Efficacy of Afternoon Plerixafor Administration for Stem Cell Mobilization

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Cynthia El Rahi[1], James Eldin Cox[1], Romelia May[2], George Carrum[3], Gloria Obi Anyadike[4], Audrey Scholoff[4] and Rammurti Kamble[3]

[1]Department of Pharmacy, Houston Methodist Hospital, Houston, TX, USA. [2]Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA. [3]Department of Medicine, Baylor College of Medicine and Houston Methodist Hospital, Houston, TX, USA. [4]Cell and Gene Therapy, Baylor College of Medicine and Houston Methodist Hospital, Houston, TX, USA.

ABSTRACT

BACKGROUND: When used for hematopoietic stem cell mobilization, plerixafor was originally recommended to be administered 11 hours prior to apheresis based on the peak effect of 10 to 14 hours translating into an administration time of 10 to 11 PM. Reports of post-plerixafor anaphylactic reactions mandated labeling change by the Food and Drug Administration with recommendation of monitoring patients after administration. Based on data suggesting sustained plerixafor activity at 18 hours, we changed our administration time to 4 PM at our center.

OBJECTIVE: The objective of this study is to compare the stem cell collection efficiency before and after the practice change at our institution.

METHODS: A retrospective chart review for patients with multiple myeloma, Hodgkin lymphoma, and non-Hodgkin lymphoma who received a plerixafor-containing mobilization regimen was conducted. The primary end point was the percentage of patients achieving the minimal $CD34^+$ cell goal in ⩽2 apheresis days. The secondary end points included the percentage of patients achieving the preferred CD34+ cell goal in ⩽2 apheresis days, days of apheresis, total $CD34^+$ cells Collected, and engraftment time.

RESULTS: A total of 208 patients (4 PM group n = 68, 10 PM group n = 140) with multiple myeloma (n = 112), Hodgkin lymphoma (n = 10), and non-Hodgkin lymphoma (n = 86) were included in the analysis. About 91% and 89% ($P = .804$) of the patients in the 4 and 10 PM groups, respectively, collected minimum cell dose. Preferred $CD34^+$ cell goal was achieved in 57% and 53% of patients in the 4 and 10 PM groups, respectively.

CONCLUSIONS: Late afternoon administration of plerixafor provides efficient stem cell mobilization.

KEYWORDS: Bone marrow transplantation, hematology, oncology

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CORRESPONDING AUTHOR: Cynthia El Rahi, Department of Pharmacy, Houston Methodist Hospital, 6565 Fannin Street, MS DB1-09, Houston, TX 77030, USA.
Email: Celrahi@houstonmethodist.org

Background

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) is a standard treatment for patients with multiple myeloma (MM), Hodgkin lymphoma (HL), and non-HL (NHL).[1–3] Cytokine mobilization with granulocyte colony-stimulating factor (G-CSF—filgrastim, pegfilgrastim) or granulocyte macrophage-CSF (GM-CSF—sargramostim) with or without chemotherapy has been used to mobilize hematopoietic progenitor cells (HPCs).[3–5] Heavily pretreated patients or those receiving external beam radiation run approximately 20% to 25% risk of failing to collect sufficient stem cells.[4] Interaction of the stromal cell–derived factor 1 (SDF-1) expressed on bone marrow stromal cells and the chemokine receptor 4 (CXCR4) expressed on HPCs has been shown to play a major role in retaining $CD34^+$ cells in the bone marrow regulating HPCs migration to the peripheral circulation.[6,7] Plerixafor, a CXCR4 inhibitor, has improved mobilization by inhibiting the binding of SDF-1 and CXCR4 which results in HPCs' migration from the bone marrow to the peripheral blood (PB).[3,8] Plerixafor is indicated in combination with G-CSF for HPCs' mobilization prior to ASCT.[8]

