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ORIGINAL RESEARCH

Cellular Therapies

TRANSFUSION

Comparison of the efficacy of a generic plerixafor versus Mozobil as adjunct peripheral blood stem cell mobilization agents in multiple myeloma patients

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Abstract

Background: Plerixafor is an adjunct peripheral blood stem cell (PBSC) mobilization agent with well-demonstrated safety and efficacy. The routine use of the originator brand drug (Mozobil) has been limited by cost. This retrospective study was conducted to compare the mobilization efficacy of a lower-cost generic plerixafor and Mozobil in multiple myeloma (MM) patients.

Study Design and Methods: The study included two near-concurrent cohorts of MM patients mobilized with brand ($n = 64$) or generic ($n = 61$) plerixafor in addition to filgrastim. Collection and early engraftment outcomes were compared.

Results: The two cohorts had comparable distributions of sex, age, and weight. Previous treatment histories and proportions of upfront versus just-in-time plerixafor use were similar. There was no significant difference in their median overall cumulative total yield (10^6 CD34+ cells/kg) (brand, 5.91; generic, 5.80; $p = .51$). However, the generic cohort had a significantly higher median yield after the first dose (4.79 vs. 3.78, $p = .03$), and consequently lower median numbers of plerixafor doses ($p = .001$) and collection days ($p = .002$). Only 31.1% of patients in the generic arm required more than one dose versus 59.4% of patients in the brand arm ($p = .006$).

All transplanted patients in the brand and generic arms (90.6% and 85.2% respectively, $p = .42$) achieved engraftment. There was no significant difference in their median times to platelet and neutrophil engraftment, nor their transfusion requirements during the first 30 days post-transplant.

Conclusion: The generic plerixafor produced comparable cumulative collection yields and early engraftment outcomes as Mozobil, but fewer doses and collection days were needed to reach collection goal.

Abbreviations: ASCT, autologous stem cell transplantation; AWP, average wholesale price; G-CSF, granulocyte colony stimulating factor; MM, multiple myeloma; JIT, just-in-time (use of plerixafor); PBCD34+, peripheral blood CD34+ cell(s); PBSC, peripheral blood stem cell; PLT, platelet; RBC, red blood cell; SDF-1, stromal-derived-factor 1.

KEYWORDS
peripheral blood stem cell mobilization, transplant-stem cell

1 | BACKGROUND

The collection of an adequate number of peripheral blood stem cells (PBSCs) is crucial to attaining successful autologous stem cell transplantation (ASCT) outcomes. The minimum dose widely considered necessary to achieve durable engraftment is 2×10^6 CD34+ cells/kg.[1,2] For MM patients, when the aim is to collect enough PBSCs for two ASCTs, the collection target is doubled, and is usually $4–6 \times 10^6$ CD34+ cells/kg for most MM patients at our center. Multiple factors may adversely affect PBSC mobilization, including age, prior radiation, and extended exposure to agents such as daratumumab and lenalidomide, which are commonly used in MM patients.[3,4] Not surprisingly many MM patients have difficulty reaching their collection goal with conventional mobilization regimens using granulocyte colony stimulating factor (G-CSF), or granulocyte macrophage colony stimulating factor (GM-CSF), with or without preceding chemotherapy.

Plerixafor is a newer, adjunct mobilization agent, which can be used in conjunction with conventional mobilization regimens. Mechanistically, it is a reversible CXCR4 inhibitor that enhances stem cell mobilization by interfering with the binding of CXCR4 expressed on stem cells to its ligand, SDF-1 (stromal-derived-factor 1) on marrow stromal cells.[5] Plerixafor, which gained FDA approval for use in MM and NHL patients in 2009 following two Phase III prospective randomized trials,[6,7] was initially exclusively marketed as Mozobil (Sanofi-Aventis, France). The safety and clinical efficacy of Mozobil have been well demonstrated in patients with a variety of diagnoses and in different clinical settings, including as upfront mobilization agent, or as just-in-time (JIT) rescue agent for patients mobilizing poorly with conventional regimens, or as remobilization adjunct agent in patients who have failed previous mobilization attempts.[8–10]

