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Pharmacoeconomics of Hematopoietic Stem Cell Mobilization: An Overview of Current Evidence and Gaps in the Literature

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A B S T R A C T

Adequate hematopoietic stem cell (HSC) mobilization and collection is required prior to proceeding with high dose chemotherapy and autologous hematopoietic stem cell transplant. Cytokines such as G-CSF, GM-CSF, and peg-filgrastim, alone or in combination with plerixafor, and after chemotherapy have been used to mobilize HSCs. Studies have shown that the efficiency of HSC mobilization and collection may vary when different methods of mobilization are used. No studies have shown that survival is significantly affected by the method of mobilization, but some studies have suggested that cost and resource utilization may be different between different mobilization techniques. After the FDA approval of plerixafor with G-CSF to mobilize HSCs many transplant centers became concerned about the cost of HSC mobilization. A panel of experts was convened ant this paper reviews the current literature on the pharmacoeconomics of HSC mobilization.

INTRODUCTION

High-dose chemotherapy followed by hematopoietic stem cell rescue is a frequently used strategy in the treatment of hematological malignancies. Autologous hematopoietic stem cell transplantation (aHSCT) is used routinely in the treatment of relapsed non-Hodgkin lymphoma (NHL) and Hodgkin's lymphoma [1-3], and it has been shown to improve both depth of response and overall survival in patients with multiple myeloma (MM) [4-11]. The ability to improve patient outcomes with aHSCT is directly dependent, however, on successful mobilization and collection of stem cells. Historically, stem cell mobilization options have been limited to either growth factors alone or chemotherapy in combination with growth factors [12]. Granulocyte colony-stimulating factor (filgrastim, G-CSF) and granulocyte macrophage colony-stimulating factor (sargramostim, GM-CSF) are US Food and Drug Administration (FDA)-approved for hematopoietic stem cell (HSC) mobilization [12]. Chemomobilization (CM) regimens often include agents, such as cyclophosphamide, etoposide, or cytarabine, and may incorporate rituximab for lymphoma patients. A CM strategy may be chosen over growth factors alone in an effort to produce higher stem cell yield or reduce tumor burden and possible tumor contamination of the stem cell product [13,14].

In this paper, we review the current literature on the pharmacoeconomics of mobilization in HSCT. Our goals are to summarize economic evaluations to date with an emphasis on the issues that are somewhat unique to outcomes studies of HSCT and to better understand the value of recent developments in HSCT, particularly plerixafor. First, we provide an overview of the literature on the clinical and economic outcomes associated with traditional mobilization strategies. Second, we examine the pharmacoeconomic evidence on novel mobilization approaches, focusing on the novel agent plerixafor. This is accompanied by a general overview of methods used in economic evaluations of healthcare interventions, followed by a discussion of the limitations of the current literature and suggestions for future studies.

Standard Mobilization Costs

The costs and consequences associated with traditional mobilization strategies vary. Over the past 15 years, reported costs of mobilization with growth factors alone have ranged from approximately $6000 up to $20,000 per patient [15-18]. When CM is used as a stand-alone cycle apart from standard induction or salvage therapy, this results in additional expenses for chemotherapy, hospitalization for chemotherapy administration, and management of chemotherapy-related complications, including febrile neutropenia. Costs with this approach are therefore higher, with reports ranging

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from $11,000 up to $52,000 per patient, depending on the regimen [19-21]. CM readmission rates at some centers have been reported to be 20% to 26%, and the additional hospitalization generates $7000 to $10,000 in increased costs [19,20,22]. A recent cost analysis of CM demonstrated that this approach is associated with an 80% chance of a nonideal outcome (ie, collections below target, additional apheresis sessions, and complications), which was, in turn, associated with higher mobilization costs [19]. Other disadvantages of CM include the unpredictability of the apheresis schedule, increased costs to patients and caregivers by missed work, frequent clinic visits and admissions, and housing costs [23,24]. Much of these increased costs associated with CM are abrogated by mobilizing stem cells after a planned cycle of chemotherapy rather than administering CM as a standalone regimen, although this approach will not eliminate unpredictable apheresis scheduling. One multicenter retrospective review found that, in addition to an increase in apheresis costs of nearly $3000 per patient, CM resulted in increased weekend apheresis, with 12.6% of patients beginning apheresis on a Thursday or Friday, and 13.3% beginning on a weekend [24].