In pharmacodynamic studies of plerixafor in conjunction with G-CSF in healthy volunteers, a sustained elevation in the PB $CD34^+$ count was observed from 4 to 18 hours after plerixafor administration with a peak $CD34^+$ count between 10 and 14 hours.[6] In response to this, the manufacturer initially recommended self-administration of plerixafor approximately 11 hours prior to initiation of apheresis. This translated into a late night administration time of 10 to 11 PM.[8] In June 2013, the Food and Drug Administration (FDA) added language to the safety labeling of the risk of serious hypersensitivity reactions, including anaphylactic-type reactions, and recommended that patients be monitored for 30 to 60 minutes after administration.[9] Following this guidance, continued self-administration of plerixafor at home was no longer possible. Based on pharmacodynamic data suggesting sustained effects of plerixafor at 18 hours, we at the Center for Cell and Gene Therapy changed our practice in July 2013 to administer plerixafor at 4 PM at our outpatient bone marrow

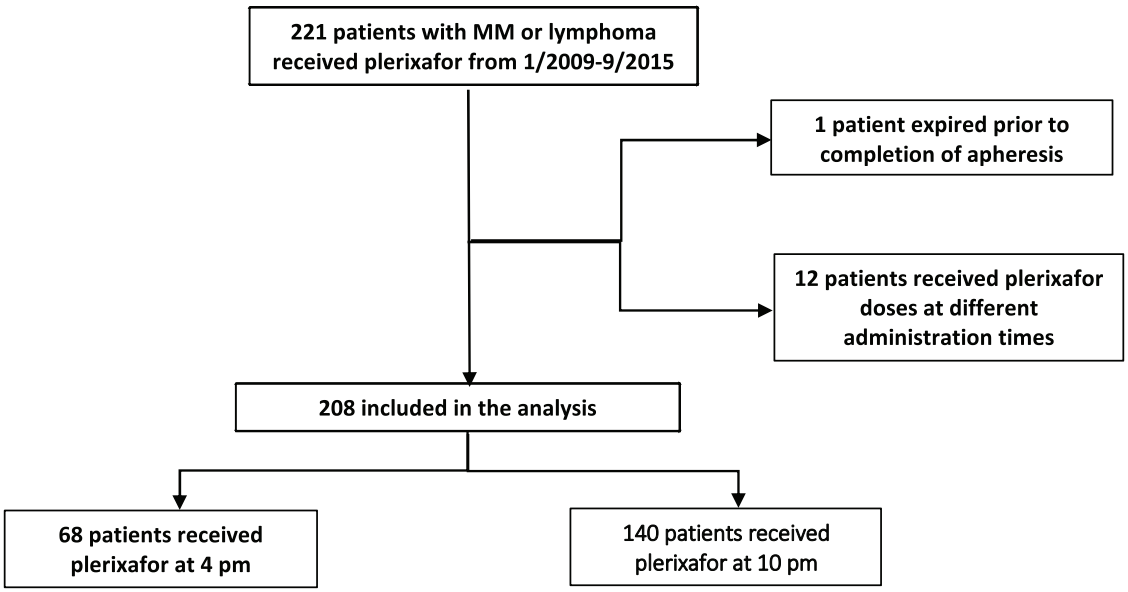

Figure 1. Patients accrual (January 2009-September 2015). MM indicates multiple myeloma.

transplant clinic. To date, there are few studies reporting the efficacy of alternative timing of plerixafor administration.[10–13] We herein report outcomes of 2 different timings of plerixafor dosing from a single institution.

