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Research paper

Clinical and cost outcomes of pre-emptive plerixafor administration in patients with multiple myeloma undergoing stem cell mobilization

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ABSTRACT

Purpose: The stem cell mobilization agent plerixafor significantly improves CD34$^+$ stem cell procurement in patients with multiple myeloma undergoing autologous stem cell transplant. We compared mobilization success rates and costs of two regimens of plerixafor administration: pre-emptive (P-PL, initiated the evening prior to the first day of stem cell collection) and standard (S-PL, initiated the evening prior to the second day of stem cell collection in the event of inadequate collection on the first day).

Methods: Patients with multiple myeloma undergoing mobilization were categorized as either P-PL or S-PL. Stem cell collection success was evaluated using logistic regression models. Associated costs were aggregated in terms of average collections per patient in each mobilization option (patient level), and escalated to a panel of 5000 patients (population level).

Results: 299 patients were evaluable; 241 received P-PL and 58 received S-PL. Patients receiving P-PL had higher median CD34$^+$ count pre-collection and higher median total CD34$^+$ cell harvest on the first collection (6.75×10^6/kg for P-PL, 1.96×10^6/kg for S-PL; $P < 0.01$). In multivariable analyses, P-PL remained significantly associated with the ability to collect $\geq 2 \times 10^6$/kg CD34$^+$ on the first day (OR = 4.05, 95% CI, 1.19–13.83, $P = 0.03$) and $\geq 5 \times 10^6$/kg CD34$^+$ in total (OR = 3.09, 95% CI, 1.04–9.23, $P = 0.04$). P-PL saved $11,248 (46%) per patient compared with S-PL.

Conclusion: P-PL significantly enhanced collection efficiency, with most patients completing collection in 1 day, resulting in substantial cost savings.

1. Introduction

High-dose chemotherapy with autologous stem cell transplantation (ASCT) is currently a standard of care for patients with multiple myeloma and non-Hodgkin's lymphoma [1]. Collection of an adequate number of CD34$^+$ peripheral blood progenitor cells (CD34$^+$ cells) is therefore a critical aspect of this treatment modality [2]. CD34$^+$cells can be effectively mobilized from the bone marrow to the peripheral blood using several techniques and agents. To ensure timely engraftment, it is generally considered that a minimum dose of 2×10^6 CD34$^+$

Abbreviations: CD34$^+$, cluster of differentiation 34; G-CSF, granulocyte colony-stimulating factor; P-PL, pre-emptive plerixafor; S-PL, same-day plerixafor

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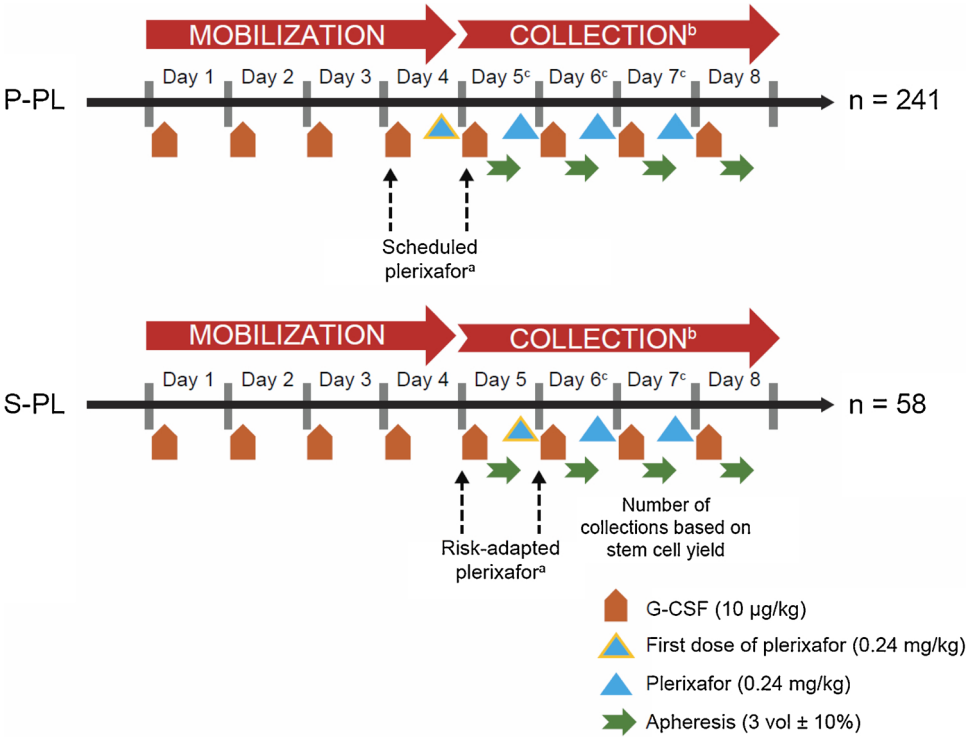

