engraftment post HDM were documented with engraftment for neutrophil being taken as an ANC of >500/ μL for 03 consecutive days and platelet engraftment considered at a unsupported platelet count of >20,000/ μL for 07 days.

Results

A total of 26 consecutive patients were included in the study. The demographic profile of patients included in the study, pre-ASCT Lenalidomide based treatment protocols and number of cycles administered are as given in Table 1.

Table 1 Demographics and baseline characteristics of patients undergoing G-CSF + plerixafor mobilization (n = 26)

Median age (range), y	55 (36–69)
Male sex, n (%)	16 (61)
Stage of disease at initial diagnosis, n (%)	
ISS I	4 (15)
ISS II	6 (23)
ISS III	16 (62)
Remission status at enrolment, n (%)	
First CR	7 (27)
First VGPR	6 (23)
First PR	10 (38)
Second PR	3 (12)
Types of combination of chemotherapy prior to enrolment, n (%)	
One	13 (50)
Two	10 (38)
More than two	3 (12)
Prior radiotherapy, n (%)	
Yes	7 (27)
No	19 (73)
Pre ASCT Therapy, n (%)	
VRD	16 (62)
LD	6 (23)
Lenalidomide + cytotoxic chemotherapy	4 (15)

Table 2 Adverse events profile of Plerixafor

Srl No	Adverse event	n (%)
1	Gastrointestinal adverse events	
	a) Diarrhoea	6 (23)
	b) Nausea	8 (30)
	c) Vomiting	4 (15)
2	Fatigue	4 (15)
3	Injection site erythema	9 (34)
4	Musculoskeletal–	
	a) Bone pains	7 (26)
5	Nervous system	
	a) Headache	7 (26)
	b) Paraesthesias	9 (34)

62% patient received VRD based therapy, 23% received Len/Dex protocol and 15% received Lenalidomide with other cytotoxic agent based therapy. The median number of Lenalidomide cycles in combination was 07 (range 5–8). The most commonly used drugs in addition to VRD/LD protocol were lipodoxorubicin, cyclophosphamide and thalidomide. The number of patients in CR, VGPR or stable PR at the time of ASCT was 27, 23 and 50%, respectively. Of the 26 patients, 7.6% ($n = 02$) patients failed to mobilise the predefined minimum cell dose of CD34 and were not taken up for ASCT. 7.6% ($n = 02$) patients required 02 sittings of stem cell mobilization procedure. 84% ($n = 22$) patients underwent successful mobilization with one sitting of stem cell harvest post a single dose of Inj Plerixafor. The median PB TLC prior to harvest was $40,000/\mu\text{L}$ ($13.75 \times 10^3/\mu\text{L}$). The median CD34% of the harvest bag sample was 0.33% (range 0.1–0.97%). The median total MNC and CD34 dose harvested were $4.8 \times 10^8/\text{Kg}$ (range $1.8\text{--}12 \times 10^8/\text{Kg}$) and $5.55 \times 10^6/\text{Kg}$ (range $1.2\text{--}12.97 \times 10^6/\text{Kg}$) respectively. Injection site erythema (34%), paresthesia's (34%) and nausea (30%) were the commonest adverse events reported post Inj Plerixafor. The details of various adverse events are as given in Table 2. The median neutrophil and platelet engraftment days were 10 days (range 8–25 days) and 11 days (range 9–35 days), respectively. There was no transplant related mortality and all patients were discharged by D 21.

Discussion

The reported mobilization failure rate with steady state mobilization with G-CSF ($5\text{--}16 \mu\text{g/kg/day}$) are as high as 38% [11–18] and studies have shown that although chemomobilization (CM) will mobilize more stem cells than G-CSF alone [19–24], the failure rates are similar, thereby

suggesting that CM works best in those already likely to do well. Recent studies have shown mobilization failure rates of around 15% in patients with up-front-treated myeloma without any high risk of failure [25]. Chemomobilisation is also associated with a 7% risk of neutropenic sepsis [26]. Although the recommended stem cell collection target for ASCT in MM is $3\text{--}5 \times 10^6/\text{Kg}$, the minimum recommended stem cell dose is $2 \times 10^6/\text{Kg}$ [5]. The risk factors for failure to mobilize a minimum CD34 cell dose for ASCT in MM patients include advanced age, diabetes, previous radiation therapy or extensive chemotherapy, previous treatment with Lenalidomide or a purine analog, previous mobilization failure, and low preapheresis circulating PB CD34+ cell counts [27–36]. The clinical risk factors has been found to be controversial and measurement of preapheresis CD34+ cells in PB is the most robust and recommended indicator to identify potential poor mobilisers [37, 38].