Materials and Methods

Our standard operating procedure (SOP) allows plerixafor administration when day 4 PB CD-34$^+$ cell count with G-CSF alone is less than 10 to 20 cells/μL when G-CSFs are used as the mobilization strategy. In addition, plerixafor can be used at physician's discretion in patients deemed high risk of poor mobilization.[4] To further elaborate, patients with HL, NHL, and MM, planned to undergo a autologous ASCT, are typically started on filgrastim at a dose of 10 μg/kg daily on a Friday with a (PB) CD-34$^+$ level to be checked on Monday morning. Based on the (PB) CD-34$^+$ and patients' risk factors for poor mobilization, decision is made by the treating physician whether to add plerixafor or not prior to proceeding to collection of CD-34$^+$ cells. Collection of CD-34$^+$ is typically started when (PB) CD-34+ reaches more than 10 to 20 cells/μL. Chemotherapy plus G-CSF can be used for mobilization especially in salvage mobilization. Depending on the chemotherapy regimen used for mobilization, G-CSFs are typically started on days 5 to 7 after chemotherapy with plerixafor added after white blood cells' recovery (typically starting day 11) if (PB) CD-34$^+$ cell count with chemotherapy and G-CSF alone is less than 10 to 20 cells/μL. The dose of plerixafor used was initially 0.24 mg/kg when we first started using plerixafor at our institution; however, more recently, we have transitioned to using a fixed dose of 24 mg (vial size) adjusted for kidney function as appropriate. This could have created some dosing variation between patients who received plerixafor soon after it was first marketed when a weight-based approach was more commonly used compared with a fixed 24 mg dose strategy recently. Following approval from the hospital Institutional Review Board, patients with HL, NHL, and MM, who received a plerixafor-containing mobilization regimen, were identified using patients' medical records and cell processing databases.

The primary efficacy end point was the percentage of patients achieving the minimal CD-34$^+$ cell goal (defined as 2×10^6 CD-34$^+$ cells/kg) in ≤2 apheresis days. The secondary efficacy end points were the proportion of patients achieving the preferred CD-34$^+$ cell goal (defined as 5×10^6 CD-34$^+$ cells/kg) in ≤2 apheresis days, the fold increase in PB CD-34$^+$ cells after administration of plerixafor, days of apheresis to achieve minimal and preferred CD-34$^+$ cell goals, total days of apheresis, number of doses of plerixafor administered, total CD-34$^+$ cells collected, and the number of days to neutrophil and platelet engraftment. Neutrophil engraftment was defined as an absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days. Platelet engraftment was defined as platelet count $\geq 20 \times 10^9$/L without a transfusion for the preceding 7 days.

Statistical Analysis

The χ^2 and Fisher exact tests were used to compare the proportion of patients meeting the primary end point between the groups and for categorical data analysis. The Mann-Whitney test was used for numerical data analysis.

Results

A total of 208 patients received plerixafor-facilitated mobilization for ASCT. Of these, 140 patients received plerixafor at 10 PM and 68 received plerixafor at 4 PM (Figure 1). Patients' baseline characteristics, disease- and transplant-related characteristics are reported in Table 1. Risk factors associated with poor mobilization such as advanced age, diagnosis of NHL, numerous cycles of chemotherapy, previous exposure to cytotoxic therapies, lenalidomide therapy (≥5 cycles), previous radiation to the bone marrow, and thrombocytopenia were

Table 1. Baseline characteristics.

	4 PM PLERIXAFOR (N=68)	10 PM PLERIXAFOR (N=140)	*P* VALUE
Median age (range)	62 (24-77)	59 (25-78)	.261
Gender, %			
Female	16 (23)	58 (41)	.007
Male	52 (76)	82 (59)	.007
Cancer type, %			
Hodgkin lymphoma	1 (1)	9 (6)	.171
Multiple myeloma	40 (59)	72 (51)	.312
Non-Hodgkin lymphoma	27 (40)	59 (42)	.737
Current remission state, %			
Complete remission	24 (35)	43 (31)	.512
Partial remission	44 (65)	93 (66)	.807
Refractory disease	0 (0)	2 (1)	1.000
Stable disease	0 (0)	2 (1)	1.000
Apheresis started prior to first dose of plerixafor	23 (34)[a]	31 (22)[b]	.082
Prior chemotherapy lines received, %			
1	42 (62)	72 (51)	.154
2	19 (28)	48 (34)	.348
⩾3	7 (10)	20 (14)	.398
Prior cytotoxic therapy[c], %	62 (91)	124 (86)	.551
Prior lenalidomide therapy, %	30 (44)	54 (39)	.447
⩾5 cycles of lenalidomide	13 (19)	17 (12)	.206
Prior radiation, %	13 (19)[d]	21 (15)[e]	.466
Mobilization strategy in addition to plerixafor, %			
G-CSF	64 (94)	137 (98)	.219
G-CSF plus chemotherapy	4 (6)	3 (2)	.219
Salvage mobilization	4 (6)	13 (9)	.590
Median WBC when mobilization started, k/μL (range)	4.57 (0.1-22.91)	4.86 (0.4-12.96)	.489
Median baseline platelets count, k/μL (range)	172 (25-566)	170 (17-455)	.818