Fig. 1. Dosing schedules of plerixafor: Pre-emptive (P-PL) versus standard (S-PL) administration.

cells per kg body weight is required per transplant, although a higher yield would be required to procure enough $CD34^+$ cells for two transplants, as is sometimes utilized in multiple myeloma [2–5]. Failure to collect an adequate $CD34^+$ cell count with growth factor mobilization leads to treatment delays and potential need for higher intensity regimens, such as chemomobilization [4,6–8]. Infusion of suboptimal $CD34^+$ cell numbers risks delayed or failed engraftment [9–12]. Both of these scenarios increase the risk of peri-transplant morbidity and can lead to increased healthcare costs [6,9–12].

Conventional strategies for stem cell mobilization involve administration of granulocyte colony-stimulating factor (G-CSF) alone or in combination with chemotherapy or chemokine receptor antagonists [13]. G-CSF has pleiotropic effects on the bone marrow microenvironment, including increased expression of the chemokine receptor CXCR4 and decreased expression of the chemokine stromal cell-derived factor 1 (SDF-1) in bone marrow, leading to loss of CXCR4/SDF-1 interaction and subsequent stem cell mobilization to the peripheral blood [13,14]. Plerixafor (Sanofi, Paris, France), a small-molecule antagonist of the CXCR4 receptor, reversibly inhibits binding of SDF-1 to CXCR4 and is indicated in combination with G-CSF (with or without chemotherapy) to improve stem cell mobilization [15,16]. Phase III studies have demonstrated that administration of plerixafor in combination with G-CSF can significantly improve the likelihood of successful $CD34^+$ cell collection compared with G-CSF alone in patients with multiple myeloma and non-Hodgkin lymphoma [17,18]. In addition, plerixafor has been shown to be effective in patients who have failed prior stem cell mobilization attempts or who are predicted to be poor mobilizers [19–21].

Resource utilization is a critical aspect of transplant program clinical operations, and apheresis scheduling is a key element of timely patient care. In most institutions, in addition to stem cell collection apheresis units serve a variety of customers, with neurology being the largest customer in many institutions. Because of the growth of our transplant program and overall increasing demands for apheresis resources, in order to prevent scheduling delays for autologous stem cell procurement a programmatic decision was made to change our mobilization algorithm.

Therefore, in order to improve stem cell collection efficiency, the Ohio State University Blood and Marrow Transplant Program began a policy of administering plerixafor to multiple myeloma patients on the evening prior to the first day of stem cell collection. Here we evaluate the cost outcomes of this policy change, when compared with patients who received plerixafor only after inadequate collection parameters were identified, using a treatment algorithm based on initial stem cell yield. We compared the peripheral blood $CD34^+$ cell number prior to collection, collection success, engraftment of neutrophils and platelets, and costs associated with both collection strategies.

2. Materials and methods

Eligible patients were adults with myeloma undergoing growth factor mobilization who had received either filgrastim alone or at least one dose of plerixafor during stem cell mobilization prior to ASCT. The study was approved by the Institutional Review Board of The Ohio State University. Patient data were obtained from the electronic medical record (IHIS/EPIC) of The Ohio State University Wexner Medical Center as well as the Blood and Marrow Transplant Program data repository. Patients were excluded if they had received chemotherapy prior to stem cell mobilization, or if they did not proceed with transplantation after successful collection.

2.1. Study design

This retrospective study compared the mobilization success rates of two dosing schedules of plerixafor: pre-emptive, where plerixafor was initiated the evening prior to the first day of stem cell collection (P-PL), and standard, where plerixafor was initiated the evening prior to the second day of stem cell collection, using a treatment algorithm based on $CD34^+$ cell count (S-PL) (Fig. 1). The primary objective was to describe the impact of the dosing schedule on collection outcomes, including total $CD34^+$ stem cell number procured and the number of apheresis procedures required for collection. Successful collection was defined as the proportion of patients achieving a minimum collection of 2×10^6

Table 1
Baseline Patient and Disease Characteristics.