However, the high cost of Mozobil has limited its routine use. In an effort to increase cost-effectiveness, various strategies, and risk-based algorithms have been developed to prioritize its use in patients with demonstrated mobilization failure or risk factors.[11] Of note, in MM patients, due to the higher collection goal, prevalence of risk factors for poor mobilization, and cost savings that can be achieved by reducing the number of apheresis collection days, some studies have shown that the routine administration of upfront plerixafor in addition to G-CSF to all MM patients can be both efficacious and cost-effective.[12–15]

Encouragingly, generic forms of plerixafor have been developed by the pharmaceutical industry and became available first in Asia and Europe, and finally in the United States in 2023 at significantly reduced costs compared to Mozobil (Table 1). In early studies of limited numbers of MM and lymphoma patients, the generic forms of plerixafor offered promising collection outcomes and similar side effect profiles as Mozobil.[16,17] In this study, we aimed to assess if a generic plerixafor has comparable mobilization efficacy as the originator, brand plerixafor (Mozobil) when used in conjunction with G-CSF in MM patients. We evaluated both collection results as well as early post-transplant engraftment outcomes.

2 | METHODS

2.1 | Patient inclusion

This retrospective study and the associated data collection were approved by the City of Hope Institutional Review Board.

Our institutional pharmacy switched from using Mozobil to a generic plerixafor (Meitheal Pharmaceuticals, Chicago, IL) on September 5, 2023. Two near-concurrent

TABLE 1 Comparison of the average wholesale prices (AWPs) of the originator, brand plerixafor (Mozobil) and generic plerixafor by several manufacturers as of June, 2024.

Manufacturer	Average wholesale price (AWP) per 24 mg/1.2 mL vial
Generic plerixafor	
Amneal Pharmaceuticals	$1268.40
Eugia US	$600.00
Dr Reddy's Laboratories	$1440.00
Fresenius Kabi	$2040.00
Meitheal Pharmaceuticals	$600.00
Novadoz Pharmaceuticals	$1315.79
Teva Pharmaceuticals	$1440.00
Zydus Pharmaceuticals	$1440.00
Brand plerixafor (Mozobil®)	
Sanofi-Aventis	$11961.68

cohorts of MM patients mobilized with plerixafor during their initial mobilization and collection attempt were identified from our apheresis database and pharmacy records. This included 64 consecutive patients mobilized with the brand originator in the 14 weeks prior to the switch, and another 61 consecutive patients mobilized with the generic plerixafor in the 11 weeks following the switch. Patient baseline data including age, sex, weight, prior radiation, and chemotherapy treatment histories were recorded.

2.2 | Mobilization and collection

Patients in both cohorts were mobilized with G-CSF (filgrastim) at 10 μg/kg/day for 4 days, brand (Mozobil) or the generic plerixafor was given subcutaneously either upfront in unselected patients in the evening of day 4 prior to starting collection on day 5, or added-on in patients who had been mobilized with G-CSF alone as the just-in-time (JIT) rescue agent in the evening of day 5 due to poor peripheral blood CD34+ cell (PBCD34+) count (<20/μL) and/or collection yield ($<1.75 \times 10^6$ CD34+ cells/kg) from that day. Higher PBCD34+ count or collection yield thresholds may be used for adding JIT plerixafor at the apheresis physician's discretion (e.g., the physician may choose to initiate JIT plerixafor at a higher PBCD34+ count and/or collection yield than those stated above if there is a need to minimize the number of collection days, or shorten the collection procedures, due to poor patient tolerance of the apheresis procedure or scheduling constraints).

Daily plerixafor injections continued until the collection goal was reached at a dose of 0.24 mg/kg, or 0.16 mg/kg for patients with creatine clearance <50 mL/min, or at a capped dose of 24 mg (one single-use vial) in patients who weighed >100 kg to minimize wastage per institutional policy.[18] PBCD34+ count was measured prior to the first collection after the first dose to assess response to plerixafor in both upfront and JIT cases.