Abbreviations: G-CSF, granulocyte colony-stimulating factor; WBC, white blood cell.
[a]Days of apheresis completed prior to first plerixafor dose: 1 (n=23).
[b]Days of apheresis completed prior to first plerixafor dose: 1 (n=29), 2 (n=2).
[c]Any of the following agents: anthracycline, bortezomib, cyclophosphamide, melphalan, and vincristine.
[d]Radiation location (spine n=7, abdomen n=3, jaw/neck n=2, pelvis n=1, groin n=1).
[e]Radiation location (spine n=5, arm/shoulder n=4, chest n=4, abdomen n=3, mediastinum n=2, pelvis/sacrum n=2, testis n=2, brain n=1, neck n=1, sinus n=1).

comparable between both groups (Table 1). Most of the included patients had a diagnosis of MM followed by NHL and were almost evenly distributed between the 4 and 10 PM plerixafor groups. Most patients were in partial remission at the time of mobilization: 65% and 66% in the 4 and 10 PM groups, respectively. About 62% of the patients in the 4 PM group and 51% of the patients with the 10 PM had received one line of chemotherapy prior to starting mobilization with lenalidomide/dexamethasone (±bortezomib) and RCHOP (rituximab, cyclophosphamide, doxorubicin, and vincristine) being the most commonly used first-line regimen in MM and NHL, respectively. Most of the patients received G-CSF in addition to plerixafor with 4 patients (6%) in 4 PM group and 3 patients (2%) in the 10 PM group receiving G-CSF

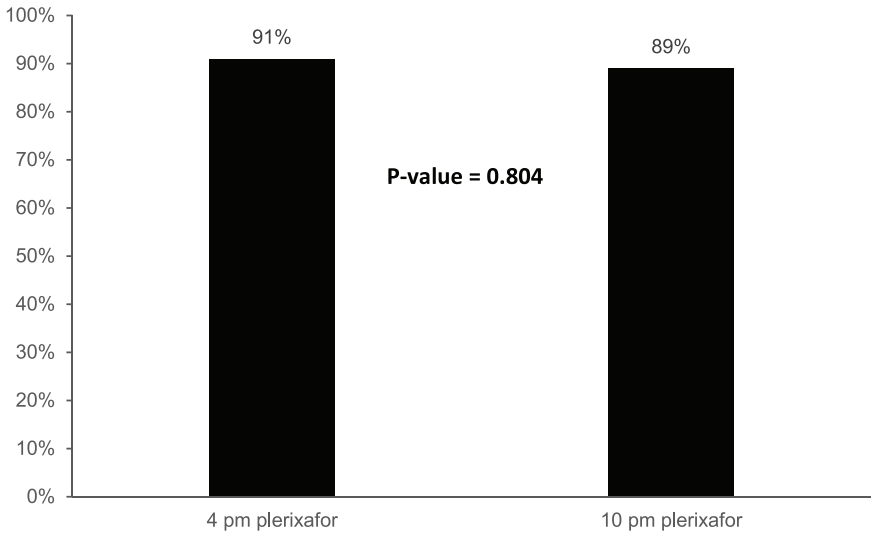

Figure 2. Primary end point.
Percentage of patients achieving minimal (2×10^6 CD34$^+$ cells/kg) CD-34$^+$ cell goal in ⩽2 apheresis days.

Table 2. Secondary end points.