	All (N = 299)	P-PL (n = 241)	S-PL (n = 58)	*P*
Sex, n (%)				0.24
Male	165 (55)	137 (57)	28 (48)	
Female	134 (45)	104 (43)	30 (52)	
Race, n (%)				0.26
Caucasian	260 (87)	211 (88)	49 (84)	
Black	35 (12)	28 (12)	7 (12)	
Other	4 (1)	2 (1)	2 (3)	
Age, median (range)	60 (35 to 72)	60 (35 to 72)	61 (38 to 71)	0.80
Karnofsky performance status, n (%)				0.06
≤ 90	265 (89)	218 (90)	47 (81)	
> 90	34 (11)	23 (10)	11 (19)	
ISS score, n (%)				0.40
1	88 (40)	75 (42)	13 (32)	
2	68 (31)	55 (31)	13 (32)	
3	64 (29)	49 (27)	15 (37)	
Missing	79	62	17	
CCI, median (range)	2 (0 to 9)	2 (0 to 9)	3 (0 to 7)	0.48
Lines of prior chemotherapy, median (range)	1 (1 to 9)	1 (1 to 9)	1 (1 to 5)	0.54
Prior lenalidomide, n (%)				0.46
Yes	170 (57)	134 (56)	36 (62)	
No	129 (43)	107 (44)	22 (38)	
Diabetes, n (%)				
Yes	44 (15)	36 (15)	8 (14)	1.00
No	255 (85)	205 (85)	50 (86)	
Remission status at transplant, n (%)				
Complete response	37 (12)	33 (14)	4 (7)	0.31
Partial response	237 (79)	188 (78)	49 (84)	
Stable disease	19 (6)	14 (6)	5 (9)	
Progressive disease	6 (2)	6 (2)	0	

CCI, Charlson Comorbidity Index; ISS, international staging system; P-PL, preemptive plerixafor; S-PL, standard plerixafor.

$CD34^+$ cells/kg or an optimal collection of ≥ 5×10^6 $CD34^+$ cells/kg. Secondary objectives were to evaluate risk factors and patient-specific characteristics that may lead to poor mobilization (age, number of prior chemotherapy regimens, previous lenalidomide therapy, prior history of type 2 diabetes, and remission status at time of transplant) and evaluate differences in transplantation outcomes, defined as the number of days from transplant to neutrophil and platelet engraftment. In addition, a cost analysis assessed the costs of P-PL versus S-PL at the patient level in terms of the average cost per patient and escalated to the population level for a panel of 5000 cover patients.

2.2. Statistical considerations

Patient clinical characteristics and collection outcomes were summarized using descriptive statistics. Associations between the plerixafor administration schedule and baseline clinical variables were assessed using Fisher's exact test or the non-parametric Wilcoxon rank sum test for categorical and continuous variables, respectively. Logistic regression models were used to assess mobilization success as a function of the plerixafor administration schedule while adjusting for covariates and risk factors including age, gender, race, Karnofsky performance status, Charlson Comorbidity Index (CCI), number of prior chemotherapy regimens, previous lenalidomide treatment, prior history of type 2 diabetes, remission status at time of transplant, and peripheral blood $CD34^+$ count before first collection. Univariable models were fit first, then multivariable models were constructed using the method of forward selection from the univariable models using $P < 0.05$ as the model entry criteria. All tests were two-sided and statistical significance was set at $\alpha = 0.05$. The SAS 9.4 program (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

2.3. Cost analysis

The cost analysis assumed that only the collection of $CD34^+$ cell harvest, and not the clinical efficacy of ASCT, was affected by the mode of mobilization. Consistent with the patient eligibility criteria, patients who did not proceed with transplantation after successful collection were not included. The analysis included only direct and differential cost determinants related to mobilization and excluded common costs across arms (including catheter placement). The cost-benefit analysis focused on budget impact, did not consider indirect costs, and was from the payer perspective.

The CMS average sales price (ASP) of medications, CMS costs for procedures, and, optionally, the incremental cost of hospitalization were aggregated in terms of the average collections per patient needed to reach the required dose of $CD34^+$ cells (patient level). The costs were then escalated to a panel of 5000 patients for each group (population level). Cost inputs included medications, medication- and collection-related procedures, and, optionally, the incremental hospitalization cost for the additional hospital stay observed for the P—PL group. Four scenarios with varying clinician-administered versus patient self-administered filgrastim doses were considered. Costs were presented in 2017 USD, except for hospitalization day, where the 2015 USD cost [24] was adjusted to 2017 USD per the medical consumer price index) [25].