In general, apheresis collection proceeded regardless of PBCD34+ counts in patients who had already received a dose of plerixafor, but was not performed if the PBCD34+ count was <20/μL in patients who had not receive plerixafor. PBSC collections were performed using a Spectra Optia (Terumo BCT, Lakewood CO) or Amicus (Fresenius Kabi, Bad Homburg, Germany) apheresis instrument with the aid of the respective software for mononuclear cell collection procedures. Approximately 14–18 L of blood were processed over 5–6 hours. The goal for most patients was to maintain the apheresis flow rate on average around 50 mL/min over the duration of the procedure. However, a slower average rate, which led to lower overall volume processed, was necessary in patients with suboptimal vascular access, small body volume, citrate sensitivity or other issues resulting in poor tolerance of apheresis. CD34+ cell collection yields were determined via standard flow cytometry analyses and calculations.

For single ASCT candidate 2 and 3×10^6 CD34+ cells/kg were the collection minimum and target. For patients who might need a second ASCT the collection minimum and target were 4 and 6×10^6 CD34+ cells/kg, respectively. Collection failure was defined as collecting $<2 \times 10^6$ CD34+ cells/kg.

For patients who proceeded to ASCT, the number of days to engraftment was determined. Neutrophil engraftment was defined as the first day when the absolute neutrophil count exceeded 500×10^6/L for three consecutive days. Platelet (PLT) engraftment was defined as the first day when PLT count exceeded 20×10^9/L for three consecutive days, and no PLT transfusions in the preceding 7 days. In addition, RBC and PLT transfusion data between day 0 and day 30 after transplant were extracted from the blood bank electronic database, and the cumulative numbers of RBC and PLT units transfused were tallied. All RBC and PLT units transfused were leukoreduced and irradiated to a minimum of 25 Gy. All PLT units were single-donor apheresis units. Transfusion thresholds used were defined by institutional guidelines and consistent with AABB and American Society of Clinical Oncology clinical practice guidelines.[19–21]

2.3 | Statistical analyses

Categorical variables between cohorts such as patient demographics, clinical and treatment history were compared using chi-square tests or Fisher exact tests, as appropriate. Continuous variables such as age and collection yields were summarized using medians and ranges and compared using Wilcoxon Rank Sum tests. Time-to-event engraftment data among two cohorts were compared using Wilcoxon-Breslow or Log-rank tests, as appropriate. The proportional hazards assumption was tested graphically using a plot of the log cumulative hazard. A two-tailed P-value <.05 was considered statistically significant. All statistical calculations were performed using Stata SE, version 18.1 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Patient characteristics

The study included two near-concurrent cohorts of consecutive MM patients who underwent first-time PBSC

mobilization with the brand ($n = 64$) or generic ($n = 61$) plerixafor in addition to G-CSF.

Baseline patient characteristics are summarized in Table 2. There was no significant difference between the two cohorts in age, sex, and weight distributions. The two cohorts had comparable previous treatment histories in terms of the proportions of patients who had received radiation therapy prior to mobilization (brand, 14.1%; generic, 9.84%; $p = .59$), and the number of chemotherapy lines received by each patient ($p = .76$).

Similar proportions of patients received 0.24 mg/kg, 0.16 mg/kg or the capped dose (24 mg, or one vial) of plerixafor ($p = .97$) in the brand and generic cohorts. Plerixafor was well tolerated with no severe adverse effects reported in either cohort.

3.2 | PBSC collection outcomes

Collection outcomes are summarized in Table 3. Overall, only 4.69% and 3.28% in the brand and generic cohort failed to collect 2×10^6 CD34+ cells/kg ($p = 1.00$). There were no significant differences in median total collection yield ($\times 10^6$ CD34+ cells/kg) after initiating plerixafor (brand, 5.38; generic, 5.47; $p = .44$) and median overall cumulative total yield, which includes cells collected prior to initiating plerixafor (brand, 5.91; generic, 5.80; $p = .51$).

However, after the first dose of plerixafor, the generic cohort patients had a higher median PBCD34+ count (59.0/μL) compared to brand cohort patients (43.5/μL), and this difference was nearly statistically significant ($p = .055$). Furthermore, generic cohort patients also had a significantly higher median collection yield (4.79×10^6 CD34+ cells/kg) than brand cohort patients (3.78×10^6 CD34+ cells/kg) from the collection after the first dose of plerixafor ($p = .03$).

