Addition of plerixafor in poorly mobilized allogeneic stem cell donors

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Abstract

Background: Peripheral blood stem cells (PBSCs) are the predominant graft source for adult allogeneic hematopoietic stem cell transplantation (HSCT). In poorly mobilized autologous donors, plerixafor improves collection outcomes. We examine plerixafor use in allogeneic donors who mobilize poorly with granulocyte colony-stimulating factor (G-CSF) in those who are healthy and those with pre-existing medical conditions, and determine the optimal threshold to add plerixafor.

Study Design/Methods: We retrospectively examined all allogeneic PBSC collections from January 2013 to October 2020 at our center. Donors received G-CSF 10 mcg/kg daily for 4 days before undergoing apheresis collection on day 5. Plerixafor was added based on poor CD34+ cell collection yield after the first or second collection day.

Results: Of the 1008 allogeneic donors, 41 (4.1%) received one dose of plerixafor in addition to G-CSF due to poor collection yield. After starting plerixafor there was a 0.75- to 7.74-fold (median 2.94) increase in CD34+ yield from the previous day. No donors with G-CSF-only mobilization who collected <2.0 x 10^6 CD34+ cells/kg recipient weight on day one achieved the goal of ≥4.0 x 10^6 CD34+ cells/kg recipient weight total over 2 days but 59.2% of donors who used rescue plerixafor did.

Conclusion: Donors both healthy and those with pre-existing disease responded well to plerixafor with minimal side effects. If the first-day collection yield is less than ~63% of the collection goal, addition of plerixafor may be necessary to reach the collection goal and limit the number of collection days in allogeneic donors.

KEYWORDS
plerixafor, stem cell collection

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HSC(s), hematopoietic stem cell(s); HSCT, hematopoietic stem cell transplant; PBSC(s), peripheral blood stem cell(s).
1 | INTRODUCTION

The predominant graft source for adult allogeneic hematopoietic stem cell transplants (HSCT) is peripheral blood.1 Use of granulocyte colony-stimulating factor (G-CSF) is standard of care to mobilize stem cells in donors, however, 2% to 49.2% of allogeneic donors do not reach the target cell dose in one collection.2-7 Plerixafor is a well-known rescue agent in autologous peripheral blood stem cell (PBSC) collection when G-CSF is insufficient to mobilize enough stem cells for transplantation.8 Plerixafor decreases collection days and obviates the need for stem cell collection from the bone marrow. It reversibly binds and blocks the interaction between the chemokine receptor 4 expressed on hematopoietic stem cells (HSC) and the bone marrow stromal cells, therefore resulting in increased release of HSCs from the bone marrow stroma into circulation.8,9 It is approved by the FDA for non-Hodgkin lymphoma and multiple myeloma patients as a HSC mobilization agent, but its use has been extended to patients with other diagnoses including germ cell tumor and Hodgkin lymphoma.10-14 In addition, plerixafor has crossed over for use in allogeneic collections. This has been documented in literature for more than a decade where it has been used as the single mobilization agent or as a rescue agent in donors with sub-optimal mobilization with G-CSF.2,3,15-35

In allogeneic donors there is a 2% to 4.6% collection failure rate (<2.0 × 10^6 CD34+ cells/kg recipient weight collected) using G-CSF alone. Due to the small numbers of allogeneic donors who mobilize poorly, there are only case reports and small studies to support using plerixafor only3,19,30,31 or in combination with G-CSF.2,15,20,22,26,29,32-36 All literature so far on low-yield CD34+ donors mobilized with G-CSF and plerixafor rescue in allogeneic donors have demonstrated increased CD34+ collection yield with plerixafor use.2,15,21,22,26,29,34-36

At our medical center plerixafor has been used as a rescue agent for the past 8 years in allogeneic donors, with increased use in recent years. Our study differs from those studies by including a large concurrent cohort of poorly mobilized allogeneic donors who did not receive plerixafor, which is used to determine the optimal threshold to use rescue plerixafor. In addition, our study includes allogeneic donors with pre-existing medical conditions. This is also the largest case series to date on rescue plerixafor use in poorly mobilized allogeneic donors.