3. Results

3.1. Patients

From 2009–2014, 299 patients received plerixafor during stem cell mobilization and were available for evaluation. Median age was 60 years (range 35–72); 55% of patients were male; 241 received P—PL and 58 received S—PL. There were no significant differences between patient groups with respect to gender, age, race, Karnofsky performance status, International Staging System score, CCI, number of prior therapies, prior lenalidomide, type 2 diabetes status, or disease status at the time of stem cell mobilization (Table 1). No patients had received chemotherapy for stem cell mobilization. As this was not a prospective analysis, patients underwent a variety of induction regimens prior to transplant. The most common regimens included bortezomib, lenalidomide, and dexamethasone (n = 88), velcade plus dexamethasone (n = 85), and lenalidomide plus dexamethasone (n = 40). Some patients also received radiation therapy for symptom control around the time of induction (n = 78). The remainder of patients required multiple courses of combination regimens or changes in the treatment plan to achieve remission sufficient for transplantation (n = 94). The majority of patients were in either a first complete or partial remission at the time of transplantation (n = 274). Nineteen patients had achieved only stable disease after initial therapy, and 5 patients were not in remission at the time of transplant and had overt disease progression after either primary induction or salvage therapy. The remainder of the patients were in second or subsequent remission. Twenty patients had undergone prior autologous transplantation. Three patients were lost to follow up after stem cell procurement and did not proceed to autologous transplantation. In keeping with the eligibility criteria, these patients were not considered in subsequent analyses.

3.2. Stem cell collection

Patients who received P—PL showed significant improvements in stem cell collection compared with patients who received S—PL. Peripheral blood $CD34^+$ counts were analyzed prior to initiation of the first collection procedure. Patients receiving P—PL had a median $CD34^+$ cell count in peripheral blood of 21 (range 0–162) compared with 8 (range 3–90) for patients receiving S—PL ($P < 0.01$) (Table 2). The median total $CD34^+$ cell count collected on the first day of stem cell collection was 6.75×10^6 in patients receiving P—PL versus 1.96×10^6 in the patients receiving S—PL ($P < 0.01$). There was no significant

Table 2
Collection and Transplant Outcomes.

	All (N = 299)	P-PL (n = 241)	S-PL (n = 58)	*P* value
PB $CD34^+$ count per mm^3 before first collection				< 0.01
Median (Range)	20 (0–162)	21 (0–162)[a]	8 (3–90)	
Missing	61	28	33	
PB $CD34^+$ count on the day of first collection				< 0.01
Median (Range)	80 (10–471)	93 (12–471)[a]	25 (10–218)	
$CD34^+$ collected at first collection, 10^6 cells/kg				< 0.01
Median (Range)	6.01 (0.59–33.98)	6.75 (1.02–33.98)	1.96 (0.59–17.40)	
PB $CD34^+$ count on the day of second collection				0.39
Median (Range)	35 (5–126)	33 (5–126)	36 (8–124)	
Not available [b]	191	186	5	
$CD34^+$ collected at second collection				0.70
Median (Range)	2.90 (0.54–9.35)	2.96 (0.54–9.17)	2.71 (0.72–9.35)	
Not available [b]	191	186	5	
PB $CD34^+$ count on the day of third collection				0.10
Median (Range)	27 (5–96)	8 (6–27)	29(5–96)	
Missing	1	0	1	
Not available [c]	275	238	37	
$CD34^+$ collected at third collection				0.09
Median (Range)	1.91 (0.48–5.55)	0.67 (0.63–1.94)	2.24 (0.48–5.55)	
Not available [c]	275	238	37	
Total $CD34^+$ collection ≥ $5x10^6$/kg, n (%)				0.01
No	63 (21)	41 (17)	22 (38)	
Yes	236 (79)	200 (83)	36 (62)	
Number of plerixafor doses				0.30
Median (range)	1 (1–3)	1 (1–3)	1 (1–3)	
Total collections, n (%)				< 0.01
1	191 (64)	186 (77)	5 (9)	
2–4[d]	108 (36)	55 (23)	53 (91)	
$CD34^+$ infused, 10^6 cells/kg				0.02
Median (range)	3.98 (1.92–15.65)	4.16 (1.92–15.65)	3.67 (2.16–8.70)	
Length of hospital stay for SCT				< 0.01
Median (range)	16 (9–50)	17 (12–50)	15.5 (9–29)	
Day of ANC engraftment > $0.5x10^9$/L for 5 days				< 0.01
Median (range)	11 (9–20)	11 (9–20)	10 (9–12)	
Missing	1	0	1	
Day of platelet engraftment > $20x10^9$/L				0.67
Median (range)	19 (10–78)	19 (10–78)	19 (11–51)	
Missing	5	3	2	
Day of platelet engraftment > $50x10^9$/L				0.88
Median (range)	19 (12–78)	19 (12–78)	20 (15–51)	
Missing	6	3	3	