Consequently, patients in the generic cohort required a median of one dose of plerixafor (interquartile range or IQR: 1–2) versus two doses by patients in the brand arm (IQR: 1–2) to reach the desired collection target ($p = .001$). Only 31.1% of the

TABLE 2 Comparison of the baseline patient characteristics and plerixafor dosing in the brand and generic plerixafor cohorts.

	Brand ($N = 64$)	Generic ($N = 61$)	*P*-value
Male, *N* (%)	42 (65.6%)	37 (60.7%)	.70[a]
Age, median [IQR]	62 [53–67]	64 [60–67]	.30[b]
Weight (kg)			
Median [IQR]	80.5 [66.5–93.3]	87.0 [73.0–101]	.19[b]
Mean (range)	82.0 (41.0–134)	86.9 (48.0–146)	.20[c]
Any previous radiation therapy, *N* (%)	9 (14.1%)	6 (9.84%)	.59[d]
Lines of chemotherapy prior to remission/partial remission			
Median [IQR]	1 [1–2]	1 [1–2]	.76[b]
1 line, *N* (%)	45 (70.3%)	41 (67.2%)	.70[d]
2 lines, *N* (%)	18 (28.1%)	20 (32.8%)	
3 lines, *N* (%)	1 (1.56%)	0 (0%)	
Dosing			
0.24 mg/kg	36 (56.3%)	35 (57.4%)	.97[d]
0.16 mg/kg	18 (28.1%)	16 (26.2%)	
24 mg capped dose	10 (15.6%)	10 (16.45)	
Upfront use of plerixafor, *N* (%)	40 (62.5%)	45 (73.8%)	.25[a]
JIT users of plerixafor, *N* (%)	24 (37.5%)	16 (26.2%)	.25[a]
Median [IQR] PBCD34+ (/μL) before JIT plerixafor	12 [10–19]	17 [11.8–26.0]	.33[b]
Median [IQR] collection yield ($\times 10^6$ CD34+ cells/kg) before JIT plerixafor	1.43 [1.03–2.14]	1.52 [1.07–2.15]	.52[b]

Abbreviations: IQR, interquartile range; JIT, just-in-time; PBCD34+, peripheral blood CD34 cell count.
[a]Chi-square test.
[b]Wilcoxon rank sum test.
[c]Welch two-sample *t*-test.
[d]Fisher's exact test.

TABLE 3 Comparison of the brand and generic plerixafor cohorts in collection yields, number of collection days and plerixafor doses required to reach collection target.

	Brand ($N = 64$)	Generic ($N = 61$)	*P*-value
Post first dose plerixafor peripheral blood CD34 count (/μL), median [IQR]	43.5 [25.0–67.5]	59.0 [32–96]	.055[a]
Post first dose plerixafor yield ($\times 10^6$ CD34+ cells/kg), median [IQR]	3.78 [2.10–5.32]	4.79 [3.32–7.21]	.03[a]
Post-plerixafor total yield ($\times 10^6$ CD34+ cells/kg), median [IQR]	5.38 [3.87–6.72]	5.47 [4.17–7.99]	.44[a]
Cumulative (pre- and post-plerixafor) collection yield ($\times 10^6$ CD34+ cells/kg), median [IQR]	5.91 [4.52–6.97]	5.80 [4.99–8.23]	.51[a]
Failure to collect ≥2.0 × 10^6 CD34+ cells/kg, *N* (%)	3 (4.69%)	2 (3.28%)	1.00[b]
Total no. of collection days, median [IQR]	2 [1–2]	1 [1–2]	.002[a]
1 day, *N* (%)	18 (28.1%)	33 (54.1%)	.02[b]
2 days, *N* (%)	30 (46.9%)	21 (34.4%)	
3 days, *N* (%)	12 (18.8%)	6 (9.84%)	
4 days, *N* (%)	4 (6.25%)	1 (1.64%)	
Total no. of doses required, median [IQR]	2 [1–2]	1 [1–2]	.001[a]
1 dose, *N* (%)	26 (40.6%)	42 (68.9%)	.006[b]
2 doses, *N* (%)	27 (42.2%)	15 (24.6%)	
3 doses, *N* (%)	10 (15.6%)	3 (4.92%)	
4 doses, *N* (%)	1 (1.56%)	1 (1.64%)	

[a]Wilcoxon rank sum test.
[b]Fisher's exact test.

generic arm patients required more than one dose of plerixafor, versus 59.4% of the brand arm ($p = .006$). The median total number of collection days was also one in the generic cohort versus two in the brand cohort ($p = .002$). Only 45.9% of generic arm required more than one collection day versus 71.9% of brand arm, and only 11.5% of generic cohort patients required more than 2 days of collection, versus 25.1% in the brand cohort ($p = .02$) (See Table 3).