The advantages of CM include providing standard salvage therapy for relapsed NHL or Hodgkin's Disease patients and greater $CD34^+$ cell collections compared to cytokine-only mobilization. However, no studies to date have shown any difference between CM and cytokine-only mobilization in the amount of tumor contamination of the stem cell product and transplantation outcomes, such as engraftment and survival.

Costs Associated with Poor Mobilization/Failure to Mobilize

Various patient-related and disease-related characteristics have been identified as having a negative impact on mobilization success rates. These include advanced age [25-27]; diagnosis of NHL [25]; prior radiation therapy, extensive prior chemotherapy, or prior treatment with lenalidomide or purine analogs [26-38]; a hypocellular marrow, marrow involvement at diagnosis, low platelet count, and refractory disease [25]; and prior mobilization failure. Historical failure rates with traditional mobilization approaches have been reported to be as high as 18% to 38% [18,39-42], although more recent studies consistently show mobilization failure rates to be below 15% in patients with up-front–treated MM [43-45] and below 10% when CM is incorporated into planned chemotherapy cycles for patients with NHL [46-48]. For those patients who do fail initial mobilization attempts, however, remobilization failures reach 77% [39].

In addition to being potentially unsuccessful, remobilization attempts are expensive. Standard remobilization strategies include dose-escalated G-CSF [49-51], G-CSF plus GM-CSF (G + GM) [52-54], and CM [27]. In 2004, G + GM remobilization was estimated to cost $5900 per patient, whereas remobilization with G-CSF alone averaged $9000 per patient [55]. A recent cost assessment of CM remobilization of MM patients with hyper-cyclophosphamide, vincristine, adiamycin, and dexamethasone chemotherapy followed by G-CSF was shown to be $45,000 per patient, with 37.5% of those incurring an additional $13,000 in charges for hospital readmissions [20]. Poor mobilization is associated not only with an increase in cost, but also escalated resource consumption, including increased growth factor, antibiotic, and transfusion support; more frequent hospitalization; more apheresis procedures; and delayed engraftment [19,42]. Table 1 summarizes the costs and consequences of poor mobilization.

Options are limited for those patients who fail to collect sufficient stem cells for transplantation on multiple mobilization attempts. Bone marrow harvest and subsequent autologous bone marrow transplantation (BMT) add considerable cost and are associated with more complications than peripheral blood stem cell transplantation (PBSCT). The cost of the harvest procedure itself ranges from nearly $5000 to $8500 [15,56,57], and early comparisons of autologous BMT to PBSCT showed an average 20% to 30% increase in total transplantation costs with BMT [15,56,58]. BMT has also been associated with poorer engraftment and reduced quality of life (QoL) when compared with PBSCT [58]. Allogeneic stem cell transplantation may be an option in select patients who fail multiple mobilization attempts, but it is associated with increased morbidity and mortality and is not available to all patients because of lack of a suitable donor. For these patients, further treatment options become limited to salvage or maintenance chemotherapy without transplantation, which may be associated with increased risk of relapse.

Novel Mobilization Approaches

In 2008, the novel agent plerixafor, a CXCR4 chemokine receptor antagonist, was approved for use by the FDA in the United States. Plerixafor is indicated for first-line mobilization of hematopoietic stem cells into the peripheral blood for collection and subsequent autologous transplantation in patients with NHL and MM. Several studies, including the initial phase III trials of plerixafor and G-CSF compared with G-CSF and placebo, have demonstrated that plerixafor can overcome some of the known risk factors for poor stem cell mobilization [26,43,59-61], and may reduce overall mobilization failure rates from as high as 30% to <10% [16,21,62-68]. Unfortunately, the acquisition cost of plerixafor has limited its use in up-front mobilization despite the FDA indication, as expensive agents within institutions are often restricted because of budget constraints. In such situations, pharmacoeconomic (PE) analysis methods are essential to determine if the superior effectiveness warrants the higher price.