	4 PM PLERIXAFOR (N = 68)	10 PM PLERIXAFOR (N = 140)
Percentage of patients achieving preferred[a] CD-34$^+$ cell goal in ⩽2 apheresis days	39 (57)	74 (53)
Median days of apheresis (range)	2 (0-4)[b]	2 (0-3)[c]
Median peripheral blood, CD-34$^+$ cells/μL (range)		
Pre-plerixafor	10 (1-44)	8 (0-37)[d]
Post-plerixafor	60 (2-240)	42 (1-210)[d]
Ratio post:pre	5.9 (1.9-29.0)	4.9 (1.0-56.0)[e]
Median number of doses of plerixafor administered (range)	1 (1-4)	1 (1-4)
Median total CD34$^+$ cells collected, cells/kg (range)	5.677×10^6 ($0\text{-}17.280 \times 10^6$)	5.34×10^6 ($0\text{-}11.740 \times 10^6$)

[a]5×10^6 CD34$^+$ cells/kg.
[b]One patient did not get apheresis due to low peripheral CD-34 (+).
[c]Three patients did not get apheresis due to low peripheral CD-34 (+).
[d]Three patients were excluded due to unavailable pre-plerixafor peripheral CD-34(+) count.
[e]Pre-plerixafor peripheral CD-34(+) count of 0 were rounded to 1 for ratio calculation (n = 9).

receiving chemotherapy in addition to G-CSF and plerixafor as a mobilization strategy. Five out of these 7 patients receiving chemotherapy were undergoing salvage mobilization with cyclophosphamide being the most commonly used chemotherapy. The percentage of patients achieving the minimal CD-34$^+$ cell goal was 91% and 89% in the 4 and 10 PM group, respectively ($P = .804$, Figure 2). Secondary efficacy end points were comparable between both groups with 57% of patients achieving the preferred CD34$^+$ cell goal in the 4 PM group compared with 53% in the 10 PM group. The fold increase in PB CD-34$^+$ cells after the administration of plerixafor was 5.9 in the 4 PM group compared with 4.9 in the 10 PM group. Patients received a median of 2 days of apheresis and 1 dose of plerixafor in both groups. The median total CD-34$^+$ cells collected was 5.677×10^6cells/kg (range, $0\text{-}17.280 \times 10^6$) in the 4 PM group compared with 5.34×10^6cells/kg (range, $0\text{-}11.740 \times 10^6$) in the 10 PM group (Table 2). The time to achieve the minimal CD-34$^+$ cell goal was comparable between both groups with a median of 1 day in both the 4 PM (range, 1-3) and 10 PM (range, 1-2) groups (Figure 3). This finding demonstrates that most of the patients in the 10 PM group were able to collect the minimum number of stem cells to proceed to transplant after only 1 day of apheresis. Similarly, the time to achieve the preferred CD-34$^+$ cell goal was comparable between both groups with a median of 2 days in the 4 PM (range, 1-4) and 10 PM group (range, 1-3) (Figure 4). In all, 62 of 68 patients in the 4 PM plerixafor group and 114 of 140 patients in the 10 PM plerixafor group underwent ASCT. Median time to engraftment for neutrophils was 14 days and that for platelets was 19 days in both groups. No anaphylactic