ANC, absolute neutrophil count; KW; P-PL, pre-emptive plerixafor; SCT, stem cell transplantation; S-PL, standard plerixafor..
[a] One patient had peripheral blood $CD34^+$ count of 162 per mm^3 on the day before first collection and 471 on the next day.
[b] "Not available" refers to the patients not in the analysis because collection was completed on the first day.
[c] "Not available" refers to the patients not in the analysis because collection was completed collections in the first 2 days.
[d] Only one patient had a fourth collection, which yielded $0.349*10^6$ cells/kg.

difference in the stem cell collection efficiency between the P—PL and S—PL patient groups on Days 2 and 3 of stem cell collection. There was no difference in the numbers of doses of plerixafor received, with both patient groups (P—PL and S—PL) receiving a median of one plerixafor dose (range 1–3 for both patient groups). The majority (99%) of patients receiving P—PL versus 64% of patients receiving S—PL completed stem cell collection in one or two collection procedures ($P < 0.01$), with 77% of P—PL patients and 9% of S—PL patients achieving the stem cell collection goal of $2x10^6$ $CD34^+$ cells/kg in one collection procedure ($P < 0.01$). Eighty-three percent of P—PL patients eventually achieved a collection goal of 5×10^6 $CD34^+$ cells/kg versus 62% of S—PL patients ($P = 0.01$). One patient in the P—PL group failed to collect > $2x10^6$ $CD34^+$ cells/kg. In terms of engraftment, there was no difference between the P—PL and S—PL patient groups with respect to platelet engraftment (as defined as a total platelet count of 20×10^6/L × 3 consecutive days), however compared with patients receiving S—PL, patients receiving P—PL had a significantly longer ANC engraftment time ($P < 0.01$) and a longer stay in hospital ($P < 0.01$) (Table 2).

In the univariable analysis, peripheral blood $CD34^+$ count before first collection and P—PL administration were the only two factors significantly associated with a likelihood of achieving a stem cell collection of at least 2×10^6 $CD34^+$ cells/kg during the first stem cell collection (both $P < 0.01$). In multivariable analysis, where these two variables were simultaneously included in the model, the odds of achieving the collection of at least $2x10^6$ $CD34^+$ cells/kg on the first stem cell collection in the P—PL group was 4.05-fold greater than that in the S—PL group (odds ratio [OR] = 4.05, 95% confidence interval [CI], 1.19–13.83; $P = 0.03$). In addition, P—PL administration was significantly associated with the total collection of ≥ 5×10^6 $CD34^+$ cells. Compared with the S—PL group, the P—PL group were 3.09-fold (OR = 3.09, 95% confidence interval, 1.04–9.23; $P = 0.04$) more likely to achieve a total collection of 5×10^6 $CD34^+$ cells, adjusting for peripheral blood $CD34^+$ count before first collection ($P < 0.01$), age ($P < 0.01$), and complete or partial response at the time of collection ($P = 0.03$) (Table 3).

3.3. Cost analysis

Cost inputs and analysis results are presented in Table 4. The average number of collections per patient needed to reach the required count of $CD34^+$ cells was 1.24 and 2.29 for the P—PL and the S—PL groups, respectively. Not considering differential hospitalization costs and using the ASP as the base, average per-patient costs (escalated to 5000-patient

Table 3
Effect of Variables on Collection Outcomes.

	≥ 2 × 10^6 CD34$^+$ on first collection				≥ 5 × 10^6 CD34$^+$ in total			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	P^a	OR (95% CI)	P^b	OR (95% CI)	P^a	OR (95% CI)	P^b
Age (1-year increase)	0.98 (0.94–1.03)	0.44	—	—	0.93 (0.90–0.98)	0.0009	0.89 (0.83–0.95)	0.0006
Male versus female	1.21 (0.64–2.29)	0.55	—	—	1.15 (0.66–2.01)	0.62	—	—
Caucasian versus non-Caucasian	0.61 (0.21–1.81)	0.35	—	—	0.51 (0.19–1.37)	0.15	—	—
Karnofsky PS > 90 versus ≤ 90	0.81 (0.31–2.07)	0.66	—	—	1.63 (0.60–4.39)	0.32	—	—
CCI (1 unit increase)	0.94 (0.80–1.10)	0.44	—	—	1.00 (0.86–1.15)	0.97	—	—
Number of prior chemotherapies	0.92 (0.70–1.21)	0.55	—	—	0.88 (0.69–1.12)	0.30	—	—
Lenalidomide versus no lenalidomide	0.61 (0.32–1.20)	0.15	—	—	0.65 (0.36–1.15)	0.14	—	—
Diabetes versus no diabetes	0.54 (0.25–1.19)	0.14	—	—	0.67 (0.32–1.38)	0.29	—	—
CR/PR at transplant versus SD/PD	2.42 (0.95–6.17)	0.07	—	—	4.85 (2.09–11.27)	0.03	3.88 (1.16–13.00)	0.03
PB CD34$^+$ count before first collection	1.40 (1.19–1.66)	< 0.01	1.39 (1.17–1.65)	0.02	1.15 (1.09–1.21)	< 0.01	1.13 (1.07–1.20)	< 0.01
P-PL versus S-PL	16.14 (7.75–33.62)	< 0.01	4.05 (1.19–13.83)	0.03	2.98 (1.59–5.59)	< 0.01	3.09 (1.04–9.23)	0.04