Table 1
Costs and Consequences of Suboptimal Mobilization [25,44]

Consequence	Outcome
Failure to mobilize a sufficient number of $CD34^+$ cells	• Ineligibility for transplantation and subsequent relapse • Increased apheresis days • Need for bone marrow harvest • Added cost of remobilization attempts • Increased resource utilization
Transplantation with suboptimal apheresis product	• Delayed, partial, or failed engraftment • Prolonged hospitalization and increased hospitalization costs • Increased infections • Increased bleeding or need for transfusions
Unmeasured costs to patient/caregiver	• Transportation to/from apheresis center • Cost of housing/sustenance • Psychological strain • Missed work time
Unmeasured costs to center	• Weekend apheresis • Delay in treatment • Disruption of patient flow • Inability to proceed to transplantation

Overview of Health Economic Outcomes Research Analysis

The purpose of a PE evaluation is to analyze the costs and consequences of a health intervention and its impact on individuals, healthcare systems, and even society at large. A PE evaluation can be conducted from various perspectives, such as from the industry, payer, institution, patient, or from society in general. Types of economic evaluation methods include cost-minimization analysis; cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis; and cost-consequence analysis [69]. Although detailed discussion of these methods is beyond the purview of this article, the purpose and limitations of a few are discussed below.

PE analysis methods, in general, have limitations. It is not within the scope of a single PE analysis to account for all possible perspectives and outcomes (eg, monetary cost, economic benefit, effectiveness, utility); rather, investigators must choose those that are most relevant and discern which PE analysis method is best suited to assess those outcomes. Cost-utility analysis is considered the gold standard in PE evaluations [70,71], because it facilitates comparisons of the cost-effectiveness of interventions across health care using a common metric—cost per quality adjusted life-year (QALY). This approach, however, is challenging and often criticized on a variety of levels: methods for determining health-related QoL may be cumbersome, controversial, or lack sensitivity in certain diseases or conditions; all possible benefits of an intervention may not be accounted for by the QoL index; and it assigns equal value to all QALYs without accounting for social factors, such as severity of illness, age, or socioeconomic status of the individual [72]. Furthermore, although QoL is an important endpoint for physicians, patients, and society at large, it may not be valued as much by administrators or payers whose focus is budget impact; therefore, QALY may not be an appropriate method for evaluating complex interventions, such as those involving cancer treatment or end-of-life care [73].

A decision-analytic model is another health economic outcomes research tool that synthesizes data from real-world patients to model a disease, treatment, and outcome process; microsimulation assigns a probability to each possible event as patients move through a series of treatment cycles. It should be noted, however, that models are only as useful as the data on which they are based, and small patient populations will result in larger standard of error. A useful model incorporates many parameters, requiring extensive data best collected in a prospective manner.

Further challenges with PE research lie within the practical execution of these studies. Costs, patient populations, and standard of care often vary by institution or region, so that data obtained from a single-center PE analysis may not be applicable to a national or international audience. In addition, medical centers are often reluctant to share proprietary contract and budget information with other centers, and publishing institution-specific PE data in the public domain may be frowned upon by administrators. This presents a particular challenge when attempting to conduct a multicenter PE evaluation with more universally applicable results.

Although PE analyses involve assumptions and have limitations, they are indispensable to understanding value of novel therapies that have a high acquisition cost and substantial budget impact for payers and institutions. For expensive novel therapies that may be more effective than the standard of care, it becomes necessary to determine if the superior effectiveness of the drug outweighs the increased cost. For these reasons, various analyses of plerixafor-containing mobilization regimens have been performed to determine the effectiveness, net costs, and benefits of plerixafor use compared to standard mobilization regimens [18,21,62,63,74-78].

PHARMACOECONOMIC ANALYSES OF NOVEL MOBILIZATION REGIMENS

Up-front Plerixafor

In 2011, Shaughnessy et al. published a retrospective comparison of 34 MM and lymphoma patients who were mobilized up front with plerixafor plus G-CSF (P+G) to a similar number of matched historical controls who were mobilized with cyclophosphamide and G-CSF (CM+G) (Table 2) [21]. Data were taken from 2 institutions that participated in the plerixafor expanded access program. Historical controls were matched for age, sex, disease, stage, and number of prior therapies. The analysis compared effectiveness, cost, resource utilization, and clinical outcomes of P+G to CM+G. Costs of mobilization failure were not included in the analysis. Costs were estimated based on median Centers for Medicare and Medicaid Services national reimbursement rates and average medication sale prices.