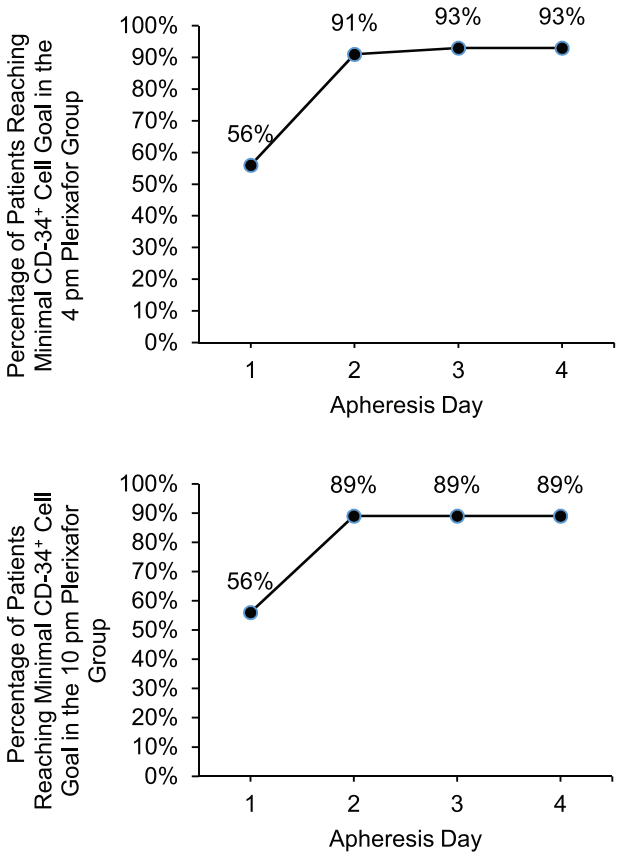

Figure 3. Minimal cell dose outcomes.
Percentage of patients reaching minimal CD-34$^+$ cell goal in function of apheresis days. The median number of days required to reach $\geqslant 2 \times 10^6$ CD34$^+$ cells/kg was 1 day (range, 1-3) in the 4 PM plerixafor group and 1 day (range, 1-2) in the 10 PM plerixafor group (5 patients and 16 patients did not reach minimal CD-34 (+) cell goal in the 4 and 10 PM groups, respectively).

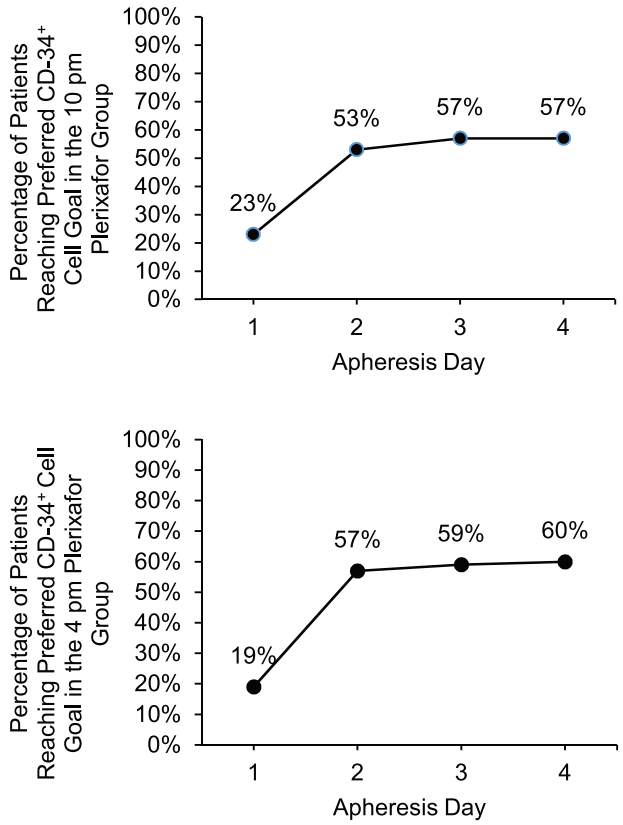

Figure 4. Preferred cell dose outcomes.
Percentage of patients reaching preferred CD-34 (+) cell goal in function of apheresis days. The median number of days required to reach $\geqslant 5 \times 10^6$ CD34$^+$ cells/kg was 2 days (range, 1-4) in the 4 PM plerixafor group and 2 days (range, 1-3) in the 10 PM plerixafor group (27 patients and 60 patients did not reach preferred CD-34 (+) cell goal in the 4 and 10 PM groups, respectively).

reactions were reported in either groups. However, 3 patients reported a plerixafor-related hypersensitivity reaction including face tightness and flushing accompanied with generalized pain (2 patients in the 4 PM group and 1 patient in the 10 PM group).