Plerixafor when combined with G-CSF has changed the scenario of stem cell mobilization in Multiple myeloma and Lymphoma, as demonstrated in two large phase III trials [4, 39]. The PREDICT trial using Plerixafor + G-CSF showed a 98 and 89% success in collecting a minimum and optimum CD34+ cell dose yields, respectively [40]. Plerixafor mobilized PBSCs have a higher proportion of cells in the growth phase, primitive CD34+ 38- progenitor cells and increased expression of VLA-4 and CXCR4 which may be associated with a greater capacity to repopulate the marrow post ASCT as compared to grafts mobilized with G-CSF alone [5].

Lenalidomide based initial therapy has been associated with increased risk of mobilization failure [27, 33, 34, 41]. This negative effect is linked to duration of exposure with the risk being higher in those receiving it for more than 4–6 cycles [28, 33]. The median number of cycles Lenalidomide combination therapy in this study was 07 (range 5–8). The delay in ASCT in the resource limited settings frequently leads to increased duration of induction therapy prior to ASCT and consequently an increased number of Lenalidomide cycles. The ASBMT consensus guidelines recommends a wash out period of 2–4 weeks between the apheresis and last exposure to Lenalidomide and considers G-CSF alone insufficient for mobilization in those with more than 4–6 cycles of Len exposure [5]. Bortezomib has not been considered to impact stem cell yield or mobilization failure rates [42–47], although the review of International Myeloma Foundation 2005-01 trial data showed trends towards slightly higher failure rates and reduced overall collections [48]. With 91.7% successful stem cell mobilisation in patients who had received a Lenalidomide based initial therapy, the use of preemptive Plerixafor was found to effectively negate the negative risk of Lenalidomide on mobilisation failure. However, INM Micallef et al. [1] reported 100% successful frontline

Table 3 PBSC mobilisation costs per patient for poor mobilisers with a median of 3 cycles for G-CSF group versus 01 cycle for G-CSF + Plerixafor group (calculated for a government setting in India based on average costs) (QALY, morbidity have not been considered)

Srl No	Variables	G-CSF* (Cost in rupees)	G-CSF + Plerixafor** (Cost in rupees)
1	Cost of G-CSF (G-CSF@ Rs 1000/- per vial, Plerixafor @ Rs 50,000/- per vial)	9000	9000 + 50,000 = 59,000
2	Additional G-CSF after D5	6000 (6 additional doses)	Nil
3	Apheresis		
	a) Apheresis Kit (@ 12,000/kit)	36,000	12,000
	b) Apheresis consumables @ 5000/session	3000	1000
	c) Apheresis machine costs (@ Rs 5000/- per session)	15,000	5000
	d) SDP support (on D6&D7) (@11,000/SDP)	Rs 22,000/-	Nil
4	Inpatient stay @ Rs 5000 pd (considering admission on D4)	04 days = 20,000	02 days = 10,000
5	IV access (catheter + manpower)	Femoral/ Jugular = 4000 + 1000 = 5000	Nil
6	PB CD34 count by flow cytometry (@ Rs 2000/- per test)	2000 × 3 = 6000	2000
7	Total	Rs. 1,22,000/- (\$1795)	Rs. 89,000/- (\$1308)

* Median of 3 cycles is taken for calculation as mobilization beyond this number is generally not attempted in the Indian setting, ** Median of 01 cycle is taken for calculation

mobilisation of minimum CD34+ cells of $2 \times 10^6/\text{kg}$ with a median of 1 day of apheresis in MM patients previously treated with Lenalidomide. This difference is likely due to the use of cytotoxics in addition to Lenalidomide in some of our cases, a higher median number of Lenalidomide cycles and increased number of types of combination therapies used prior to ASCT (refer Table 3). It is pertinent to mention here that in the PHANTASTIC study 71% of the heavily pretreated patients achieved a CD34 cell dose of $4 \times 10^6/\text{kg}$ after either 1 or 2 apheresis collection with a plerixafor + G-CSF mobilization protocol [49].