Both approaches yielded 100% successful mobilization rates, defined in this study as a minimum collection of 2×10^6 $CD34^+$ cells/kg, although significantly more patients collected an optimal target of at least 5×10^6 $CD34^+$ cells/kg [79] in the P+G arm (94% versus 76%, $P = .04$). Similar median total $CD34^+$ cells/kg were collected: 0.7×10^6 with P+G versus 11.6×10^6 with CM+G ($P = .5$). Mean total cost per patient with P+G was $20,298 versus $19,173 per CM+G patient ($P = .57$). P+G had a substantial impact on resource utilization, with 64% of P+G patients completing apheresis in 1 day compared to 39% of control patients. In addition, P+G patients received fewer doses of G-CSF, required fewer hospitalizations and transfusions, and had more predictable apheresis schedules.

Kymes et al. performed a cost-utility evaluation of G alone versus P+G as first-line mobilization, with data from Washington University that included patients who participated in the NHL Phase III plerixafor trial [78]. Data from 20 patients with diffuse large B cell lymphoma who underwent aHSCT (10 who received G-CSF alone, and 10 who received P+G) served as the basis for a Markov decision analytic model that replicated the process of stem cell mobilization, apheresis, and transplantation. The microsimulation calculated QALYs for patients who received the 2 mobilization approaches, and estimated the incremental cost-utility ratio (ICUR) over the patients' remaining lifetimes. An ICUR can be defined as the cost adding of 1 year of perfect health to a patient's life with a given treatment. The authors assumed a conservative ICUR of less than $50,000/QALY to determine cost-effectiveness, based on a non-US insurance policy maker's willingness to pay for a treatment (ie, an insurance company will pay for a medical intervention if it costs <$50,000/QALY).

Based on the microsimulation, the expected lifetime cost of care for diffuse large B cell lymphoma patients who underwent aHSCT was $93,180 if they were mobilized with P+G compared with $67,730 with G alone. However, G+P resulted in 1.75 more QALYs than G alone, which gave an ICUR for P+G of only $14,574/QALY, well within the range considered cost-effective by most insurance providers. Figure 1 is the net benefit acceptability curve from this study,

Table 2
Overview of Pharmacoeconomic Evaluations of Plerixafor for Stem Cell Mobilization