2 | MATERIALS AND METHODS

This study was a retrospective study approved by the Institutional Review Board. We retrospectively examined all allogeneic PBSC collections from January 2013 to October 2020 at our center, and reviewed records on donors who received plerixafor and those who did not receive plerixafor but had more than 1 day of stem cell collection. Donors received G-CSF 10 mcg/kg daily for 4 days before undergoing apheresis collection on day 5. Collections were performed with the mononuclear cell protocol on the COBE Spectra, Optia or Amicus apheresis instruments (COBE Spectra; Terumo BCT, Lakewood, CO; Spectra Optia, Terumo BCT; Amicus; Fresenius Kabi, Bad Homburg, Germany) and 18 to 20 L of blood were processed over 6 h. CD34+ cell yield was determined through standard flow cytometry analysis and calculations. The goal for collection was 4.0 × 10^6 CD34+ cells/kg recipient weight, and a second day of collection ensued if collection yield was less than the goal. If the CD34+ cell collection yield was ≤2.5 × 10^6 CD34+ cells/kg recipient weight after the first collection day, subsequent plerixafor was considered. Plerixafor was given at a dose of 0.24 mg/kg approximately 13 h prior to subsequent collection, and if after one dose of plerixafor the minimum acceptable CD34+ dose for transplant (generally 4.0 × 10^6 CD34+ cells/kg recipient weight) was not reached, a second dose of plerixafor was considered. All donors remained under medical supervision for 30 min after administration of the first dose, and 15 min after the second dose. The maximum number of collection days allowed was 3.

At the physician’s discretion, transplant may still proceed with total ≤4.0 × 10^6 CD34+ cells/kg recipient weight.

3 | RESULTS

Of the 1008 allogeneic donors, 41 (4.1%) received plerixafor in addition to G-CSF due to poor collection yield (<2.5 × 10^6 CD34+ cells/kg recipient weight). Most donors (35) collected for 2 days and received plerixafor before the second day of collection. Six donors collected for 3 days, which includes three donors who received plerixafor after 1 day of collection, and also required a second dose, and three donors who received one dose of plerixafor after two collections, in the evening prior to the third day of collection.

All donors were matched or haploidentical, and related to the recipient. Of those who received plerixafor, the majority of donors were female (65.9%), and the median age of donors was 58 (range: 7-73) with one donor under 18 years old, 8 in the age range of 18 to 40, 17 donors between 41 and 60 years old, and 15 above 60 years old. Most donors (63.4%) had one or more pre-existing health conditions, and the most common diseases were hypertension (22.0%) and hyperlipidemia.
(14.6%) (Table 1). The majority of recipients (78.0%) weighed more than the donors with a median donor weight 88.6% (range: 45.6%-183.0%) of the recipient. Plerixafor was well tolerated in all donors and there were no acute events during the 30- or 15-min observation period immediately after it was given. Mild symptoms of diarrhea, headache, vertigo, and/or nausea and vomiting were reported in 24.4% of donors the following day, none of which required additional medical intervention beyond acetaminophen and loperamide.

The first-day collection yield before plerixafor ranged from 0.19 to 2.38 (median 1.67) \times 10^6 CD34+ cells/kg recipient weight. The collection yield after plerixafor ranged from 1.61 to 7.85 (median 4.36) \times 10^6 CD34+ cells/kg recipient weight, which was statistically significant ($P < .00001$) from pre-plerixafor collection (Figure 1). Using plerixafor every donor was able to collect more than 2.0 \times 10^6 CD34+ cells/kg recipient weight. The collection total ranged from 2.48 to 10.22 (median 5.64) \times 10^6 CD34+ cells/kg recipient weight, and a median of 74.6% (range: 42.9%-92.9%) of total CD34+ cells collected were due to plerixafor. Compared to collection yields prior to starting plerixafor, median fold difference in collection with plerixafor was 2.94 (range: 0.75-7.74), and median absolute change with plerixafor was 2.74 (range: −0.53 to 5.88) \times 10^6 CD34+ cells/kg recipient weight. There were no statistically significant differences between the collection fold and absolute changes among different genders, ages, or pre-existing health conditions which suggests comparable response to plerixafor in older or young donors of both genders, with or without pre-existing health conditions (Table 2).