Discussion

In this study, 4 PM plerixafor administration resulted in comparable stem cell yields compared with the 10 PM administration with 91% of patients achieving at least 2×10^6 CD34+ cells/kg in $\leqslant 2$ apheresis days compared with 89% in the 10 PM group allowing most of the patients to proceed to transplant without affecting the median time to engraftment. In addition, there were no differences in the median number of plerixafor doses administered nor in the number of apheresis days between groups. These results are similar to those previously reported. Harvey et al.[10] reported an increase in the PB CD34$^+$ cell counts at 1, 3, and 17 hours after the first dose of plerixafor in patients who received plerixafor 17 hours prior to their apheresis session. In a study by Tornatta et al.,[11] G-CSF and plerixafor mobilization yielded a median 5.13×10^6 CD34+ cells/kg in a median of 2 apheresis days when plerixafor was administered at 5 PM which is comparable with the efficiency yield in our study. Finally, 47 of the 48 patients collected enough stem cells to proceed to transplant (2×10^6 CD34$^+$ cells) with 5 PM plerixafor administration in a study by Cooper et al.[13] with the minimum number of stem cells to proceed to transplant collected in the first apheresis in most of the patients similar to the results reported in our study.

The results of our analysis should be interpreted with the following limitations in mind. First, our study is a retrospective review and the decision to add plerixafor to a mobilization regimen was in some instances based on physician's discretion. Deviation from our SOP was noted in 14 patients (20%) in the 4 PM group and 11 patients (8%) in the 10 PM with plerixafor administered with pre-plerixafor PB CD-34$^+$ cell count of more 20 cells/μL. It is important to note the wide range of pre-plerixafor PB CD34$^+$ cell count in both the 4 PM (1-44 cells/μL) and the 10 PM (0-37 cells/μL) groups which might reflect that patients had a different risk for mobilization failure that could have affected the stem cell yield. Still, the median pre-plerixafor PB CD34$^+$ was comparable between both groups (10 vs 8 cells/μL in the 4 and 10 PM groups, respectively). It is widely accepted that preemptive addition of plerixafor based on predetermined PB CD34$^+$ cell count thresholds increases collection efficiency and reduces the cost of mobilization attempts; however, other factors can be considered when adding plerixafor such as high-risk baseline characteristics and

early daily apheresis yields when available.[14,15] In addition, other risk factors which can negatively affect stem cell yields were equivalent between groups (Table 1) rendering them less likely to account for a difference in collection yields between both groups. Second, apheresis was started prior to the first dose of plerixafor in 34% of patients in the 4 PM plerixafor group compared with 22% in the 10 PM plerixafor group (Table 1); despite this, pre-plerixafor collection yield was not subtracted from the patient's total collection. Although the percentage of patients starting apheresis prior to plerixafor administration was comparable between both groups ($P = .082$), this should be taken into consideration when analyzing results from our study compared with a controlled study setting where apheresis is usually started after the first dose of plerixafor.[1,2] Third, the approved labeled dose for plerixafor is a weight-based dosing of 0.24 mg/kg for patients weighing more than 83 kg and a weight-based dosing of 0.24 mg/kg or a fixed dose of 20 mg for patients weight less than 83 kg; however, the practice at our institution has changed overtime. We initially used a weight-based approach and more recently have transitioned to using a fixed dose of 24 mg (vial size) adjusted for kidney function as appropriate. This could have created some dosing variation between patients who received plerixafor soon after it was first marketed when a weight-based approach was more commonly used compared with a fixed 24 mg dose strategy recently. Furthermore, this could have led to overweight/obese patients (weighing more than 100 kg) to receive a lower than the FDA-recommended dose. Finally, most of the patients in the 10 PM group self-administered plerixafor at home compared with the 4 PM group where plerixafor was administered in the outpatient clinic by an experienced nurse which could have led to differences in administration techniques.

Conclusions

Late afternoon administration of plerixafor allows efficient stem cell mobilization and provides practical solution when used as part of the mobilization strategy in ASCT.

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Author Contributions

CER, JEC, RM, GC, and RK: Project conception or design and collection, analysis, and/or interpretation of data. CER, JEC, GC, and RK: Drafting the article or revising it critically for important intellectual content. CER, JEC, GC, GOA, AS and RK: Revising the article critically for important intellectual content approval of the version to be published.

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