Author	Design	Mobilization Regimen (N)	Outcomes Measured	Costs Assessed	Results
Shaughnessy [21]	Retrospective historical comparison (of prospectively collected data)	P+G (33) CM+G (33)	$CD34^+$ cell yield Apheresis days/ scheduling GCSF doses Hospital days Transfusions	Pre-apheresis Chemotherapy Drug (P, G, abx) Hospitalization Transfusions Laboratory Peri-apheresis Apheresis $CD34^+$ studies Storage costs	Successful mobilization 100% both cohorts, similar cell doses collected Mean total cost per patient: P+G $20,298 CM+G $19,173 ($P$ = NS) P+G: fewer G doses, hospitalizations, transfusions, weekend apheresis
Kymes [78]	Retrospective decision analytic model (of prospectively collected data)	G alone (10) P+G (10)	QALY	Drug (P, G) Apheresis Storage Transplantation Hospitalization	G+P resulted in 1.75 more QALYs than G alone ICUR for P+G $14,574/QALY
Vishnu [62]	Prospective efficacy and cost-benefit analysis	Pre-emptive P G alone (18) PEP+G (24)	$CD34^+$ cell yield Apheresis days Adverse events ANC/platelet engraftment	Drug (P, G) Stem cell collection Lost revenue	Overall mobilization success 95% (compared to historical control of 75% before PEP) Estimated cost savings with PEP: $19,300 per patient
Li [63]	Retrospective comparison/ cost analysis of patient cohorts pre- and post-P approval	Post-P approval: PEP+G (poor mobilizers, 41) UP+G (high risk for FTM, 23) G±CM (good mobilizers, 124) Pre-P approval (G±CM): Poor mobilizers (36) Good mobilizers (112)	Peripheral $CD34^+$ counts $CD34^+$ cell yield ANC/platelet engraftment	Drug (P, G) Apheresis Storage costs	Successful collections: Poor mobilizers w/PEP 93% Poor mobilizers w/o PEP 72% High risk w/UP+G 96% Good mobilizers pre-/post-P 100% Estimated costs: Poor mobilizers w/PEP $30,264 Poor mobilizers w/o PEP $27,796 High risk w/UP+G $20,761 Good mobilizers post-P $15,299 Good mobilizers pre-P $13,550
Campen [74]	Retrospective decision analytic model	P+G (8) CM + G (34)	$CD34^+$ cell yield	Drug Laboratory Apheresis	P+G more effective, less costly in 69.9% of cases
Adel [75]	Retrospective cost analysis	P+G (35) CM+G (98)	$CD34^+$ cell yield Hospital days Apheresis days	Chemotherapy Drug (P, G) Laboratory Apheresis Hospitalizations Second mobilization	P+G associated with fewer hospital days, fewer apheresis days, and fewer mobilization failures Cost of CM 1.6 times higher than P+G
Isola [76]	Retrospective historical comparison	G alone (25) P+G (25)	$CD34^+$ cell yield GCSF doses Apheresis days ANC engraftment Hospital days post-transplantation	Drugs Transfusions Hospitalization Apheresis	P+G higher $CD34^+$ cell yield, fewer apheresis days G alone had earlier neutrophil engraftment by 1 day Hospitalization days similar Cost of apheresis + hospitalization: P+G $61,632 G alone $62,949 ($P$ = NS)
Perkins [77]	Retrospective resource utilization analysis of second mobilization	P+G (38) Other [G, CM, G+GM] (58)	$CD34^+$ cell yield Apheresis days Laboratory Hospital days Transfusions IV antibiotics Clinic visits	NA	P+G higher $CD34^+$ cell yield, and reduced apheresis and hospitalization requirements
Roberts [18]	Retrospective cost-effectiveness analysis	G alone (115) CM+G (97) UP (18) PEP (63)	$CD34^+$ cell yield	Total costs of successes and failures	Successful collections/total costs: G alone 61.9%/$23,044 CM+G 70.1%/$20,736 UP 61.6%/$31,060 PEP 76.2%/$25,460

ANC indicates absolute neutrophil count; abx, antibiotics; CM, chemotherapy mobilization; FTM, failure to mobilize; G, granulocyte colony-stimulating factor; GM, granulocyte macrophage colony-stimulating factor; ICUR, incremental cost-utility ratio; IV, intravenous; P, plerixafor; PEP, pre-emptive plerixafor; pt, patient; QALY, quality-adjusted life years; NS, not significant; SC, stem cell; w/, with; w/o, without; UP, upfront plerixafor.

demonstrating that G alone would be the preferred regimen only if a decision maker's willingness to pay was below $10,000/QALY.

Pre-emptive Plerixafor

Some centers have developed algorithms for pre-emptive plerixafor use, in which patients receive traditional mobilization regimens with the addition of plerixafor as needed to salvage those who have mobilized poorly. Various PE assessments of these algorithms have been published (Table 3).

Vishnu et al. from the Mayo Clinic in Florida conducted a prospective, single-center efficacy and cost-benefit analysis of a pre-emptive plerixafor mobilization approach in NHL

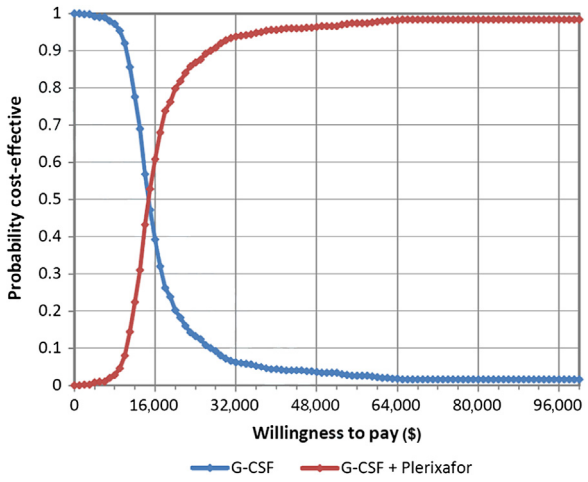

Figure 1. Net benefit acceptability curve for granulocyte colony-stimulating factor (G-CSF) versus G-CSF + plerixafor based on Markov model by Kymes et al. [78]. The steep G-CSF + plerixafor curve indicates that its relative effectiveness is greater than G-CSF alone at a willingness to pay of ~$14,500 quality adjusted life-year (QALY), and it is very stable at a willingness to pay of $36,000/QALY or more. Reprinted with permission.