Donors who started plerixafor the evening of first day of collection and collected for 2 days total yielded a range of 0.40 to 2.38 (mean 1.60) \times 10^6 CD34+ cells/kg recipient weight before plerixafor and after plerixafor collected a range of 1.61 to 7.85 (mean 4.48) \times 10^6 CD34+ cells/kg recipient weight. There was a mean 3.09-fold (range: 0.75-7.13) increase in CD34+ yield from the previous day after plerixafor, and only two donors (4.9%) collected less after plerixafor (2.14-1.61 and 2.22-1.81 \times 10^6 CD34+ cells/kg recipient weight pre and post plerixafor, respectively). Three donors collected for 2 days before plerixafor was started due to day one collection result delay past plerixafor administration time. In these donors, the first-day CD34+ collection yield was <2.0 \times 10^6 CD34+ cells/kg recipient weight.

### Table 1 Donors who received plerixafor: characteristics and CD34+ collections

| Characteristic                              | Median (Range) |
|--------------------------------------------|----------------|
| Median donor age (range)                   | 58 (7-73)      |
| Female                                     | 27 (65.9%)     |
| Common underlying health conditions        |                |
| Hypertension                               | 9 (22.0%)      |
| Hyperlipidemia                             | 6 (14.6%)      |
| Diabetes                                   | 4 (9.8%)       |
| Obesity                                    | 4 (9.8%)       |
| Asthma                                     | 3 (7.3%)       |
| History of cancer                          | 3 (7.3%)       |
| Donors with no underlying health conditions| 15 (36.6%)     |
| Donor weight kg median (range)              | 65 (25-140)    |
| Recipient weight kg median (range)          | 77 (27-164)    |
| Donor weight/recipient weight median (range)| 88.6% (46.5%-183.0%) |
| Total yield median (range) ($\times 10^6$ CD34+ cells/kg recipient weight) | 5.64 (2.48-10.22) |
| % total CD34+ cell yield collected with plerixafor median (range) | 74.6% (42.9-92.9%) |
| Pre-plerixafor CD34+ collection median (range) ($\times 10^6$ CD34+ cells/kg recipient weight) | 1.67 (0.19-2.38) |
| Post-plerixafor CD34+ collection median (range) ($\times 10^6$ CD34+ cells/kg recipient weight) | 4.36 (1.61-7.85) |
| x fold increase after plerixafor median (range) | 2.94 (0.75-7.74) |

![Figure 1](image-url) CD34+ cell collection before and after plerixafor among allogeneic stem cell donors who received plerixafor ($P < .00001$)
kg recipient weight and yield was better on the first day compared to the second day. The CD34+ collection fold increase was calculated relative to second day collection amount. Three donors collected 2 days with plerixafor, two of which had the best CD34+ collection on the first collection day with plerixafor (1.47 and 1.02, 1.8 and 0.87 × 10^6 CD34+ cells/kg recipient weight first and second day of collection with plerixafor, respectively). A third donor collected the most the second day of collection with plerixafor collecting 1.21 and 3.74 × 10^6 CD34+ cells/kg recipient weight on the first and second day with plerixafor, respectively. Fold increase in these three donors was calculated with the first and second day of collection.

All recipients proceeded with transplant except for one due to disease progression. Eleven recipients who continued with transplant expired at the time of writing due to disease progression. There were no engraftment failures among the transplanted recipients. Neutrophil engraftment, defined as absolute neutrophil count greater than 500 cells/μL on the first day of 3 consecutive days was achieved with a median of 15 and mean of 17 ± 3 days, comparable to institutional median and mean of 16 days for related allogeneic PBSC graft recipients (P = .44). Platelet engraftment defined as platelet count greater than 20000 cells/μL on the first day of 7 consecutive days without transfusion support was achieved with a median of 12 and mean of 15 ± 9 days, comparable to institutional median of 14 and mean of 17 days for related allogeneic PBSC graft recipients (P < .05). Platelet and neutrophil engraftment times between grafts from G-CSF only and G-CSF with plerixafor mobilized allogeneic donors were not significantly different.