CCI, Charlson Comorbidity Index; CI, confidence interval; CR, complete response; OR, odds ratio; PD, progressive disease; P-PL, pre-emptive plerixafor; PR, partial response; PS, performance status; SD, stable disease; S-PL, standard plerixafor.
[a] Likelihood ratio *P* value for univariable analysis.
[b] Wald *P* value for multivariable analysis.

panels) ranged from $13,131 ($65,654,941) to $13,259 ($66,296,116) for the P—PL and $24,270 ($121,349,200) to $24,507 ($122,534,276) for the S—PL group (Table 4). P—PL saved 46% of costs compared with S—PL, with savings reaching $11,248 per patient and $56,238,160 for a 5000-patient panel. When considering the incremental cost of the 1.5-day length of stay differential associated with P—PL, corresponding costs for the P—PL group ranged from $16,995 ($84,976,057) to $17,123 ($85,617,232) compared with the unchanged S—PL costs. P—PL saved 30% of costs compared with S—PL, with savings reaching $7383 per patient and $36,917,044 for a 5000-patient panel (Table 4).

Table 4
Cost Analysis Inputs and Results by Scenario and With versus Without Hospitalization Costs.

INPUTS Medications				ASP	Source
Filgrastim 30 MU/300 mcg 1 ml single				$302.40	CMS[a]
Plerixafor 1.2 ml of 20 mg/1 ml solution				$7541.40	CMS[a]
Procedures					
Subcutaneous injection (CPT 96,372)				$25.84	CMS[b]
Peripheral blood stem cell collection autologous (CPT 38,206)				$1098.22	CMS[b]
Cryopreservation (CPT 38,207)				$354.39	CMS[b]
Thawing without wash (CPT 38,208)				$354.39	CMS[b]
Other	**P-PL**	**S-PL**			
Median hospitalization length of stay (days)	17	15.5			Study
Hospitalization day cost (non-profit)			2015	$2,413	Henry J. Kaiser Family Foundation[c]
			Adjusted to 2017	$2,576	Federal Reserve[d]
Differential hospitalization cost for P-PL patients (based on 1.5 days addition length of stay)				$3,620	Calculated
Total number of collections	299	133			Study
Average number of collections needed per patient to reach required dose of CD34$^+$ cells	1.24	2.29			Calculated
RESULTS	**Per patient**		**For panel of 5000 patients**		
Without hospitalization differential	**P-PL**	**S-PL**	**P-PL**	**S-PL**	**Savings, %**
Scenario 1[e]	$13,131	$24,270	$65,654,941	$121,349,200	46
Scenario 2[f]	$13,163	$24,329	$65,815,235	$121,645,469	46
Scenario 3[g]	$13,195	$24,388	$65,975,529	$121,941,738	46
Scenario 4[h]	$13,259	$24,507	$66,296,116	$122,534,276	46
With hospitalization differential					
Scenario 1[e]	$16,995	$24,270	$84,976,057	$121,349,200	30
Scenario 2[f]	$17,027	$24,329	$85,136,350	$121,645,469	30
Scenario 3[g]	$17,059	$24,388	$85,296,644	$121,941,738	30
Scenario 4[h]	$17,123	$24,507	$85,617,232	$122,534,276	30

ASP, average sales price; CMS, Centers for Medicare and Medicaid Services; P-PL, pre-emptive plerixafor administration; S-PL, standard plerixafor administration.
[a] https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2017ASPFiles.html.
[b] https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx.
[c] http://www.kff.org/health-costs/state-indicator/expenses-per-inpatient-day-by-ownership/?activeTab=map&currentTimeframe=0&selectedDistributions=statelocal-government-hospitals.
[d] https://fred.stlouisfed.org/series/CPIMEDSL.
[e] Scenario 1: Filgrastim self-administered by patient on Days 1–4.
[f] Scenario 2: Filgrastim self-administered by patient on Days 1–3; Day 4 dose administered by clinician.
[g] Scenario 3: Days 1 and 4 Filgrastim administered by clinician; Days 2 and 3 self-administered by patient.
[h] Scenario 4: Days 1–4 Filgrastim administered by clinician.