and MM patients at high risk for failure [62]. In this trial, plerixafor was added to G-CSF–only mobilization if the day 4 peripheral blood $CD34^+$ (PB $CD34^+$) cell count was below 10 cells/μL and apheresis began on day 5. Of the 42 patients mobilized with this approach, 24 (57%) required the addition of plerixafor on day 4. The overall mobilization success rate was 95% compared with a historical success rate of only 75% before the institution of the pre-emptive strategy. By adjusting for revenue losses incurred when 25% of patients mobilized with G-CSF alone do not proceed to transplantation, they estimated a cost savings of $19,300 per patient with the use of the pre-emptive plerixafor approach.

Li et al. from Emory University conducted a single-center retrospective historical comparison of NHL and MM patients mobilized with a pre-emptive plerixafor strategy to patients mobilized at their center before plerixafor approval [63]. The pre-approval cohort included 36 poor mobilizers (defined as patients with a PB $CD34^+$ cell count of <15 cells/μL and a WBC $>10 \times 10^9$/L after at least 5 days of G-CSF) and 112 good mobilizers who received either CM+G or G-CSF alone as their mobilization regimen. The postapproval cohort included 124 good mobilizers who received only G-CSF with or without chemotherapy and 64 patients thought to be at risk for poor mobilization. Of these, 23 were high-risk patients who received scheduled P+G based on a previous failed mobilization attempt, prior lenalidomide therapy, or refractory disease with multiple prior treatment regimens and 41 poor mobilizers who received pre-emptive plerixafor plus G-CSF. Among the poor mobilizers, those who received pre-emptive plerixafor had a successful collection rate of 93% compared with 72% in the historical control group; high-risk patients who received scheduled P+G had a successful mobilization rate of 96%. Estimated mobilization costs were similar in the poor mobilizer group regardless of plerixafor use ($30,264 for those receiving plerixafor compared with $27,796 for the historical controls), lower in the high-risk patients who received scheduled P+G ($20,761), and lowest in the good mobilizer cohorts ($15,299 in the post-plerixafor phase, $13,550 for the preplerixafor cohort).

A recent report of mobilization and resource utilization outcomes for a risk-based mobilization approach was conducted by Abhyankar et al. [65]. In their algorithm, plerixafor was instituted in patients whose day 5 PB $CD34^+$ cell count was suboptimal for the target collection goal or in patients whose apheresis day 1 $CD34^+$ cell yield was less than 50% of the desired collection. A total of 159 patients who underwent aHSCT for various diagnoses were mobilized with G-CSF; of those, 55 required the addition of plerixafor based on the stated criteria. Target collection was attained in 151 patients (95%) compared with only 81% of historical controls. Use of the plerixafor algorithm had the additional benefit of reducing apheresis days to 1.7 from 3 in historical controls.

Chen et al. from the Oregon Health Science Center reviewed 49 consecutive mobilization attempts with G-CSF alone and determined that a day 4 PB $CD34^+$ cell count of 15 cells/μL correlated with a day 5 collection yield of 2×10^6 $CD34^+$ cells/kg [80]. The investigators therefore instituted a clinical guideline to initiate plerixafor in patients whose day 4 PB $CD34^+$ cell count is between 5 cells/μL and 15 cells/μL, or in those who had a poor collection yield during apheresis. A subsequent prospective analysis of 166 consecutive lymphoma and plasma cell dyscrasias patients mobilized with these guidelines demonstrated successful mobilization rates (defined as collection of $\geq 2 \times 10^6$ $CD34^+$ cells/kg) in 93% patients. Plerixafor was administered to 43% of eligible mobilization patients according to guideline. The median cell yield was 4.9×10^6 $CD34^+$ cells/kg in patients who received plerixafor, and 6.3×10^6 $CD34^+$ cells/kg in those who received only G-CSF, although comparisons could not be made between the yields because the patients who received plerixafor plus G-CSF were already predicted to be a group of patients who would not mobilize well. The median number of apheresis days and failure rates in both groups were similar. These data demonstrated that implementation of a clinical pathway based on their patient subset was highly effective in ensuring access to plerixafor and maximizing the collection and minimizing mobilization failures in a very simple manner.