Review of 96 allogeneic donors who underwent collections over multiple days without plerixafor due to adequate but <4.0 × 10^6 CD34+ cells/kg recipient weight first-day yield, donor or clinician preference, or insurance issues, showed all donors collected for 2 days. The majority (94.8%) had lower collection yields on the second day with a median decrease of 43.0% from first day of collection (P < .00001) (Figure 2). Four (4.2%) donors collected total yield <3.0 × 10^6 CD34+ cells/kg recipient weight and those recipients successfully engrafted. Twenty (20.8%) donors collected ≥3.0 and <4.0 × 10^6 CD34+ cells/kg recipient weight total with all recipients engrafting except for 2. One recipient expired 9 days after transplant from infection precluding full engraftment evaluation. The other recipient had septic shock and acute hypoxic respiratory failure in the days preceding the 3.08 × 10^6 CD34+ cells/kg recipient weight infusion and expired 27 days after transplant.

None of the six donors with G-CSF-only mobilization who collected <2.0 × 10^6 CD34+ cells/kg recipient weight on day one achieved ≥4.0 × 10^6 CD34+ cells/kg recipient weight total over 2 days. In 16 donors who collected ≥2.0 and ≤2.5 × 10^6 CD34+ cells/kg recipient weight on day one, 43.7% were able to collect total yield ≥4.0 × 10^6 CD34+ cells/kg recipient weight. In 21 donors who collected on day one >2.5 and ≤3.0 × 10^6 CD34+ cells/kg recipient weight, 66.7% achieved a total

| TABLE 2 | Comparisons of collection fold increase with plerixafor among donors |
|-----------------------------|-----------------------------|
|                            | Median fold increase (range) | P value   |
| Gender (n)                  |                            |           |
| Male (14)                   | 2.66 (0.75-5.20)           | .07       |
| Female (27)                 | 3.45 (0.82-7.74)           |           |
| Age (n)                     |                            |           |
| <60 years old (24)          | 3.12 (0.75-7.74)           | .32       |
| ≥60 years old (17)          | 2.94 (1.30-4.59)           |           |
| Pre-existing health conditions (n) |                   |           |
| None (15)                   | 3.88 (0.81-7.13)           | .19       |
| ≥1 (26)                     | 2.87 (0.75-7.74)           |           |

FIGURE 2  CD34+ cell collection on day 1 and 2 in allogeneic stem cell donors with 2 collection days using granulocyte colony-stimulating factor (G-CSF) only (P < .00001)
collection yield of $\geq 4 \times 10^6$ CD34$^+$ cells/kg recipient weight. Fifty-one of fifty-three (96%) donors who collected $>3.0$ and $<4.0 \times 10^6$ CD34$^+$ cells/kg recipient weight on day one collected a total of $\geq 4 \times 10^6$ CD34$^+$ cells/kg recipient weight over 2 days.

4 | DISCUSSION

Plerixafor has demonstrated its efficacy in both autologous and allogeneic stem cell donors to improve stem cell collections. Despite its high cost, plerixafor is used in autologous stem cell collection due to improved mobilization; without plerixafor, additional collection days or bone marrow collection is not without its associated costs. Although it is not approved for use in allogeneic donors and can have a long-term effect related to fetal harm, its urgent need may be justified when the already collected stem cell dose is too low to proceed with transplant in a patient who has been conditioned for HSCT. Moreover, plerixafor use can result in higher cell doses for improved engraftment in recipients.

Plerixafor has been shown to be effective and safe as a sole mobilization agent in most healthy donors without established poor mobilization, which can be administered shortly before collection. Four studies showed in 21, 23, 25, and 64 donors the majority collected at least $2.0 \times 10^6$/kg recipient weight with only subcutaneous plerixafor in one collection with some doing additional days of collection to achieve a higher goal. Despite these favorable results, Schroeder et al concluded plerixafor alone did not achieve a better collection result as compared to G-CSF use. The majority of donors experienced grade 1 or 2 toxicities with one study reporting one donor with grade 3 to 4 toxicity. Most commonly reported side effects were bloating, tingling, lightheadedness, nausea, flatulence, injection site discomfort, loose stools, and diarrhea.

Chen et al reported plerixafor mobilized donors experienced significantly less grade 2 to 4 toxicities compared to those mobilized with G-CSF. Despite its favorable toxicity profile over G-CSF, its use is more practical as an add-on salvage agent or as a single agent when there is an urgent need for stem cells.