In this retrospective study, we found no documentation of serious adverse effects related to either the generic or the originator plerixafor at the time of administration or within 24 hours. All patients tolerated the apheresis procedures well without serious complications.

TABLE 4 Comparison of the short-term engraftment outcomes: Days to platelet or neutrophilic engraftment and transfusion requirements during the first 30 days post-transplant.

	Brand ($N = 58$)	Generic ($N = 52$)	*P*-value
Platelet engraftment			
Time to engraftment (days), median [IQR]	19 [17–20]	17 [16–19]	$P = .08$[a]
Neutrophil engraftment			
Time to engraftment (days), median [IQR]	12 [11–12]	12 [11–12]	$P = .8$[a]
Platelet transfusion within 30 days post-transplant			
Any transfusion (%)	49 (84.5%)	37 (71.2%)	$P = .11$[b]
Among transfused, no. of units, median [IQR]	1 [1–2]	1 [1–2]	$P = .98$[c]
Red blood cell transfusion within 30 days post-transplant			
Any transfusion (%)	10 (17.2%)	13 (25.0%)	$P = .35$[b]
Among transfused, no. og units, median [IQR]	2 [1–2]	1 [1–3]	$P = .99$[c]

[a]Wilcoxon-Breslow test.
[b]Fisher's exact test.
[c]Wilcoxon rank sum test.

3.3 | Engraftment outcomes

At the time of writing, comparable proportions of patients in the brand (90.6%) and generic (85.2%) arms had undergone autologous transplant ($p = .42$), all achieved engraftment (Table 4 and Figure 1A,B). There were no significant differences between the two cohorts in their time to achieve neutrophilic engraftment (12 days for both cohorts, $p = .8$)—or platelet engraftment (brand, 19 days; generic, 17 days; $p = .08$).

During the first 30 days post-transplant, similar percentages of patients in the two cohorts required RBC (brand, 17.2%; generic, 25.0%; $p = .35$) or platelet transfusions (brand, 84.5%; generic, 71.2%; $p = .11$). Among those patients who were transfused, the numbers of RBC or platelets transfused were comparable (Table 4).

3.4 | Subgroup analyses of JIT versus upfront users

The proportions of patients who received plerixafor upfront (versus JIT) were comparable between the two cohorts (brand, 62.5%; generic, 73.8%; $p = .25$). Among