Costa et al. developed an algorithmic approach to hematopoietic stem cell mobilization to determine those patients who would most benefit from the addition of plerixafor to G-CSF [66]. Mathematical equations were developed that incorporated both the target $CD34^+$ cell collection for a given patient and the patient's day 4 PB $CD34^+$ cell count. The equations estimated the costs of proceeding beyond day 4 of mobilization with G-CSF alone versus proceeding with the addition of plerixafor, and accounted for the costs of drug (plerixafor, G-CSF), apheresis, and stem cell storage. For each target $CD34^+$ cell yield (3×10^6 $CD34^+$ cells/kg if a single transplantation was planned, 6×10^6 for tandem transplantation), investigators determined the day 4 PB $CD34^+$ cell count values at which proceeding with G alone would be more costly than proceeding with P+G. These values then became the threshold for institution of plerixafor. For example, if the target collection was 3×10^6 $CD34^+$ cells/kg and the day 4 PB $CD34^+$ cell count was below 14 cells/μL, plerixafor was started on day 4. The algorithm was prospectively validated with a cohort of 34 lymphoma and MM patients, where 97% of patients reached target collection and 94% completed apheresis within the predicted number of days. The median projected savings with G-CSF alone in good mobilizers (over the use of up-front plerixafor in all-comers) was $2589 per patient.

Table 3
Overview of Risk-Adapted Algorithms for Plerixafor Use in Stem Cell Mobilization

Study	N	Mobilization Regimens (N)	Target $CD34^+$/kg Cell Yield	Criteria for P	Costs Assessed	Outcomes
Vishnu [62]	42	PEP G alone (18) P+G (24)	2×10^6 (minimum)	D4 PB $CD34^+$ <10 cells/μL	Drug (P, G) SC collection Lost revenue	95% reached minimum collection
Li [63]	165	PEP G +/− CM (124) P+G +/− CM (41)	2×10^6 (minimum)	PB $CD34^+$ <15 cells/μL and WBC >10×10^9/L after 5 days of GCSF	Drug (P, G) Apheresis Storage	98% reached minimum collection
Costa [66]	34	PEP G alone (11) P+G (23)	6×10^6 (some MM) 3×10^6 (all others)	Mathematical equation estimating costs of proceeding w/G alone versus P+G based on D4 PB $CD34^+$	Drug (P, G) Apheresis Storage	33 of 34 (97%) of patients reached target collection 94% completed apheresis within predicted no. of apheresis days Median projected savings w/G alone in good mobilizers was $2589/patient
Costa [67]	131	PEP G-alone (16) P+G (33) Failed to complete (1) versus CM+G (81)	6×10^6 (some mm) 3×10^6 (all others)	Mathematical equation estimating costs of proceeding w/G alone versus PŦG based on D4 PB $CD34^+$	Chemotherapy Drug (P, G) Apheresis Storage FN hospital days	98% of PEP proceeded to aHSCT versus 77.8% of CM 94% of PEP reached target collection versus 76.5% of CM Cost of successful mobilization: PEP $23,893 CM+G $29,423
Abhyankar [65]	159	PEP G alone (104) P+G (55)	2.5×10^6 (single) 5×10^6 (tandem)	D5 PB $CD34^+$ <10 cells/μL: Administer P, begin apheresis D6 D5 PB $CD34^+$ ≥10 but <20 cells/μL: If target is 2.5, begin apheresis without P; if target is 5, begin apheresis but administer P that night. D5 PB $CD34^{\pm}$ ≥20: Begin apheresis without P Apheresis Day 1 cell yield <50% desired collection: administer P	None	94.9% of patients reached target collection (compared to 81% of historical control data) PEP reduced apheresis days to 1.7 from 3 in historical controls
Micallef [16]	147	PEP G alone (80) PEP+G (55) UP+G (12)	2×10^6 (minimum)	Day 5 PB $CD34^+$ <10 cells/μL or Daily apheresis yield of <0.5×10^6/kg	NA	95% of patients reached target collection compared with 78% historical success rate D4 PB-$CD34^+$ <10 or apheresis Day 1 yield <1.5 million predicted >70% patients who would receive P
Micallef [68]	592	G alone (278) PEP1+G (216) PEP2+G (98)	2×10^6 (minimum)	PEP1 Same as above PEP2 D4 PB $CD34^+$ <10 (single) or <20 cells/μL (tandem) or Apheresis Day 1 yield <1.5×10^6/kg or Any subsequent daily yield <0.5×10^6/kg	Chemotherapy Drug (P, G) Apheresis Storage	Minimum cell collection reached: G - 81% PEP1 - 95% PEP2 - 99% ($P < .001$) Average cost per patient: G $17,300 PEP1 $21,686 PEP2 $20,695
Shapiro [61]	196	G alone (124) UP+G (72)	2×10^6 in 1 apheresis	High-risk patients Group 1: 3+ lines of prior chemo; Group 2: 4+ cycles of hyper-CVAD; Group 3: 4+ cycles of lenalidomide	NA	Successful collection rates: Group 1: 67% UP versus 38% G Group 2: 47% UP versus 21% G Group 3: 100% UP versus 39% G
Chen [80]	166	PEP G alone (56) P+G: Low PB $CD34^+$ (62) Poor yield (10) Guideline not followed (36)	2×10^6 (minimum)	Day 4 PB $CD34^+$ 5 to 15 cells/μL or Poor apheresis yield (at physician discretion)	NA	93% of patients reached minimum collection
LaPorte [64]	68	PEP G alone (38) P+G (30)	4×10^6 (target) 2×10^6 (minimum)	Day 4 PB $CD34^+$ <12 cells/mm^3 or Daily apheresis yield of <1×10^6 or ≤50% of previous day's yield	NA	93% of patients reached target collection 99% of patients reached minimum collection