Plerixafor has also been shown effective as a rescue agent in allogeneic donors initially mobilized with G-CSF. Most of these studies were either small case series with $\leq 10$ subjects or single case reports which showed G-CSF mobilization and rescue plerixafor resulted in increased CD34$^+$ cell yield with successful collections. A couple of studies, one with pediatric donors only, with plerixafor use in evening of day 4 in donors with low peripheral blood CD34$^+$ after 4 days of G-CSF and first-day collection on day 5, showed a significantly increased peripheral CD34$^+$ on day 5. In the approach used in these two studies, it is unknown whether peripheral blood CD34$^+$ on day 4 accurately predicts collection yield on day 5 (and thus necessity of plerixafor use), and there is added donor inconvenience for day 4 peripheral blood CD34$^+$ test. In another study, Teipel et al showed plerixafor 0.24 mg/kg rescue in 35 donors who collected $<2.0 \times 10^6$ CD34$^+$ cells/kg recipient weight after 5 days of G-CSF resulted in increased mobilization of stem cells. This study differs from ours because it focused on cellular composition of mobilized cells rather than donor characteristics and response. Recently Cid et al reported in 30 healthy related donors with initial G-CSF mobilization failure defined as $<4.0 \times 10^6$ CD34$^+$ cells/kg recipient weight demonstrated median fold yield increase of 3.3 following plerixafor. Based on review of concurrent data of our allogeneic donors who did not receive plerixafor but required multiple days of collection, 96% of donors who collect $>3.0$ and $<4.0 \times 10^6$ CD34$^+$ cells/kg recipient weight with G-CSF on day 1 do not need plerixafor for a total yield $\geq 4.0 \times 10^6$ CD34$^+$ cells/kg recipient weight. Höllig et al showed plerixafor in 37 donors who collected $<2.0 \times 10^6$ CD34$^+$ cells/kg recipient weight on day 1 with G-CSF showed median 2.7-fold increase in yield with plerixafor rescue, and found donor age did not significantly affect mobilization response.

Our data show a cutoff of $<2.0 \times 10^6$ CD34$^+$ cells/kg recipient weight for plerixafor leaves 56.3% of donors who collect between 2.0 and 2.5 $\times 10^6$ CD34$^+$ cells/kg recipient weight unable to achieve a collection goal of $\geq 4.0 \times 10^6$ CD34$^+$ cells/kg recipient weight without plerixafor.

To our knowledge, our study is the largest in poorly mobilizing donors in which plerixafor was used as a rescue agent. The overwhelming majority of intended recipients received the plerixafor mobilized graft, and their short-term outcomes as measured in time to reach neutrophil and platelet engraftment milestones were comparable to other recipients of PBSC grafts from related donors at our center. We demonstrate plerixafor is effective in increasing collection yield in allogeneic donors when G-CSF alone is not sufficient and offer additional comparison with those who collected 2 days but did not receive plerixafor. A higher collection day yield was achieved with plerixafor in 39 of 41 donors, and only small decreases in collection yield were seen in two donors after receiving plerixafor. There was no statistical significance among different genders, ages, and pre-existing health conditions to plerixafor response.

Based on data of the decrease between first and second collection in the absence of plerixafor, when the first-day collection yield is less than $\sim 63\%$ of the collection goal or $<2.5 \times 10^6$ CD34$^+$ cells/kg recipient weight when the goal is $\geq 4.0 \times 10^6$ CD34$^+$ cells/kg recipient weight...
weight, addition of plerixafor may be necessary to reach the collection goal and limit the number of collection days. The median 2.94-fold collection yield increase with plerixafor are similar to those reported by Cid et al. in the absence of plerixafor, donors with very low first day yields may need multiple-day collections or bone marrow harvest.

Plerixafor has proven to be an effective mobilization agent in allogeneic stem cell donors and is well tolerated, with most donors experiencing mild to no side effects. Moreover, decreasing the number of collection days may be desirable if the donor must maintain a catheter during collection, has severe side effects to G-CSF or cannot do more than 2 collection days due to availability. Rescue plerixafor can also result in obtaining more stem cells for a higher cell dose and avoid bone marrow collection. In summary, the addition of plerixafor in allogeneic donors with poor collection yields can increase the likelihood of reaching the desired collection goal, while minimizing the number of collection days or the necessity of bone marrow collections. It is well-tolerated and effective in donors across age groups, of both genders, as well as those with pre-existing conditions.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
Data available on request from the authors.

ETHICS STATEMENT
The study obtained ethics approval from City of Hope Institutional Review Board, RB #12080 Study Exempt.

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