4. Discussion

Mobilization of hematopoietic progenitor cells can be achieved via administration of G-CSF alone or in combination with chemotherapy (e.g. cyclophosphamide or etoposide) or chemokine antagonists. [1] When added to G-CSF or G-CSF plus chemotherapy, plerixafor increases $CD34^+$ cell numbers and decreases mobilization failure rates [16]. Plerixafor, in combination with G-CSF, is approved as an initial stem cell mobilization regimen in lymphoma and myeloma, and is utilized in situations where stem cell mobilization may prove more difficult [19,20,22,23]. In addition, it is associated with improved stem cell collection day predictability [10].

The current study suggests that the benefits of using plerixafor as a stem cell mobilization regimen may be further enhanced by a pre-emptive schedule, where plerixafor administration is initiated on the evening prior to the first day of stem cell collection, as opposed to the standard schedule, where plerixafor administration is initiated on the evening prior to the second day of stem cell collection only if there is insufficient yield on the first day. Our retrospective study found that pre-emptive plerixafor administration significantly enhanced the efficiency of stem cell collection, with most patients (77%) achieving the minimum goal of 2×10^6 $CD34^+$ cells/kg in one collection procedure. On univariable analysis, pre-emptive plerixafor administration was the only factor associated with the likelihood of achieving this number during the first collection. Of note, on multivariable analysis, other factors significantly associated with achieving the collection goal in 1 day included complete or partial response at the time of collection (versus stable/progressive disease) and type 2 diabetes (versus no diabetes). The latter result challenges published data indicating that the presence of type 2 diabetes may lead to poor mobilization, and further clarification of this finding would require additional study in a larger patient cohort [26].

Failure to mobilize and procure adequate numbers of $CD34^+$ cells has tremendous impacts on patients who require transplantation, adding to the overall cost of care due to repeat attempts at stem cell mobilization, lost opportunity for transplantation which may be potentially curative (in the case of lymphoma), and lost potential for disease stabilization and prolongation of remission (in the case of myeloma). Multiple groups have developed algorithms to predict mobilization failure in order to predict which patients would best benefit from addition of plerixafor to the mobilization regimen. Veltri et al. evaluated lymphoma and myeloma patients undergoing stem cell mobilization who received either planned Plerixafor as part of the mobilization regimen versus an approach where plerixafor was only administered to patients likely to fail mobilization (a just-in-time approach) [27]. This study found that patients who received up-front plerixafor experience a higher $CD34^+$ yield, but at significantly increased costs even when accounting for lowered apheresis and cryopreservation costs. Musto et al. evaluated mobilization failure in newly diagnosed myeloma patients undergoing chemomobilization, a strategy which usually results in significant $CD34^+$ moblization. Their group found that older patients, those with baseline cytopenias, those who had received prior lenalidomide, and patients who had experienced prior hematological toxicity were more likely to experience mobilization failure and may benefit from addition of novel therapies [28].

While it is clear that addition of plerixafor can significantly enhance stem cell yields, the cost of the agent largely prevents routine use in patients who are not at risk of mobilization failure. For example, Micallef and colleagues performed a cost-effectiveness analysis of a risk-adapted algorithm wherein plerixafor was administered based on programmatic thresholds for either peripheral blood $CD34^+$ counts and/or daily $CD34^+$ yields. This study found that while addition of plerixafor significantly increased costs, it also resulted in improvement in peripheral blood $CD34^+$ collection, increased numbers of patients achieving $CD34^+$ goals, fewer days of apheresis, and lower rates of mobilization failure [29]. Olivieri et al. performed a retrospective study of 1318 patients with myeloma and lymphoma undergoing mobilization and developed a predictive model for mobilization failure which included increasing age, lymphoma diagnosis, disease involvement in the bone marrow, cytopenias preceding mobilization, prior mobilization failure, and use of G-CSF alone [30]. These results enable the identification of patients at very high risk of mobilization failure who would likely benefit from additional strategies to prevent mobilization failure.