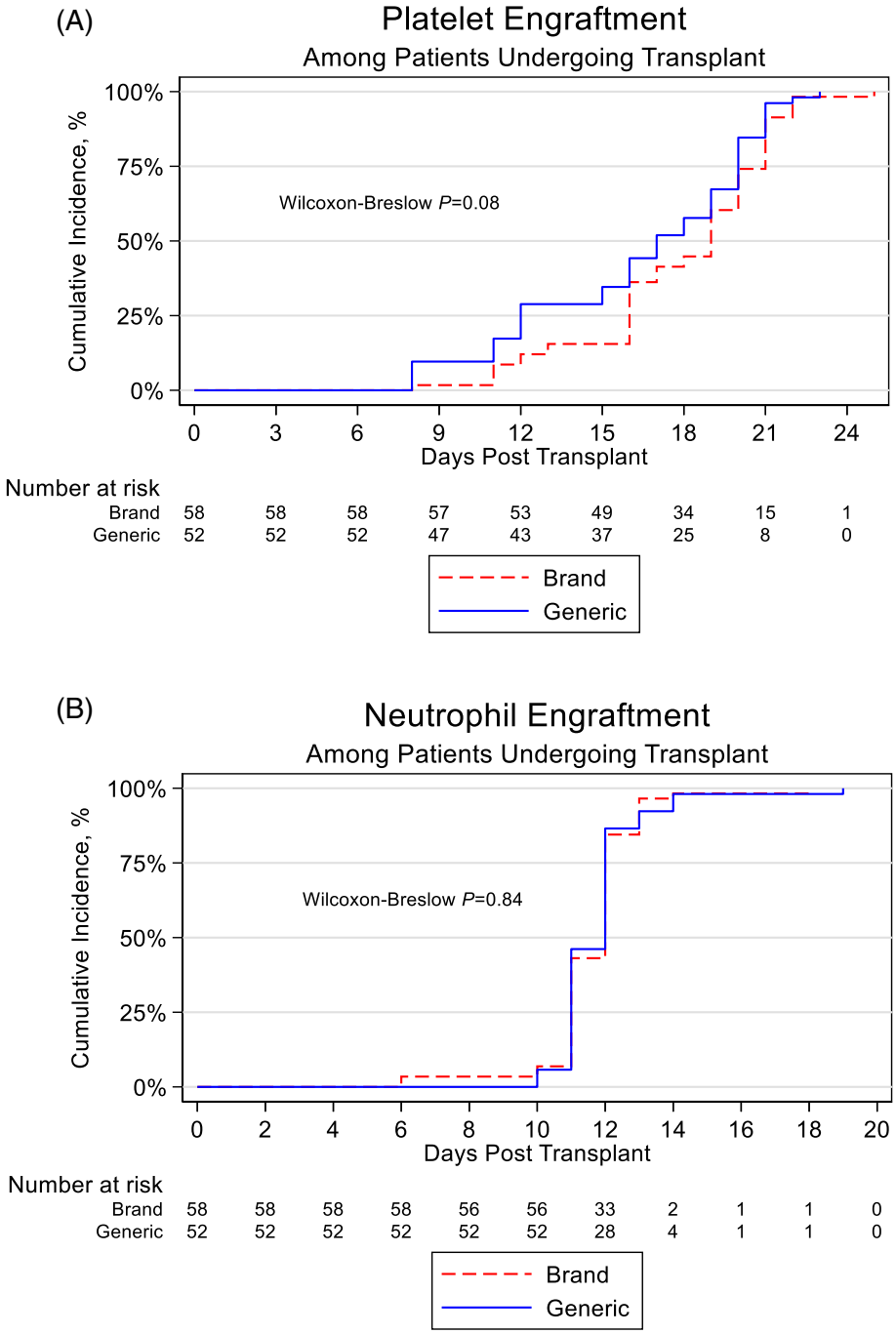

FIGURE 1 Comparison of early post-transplant platelet (A) and neutrophil (B) engraftment. [Color figure can be viewed at wileyonlinelibrary.com]

patients who received JIT plerixafor, the median PBCD34+ count (brand, 12/uL; generic, 17/uL; $p = .33$), and collection yield ($\times 10^6$ CD34+ cells/kg) before the first dose of plerixafor (brand, 1.43; generic, 1.52; $p = .52$) were similar (See Table 2). Additional subgroup analyses also confirmed that generic and brand plerixafor resulted in comparable collection and engraftment outcomes, but required fewer collection days and plerixafor doses, whether in JIT or upfront plerixafor users (See Supplement S1).

4 | DISCUSSION

Inadequate PBSC mobilization is a major barrier to successful ASCT. Plerixafor, marketed as Mozobil since 2009, has been shown as an effective and safe adjunct agent to improve mobilization outcomes. However, the high cost of Mozobil has prohibited its more widespread use, especially in developing countries. The recent availability of much lower-costing generic forms of plerixafor offers the potential to dramatically lower the economic barrier to plerixafor. The average wholesale prices (AWPs) of Mozobil and generic forms of plerixafor by several manufacturers as of June 2024 are shown in Table 1.

In this retrospective observation study, we compared the collection and early transplant outcomes of two near-concurrent cohorts of patients mobilized with either the originator, brand plerixafor (Mozobil) or a generic plerixafor. The cohorts were statistically comparable in age, gender, and weight distributions. Histories of previous radiation therapy and number of lines of chemotherapy, which could impact response to mobilization agents, were also comparable. In addition to patients who received plerixafor upfront, the two cohorts had similar proportions of patients who received plerixafor as the JIT rescue agent due comparably suboptimal pre-plerixafor baseline PBCD34+ counts and collection yields.