There are two strategies for the use of Plerixafor in stem cell mobilization: either upfront as a preemptive strategy or for remobilization following a prior mobilization failure. I Sanchez Ortega et al. [4] have shown that the use of preemptive strategy of Plerixafor is more successful than the remobilization strategy with lesser number of Plerixafor doses that are required and increased CD34 stem cell yield with lesser sessions of stem cell apheresis. The remobilization failure rates reported in a single center series were 82, 74 and 28% for G-CSF, CM and Plerixafor + G-CSF, respectively [11]. However, in the European compassionate program using Plerixafor + G-CSF for remobilization in MM patients previously treated with Lenalidomide, the minimum dose was collected only in 69% patients in a median of 2 days. The mobilization failure rates reported with preemptive Plerixafor and G-CSF is <10% [50–52]. Costa et al. showed that a preemptive and a risk adapted Plerixafor use based on pre-established PB CD34+ thresholds resulted in a significantly lower mobilization failure rates of 2 to 3% [53]. The D4 PB CD34+ cutoff used for preemptive Plerixafor is

varied, with many studies using it at <10/ μL , <15/ μL or <20/ μL [6, 54–56]. Preemptive Plerixafor is therefore economically a better option compared to its use during remobilization. The ASBMT guidelines recommend a similar approach so as to optimize mobilization outcomes [5]. We had used a cut off of <20/ μL for this study and the median D4 PB CD34 was 8/ μL (range 4–16).

Plerixafor is a costly drug and its use beyond a single dose may not be feasible in the resource limited settings. In this study we therefore considered a single dose preemptive strategy in a high risk population of possible poor mobilizers with induction therapy consisting of Lenalidomide. We had a mobilization failure rate of 7.6% which is slightly higher than reported by Costa et al. However, it appears consistent with most of the other studies [50, 52]. Also, the study population consisted of higher exposure to cytotoxics in addition to Lenalidomide. A mobilization failure rate of <10% can be considered satisfactory in this high risk group of patients.

The most common adverse events reported with Plerixafor are gastrointestinal and injection site reactions [57]. In addition to these adverse effects in our study we found 34% patients reported paresthesia's in the limb where Plerixafor had been administered. This was self-limited and resolved spontaneously.

The increase in the number of apheresis sessions in an attempt to achieve the target CD34+ counts is associated with increasing costs and morbidity. It also leads to significant drop outs and withdrawal of consent for ASCT in resource limited settings. DiPersio et al. [57] in their phase III RCT showed that with Plerixafor + G-CSF combined, the median apheresis day was 1 as

compared to 4 with G-CSF alone. In our study 84% patients achieved the minimum CD34+ cell dose in 1 apheresis session, although this was a high risk population. 91.6% patients achieved the minimum cell dose when 02 apheresis sessions were taken into account. Eliminating the need for additional apheresis sessions may improve patients' quality of life, reduce cost, and allow for more efficient use of resources [58]. Shaughnessy et al. [25] have reviewed extensively the pharmacoeconomic evaluation of costs of mobilization with Plerixafor. A comparison of the estimated costs of PBSC harvest in the Indian setting is presented in Table 3. Kumar et al. [33] reported that 7% of patients undergoing mobilization with G-CSF + Plerixafor did not proceed to collection because of low peripheral blood CD34+ cell counts. Vishnu et al. estimated that by adjusting revenue losses incurred when 25% of patients with G-CSF only mobilisation do not proceed to ASCT, pre-emptive Plerixafor provided cost savings of \$19,300 per patient [3, 59]. At the rates of PBSC harvest costs as mentioned in Table 3, the net loss with 25 and 7% patients of G & G + P group respectively (assuming 3 cycles of harvest), as cases of mobilization failures not reaching to ASCT, is Rs.3,050,000/- (\$44,852) and Rs. 1,869,000/- (\$27,485) per 100 patients mobilized, respectively. The use of PB CD34+ count thresholds (of <20/ μ L in this study) likely optimizes the use of Plerixafor in resource limited settings.

Conclusion

The use of single dose Plerixafor as a preemptive strategy for stem cell mobilization in MM patients with prior exposure to either Lenalidomide or other cytotoxic therapy based on D4 PB CD34+ cut off of <20/ μ L, post a wash out period of at least 04 weeks, leads to very high rates of successful mobilization in patients planned for ASCT, thereby optimizing the use of this costly drug in resource limited settings and reducing the need for remobilization or failure to be taken up for ASCT. As the number of apheresis sessions is significantly reduced, the morbidity associated with repeated apheresis is significantly reduced. The in-hospital stay is reduced with reduced number of apheresis sessions and the overall cost-benefit favors the use of this drug in a preemptive manner.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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