Additional studies have demonstrated that the use of plerixafor for stem cell mobilization is associated with favorable patient outcomes at comparable or lower cost [17,18]. Current practices for stem cell mobilization differ between countries and across the US, and these differences can be largely attributed to the costs associated with mobilization regimens [31,32]. Our US cost analysis, which was from the payer perspective but is also relevant to healthcare provider organizations, showed that P-PL was associated with savings of 46% compared with S-PL. When the incremental cost of the additional days of hospitalization was considered, the cost savings of P-PL still yielded significant savings of 30% compared with S-PL. The major driver of cost savings was the lower number of collections per patient observed in the P-PL cohort. Further cost-savings can be achieved with the use of biosimilar filgrastim.

To our knowledge, this manuscript is the first to describe a programmatic change in the overall mobilization strategy for the purpose of enhancing patient access to apheresis and stem cell procurement. This is also the first economic evaluation comparing the costs of P-PL and S-PL, though there have been prior economic evaluations of plerixafor in stem cell mobilization in general. A US study of multiple myeloma and non-Hodgkin lymphoma patients showed a reduction in plerixafor costs of 32% when its use was restricted to patients at risk of poor mobilization [33]. In this study, the total costs of stem cell procurement and medications (plerixafor and filgrastim) were estimated at $16,696 [33]. This is markedly higher than the $13,131 to $13,259 observed in our study when the hospitalization differential is not considered, but comparable to our study when the longer average length of stay of P-PL patients is taken into account. A UK study estimated the cost of plerixafor (re-)mobilization in patients with Hodgkin's disease, non-Hodgkin lymphoma, and multiple myeloma at £12,679/patient compared with £11,694/patient for comparable historical controls not treated with plerixafor [34]. This corresponds to, respectively, $19,019/patient and $17,541/patient at an average exchange rate of $1.5: £1.0. These costs significantly exceed our estimated P-PL costs, regardless of whether the additional length-of-stay in the P-PL cohort is taken into account. Notably, plerixafor yielded savings of (£3828)/patient, or ($5742)/patient, in patients with lymphoma but was associated with incremental costs of £5,245/patient, or $7,868/patient, in patients with multiple myeloma [34]. A micro-simulation analysis in the US of the expected lifetime cost of providing care for patients with diffuse large B-cell lymphoma using filgrastim and plerixafor versus filgrastim alone, linked an additional cost of $25,567 to an increase of 1.74 quality-adjusted life years. The incremental cost-utility ratio was $14,735 per quality-adjusted life years gained [35]. While this incremental cost is not directly comparable to our costs and savings estimates, it underscores that the additional cost of stem cell mobilization with filgrastim and plerixafor, and the quality-adjusted survival benefit gained, is cost-effective at a relatively low willingness-to-pay threshold.

This study was designed as a retrospective, observational, non-controlled, real-world study. Although such a design does not carry the rigor of a randomized controlled trial and does not permit causal inferences, observational studies provide a statistically valid method for comparing the clinical and economic outcomes associated with the two plerixafor mobilization strategies. In the absence of prospective clinical trial results, our study shows an association between pre-emptive plerixafor and a lower number of collection events required to achieve $CD34^+$ cell collection targets and a decrease of overall mobilization costs.

In conclusion, our stem cell mobilization experience suggests that pre-emptive plerixafor administration in myeloma patients undergoing ASCT may improve clinical and economic outcomes. Pre-emptive plerixafor significantly increased $CD34^+$ cell yield and the rate of adequate $CD34^+$ cells on Day 1 of collection. It is associated with substantial cost savings compared with the standard strategy.

Author contributions

Concept and design: LA, AM, SS, CH
Data acquisition and management: LA, AM, SS, CH
Statistical analysis: YH
Economic analysis: IA, NA
Interpretation of data: all authors
Drafting of manuscript: LA, AM, and IA (with editorial support as detailed above)
Critical review of manuscript: YH, KH, SS, TF, NA, CH, ED

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Declaration of Competing Interest

LA has provided advisory board and consultation services to Astrazeneca. IA owns stock in Matrix45. By company policy, he cannot hold equity in sponsor and client companies, perform services, or receive compensation independently from sponsor and client organizations. KH was an employee of Sanofi at the time of study conduct, owns stock of Sanofi, and is currently an employee of Novartis. TF was an employee of Sanofi at the time of study conduct, is currently an employee of Shire, and owns stock of Sanofi and Shire. CCH has served on advisory boards for Celgene and Teva. ED is an employee and owns stock of Sanofi. AM has received honoraria from Sanofi. All authors received editorial support from Sanofi during the development of this manuscript. YH, NA and SS have no conflicts to disclose.

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