While both cohorts had equally successful overall collection outcomes and very similar cumulative collection totals, there was a nearly statistically significant difference of higher PBCD34+ counts following the first dose of generic compared to brand plerixafor (59.0/μL vs. 43.5/μL, $p = .055$). Correspondingly, the first post-plerixafor day median collection yield was significantly higher in patients in the generic cohort (4.79 vs. 3.78 $\times 10^6$ CD34+ cells/kg, $p = .03$). Consequently, the generic cohort required fewer plerixafor doses and collection days than the brand cohort to meet the collection target.

When early post-transplant outcomes were compared, the generic plerixafor also produced outcomes that were at least equal to those associated with Mozobil. All transplanted patients from both cohorts engrafted, had similar RBC and PLT transfusion requirements in the first 30 days post-transplant, and achieved platelet and neutrophil engraftment milestones in similar numbers of days.

Additional subgroup analyses also confirmed that generic and brand plerixafor were equally effective in JIT or upfront plerixafor patients, and resulted in comparable collection and engraftment outcomes, but the usage of generic plerixafor was associated with fewer collection days and plerixafor doses in both JIT or upfront plerixafor subgroups.

Our findings were in alignment with previous smaller studies. One study evaluated 14 MM patients mobilized with Mozobil and 14 with the generic Plerksor (Gen Ilac, France).[16] Another study of 21 patients mobilized with Mozobil and 11 mobilized with the generic Mozifor (Heterfo Drugs Ltd., India),[17] included patients with MM, non-Hodgkin, and Hodkin lymphoma, and therefore fewer than five patients in each diagnosis category received generic plerixafor. Although limited by their small subject numbers, both studies showed comparable collection and early engraftment outcomes.

This study is the largest study to date comparing the efficacy of generic versus brand plerixafor, which provides reassuring data supporting the routine use of generic plerixafor as part of the mobilization regimen for MM patients. Previous studies have already shown that routine, upfront use of Mozobil in all MM patients undergoing PBSC mobilization may compare favorably in cost-effectiveness, relative to restricted use guided by algorithms identifying patients at risk for mobilization failures. In one example, a study comparing 55 MM patients who received Mozobil per algorithm (i.e., due to low pre-apheresis PBCD34+), and 74 patients who received the agent upfront, the upfront group had a lower median number of apheresis days (1.0 vs. 1.5 day, $p < .001$) and higher median number of CD34+ cells collected (8.5 vs. 6.6 $\times 10^6$ cells/kg, $p < .001$) than the per algorithm group. The authors concluded that routine upfront Mozobil usage led to increased drug costs but reduced apheresis collection cost, which resulted in a net savings of $121 per patient in total mobilization costs, even with the high cost of Mozobil at the time of the study.[15] These cost savings can only be significantly increased when generic forms of plerixafor with similar efficacy, but much lower costs are utilized.

Our study was limited by its retrospective nature. The two cohorts were not prospectively randomized concurrent cohorts, but near-concurrent cohorts that were retrospectively found to be statistically comparable in baseline characteristic including demographics and treatment histories. Despite the relatively large and homogeneous

study population, the study only reflected the mobilization and collection experiences at one center. The study was limited to multiple myeloma patients, and its findings may not be fully applicable to patients with other diagnoses or lower collection goals. Additional studies from other centers will help to confirm the efficacy, safety and cost effectiveness of generic plerixafor, and fully define the indications of generic plerixafor in patients with MM and other diagnoses.

In summary, in this single center retrospective study of MM patients, mobilization with the generic plerixafor evaluated produced similar cumulative collection yields and at least comparable early engraftment outcomes as the brand originator Mozobil, but required fewer doses and collection days, whether in JIT or upfront users. Additional studies, including those performed in patients with other diagnoses and lower collection goals may further establish the role of generic plerixafor. Similar studies may also be considered in allogeneic donors, as previous studies have shown that healthy donors could be successfully mobilized with plerixafor as a single agent given shortly before apheresis collection,[22–24] thus greatly increasing donor convenience and availability. Such future studies can lead to the development of streamlined mobilization regimens integrating the use of plerixafor and expanded access to successful autologous and allogeneic stem cell transplantations worldwide.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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