aHSCT indicates autologous hematopoietic stem cell transplantation; CM, chemotherapy mobilization; CM+G, chemotherapy mobilization with granulocyte colony-stimulating factor; D, day; FN, febrile neutropenia; G, granulocyte colony-stimulating factor; MM, multiple myeloma; P, plerixafor; PB $CD34^+$, peripheral blood $CD34^+$ cell count; PEP, pre-emptive plerixafor; UP, upfront plerixafor; CVAD, cyclophosphamide, vincristine, adiamycin, and dexamethasone.

The outcomes and costs for 50 patients mobilized with the above algorithm were subsequently compared with a historical cohort of 81 patients who underwent CM with G-CSF and GM-CSF [67]. The costs assessed in this analysis included chemotherapy, mobilization drug(s), apheresis, stem cell storage, and hospital days for febrile neutropenia admission. Thirty-three of 50 patients (66%) in the algorithm cohort required the addition of plerixafor, and 16 (32%) were

mobilized with G-CSF alone. A significantly higher proportion of patients in the algorithm group were able to proceed to aHSCT (98%) compared with 77.8% of patients in the CM cohort, $P < .01$; 94% of patients mobilized according to the algorithm reached the target collection compared with 76.5% of CM patients, and hospital admission rate was significantly lower in this group as well. The cost of successful mobilization was less in the algorithm group compared with the CM group, $23,893 versus $29,423, respectively.

DISCUSSION

Prospective PE data for first-line plerixafor-based mobilization are limited. Much of the data needed to create a useful model are simply missing from existing randomized controlled trial data, and therefore cannot be incorporated into retrospective PE evaluations of plerixafor. The resulting gap in the published literature can only be filled by a multicenter, prospective randomized health economic outcomes research study that should include the various mobilization strategies for MM and lymphoma patients undergoing aHSCT. An intent-to-treat approach would include follow-up of nonmobilizers for a more accurate assessment of outcomes. Primary endpoints would be QoL and cost, with secondary endpoints of mobilization and transplantation outcomes, efficiency of the collection process (eg, apheresis resource utilization), and survival. Standard challenges facing multicenter PE trials could be avoided to some degree by using the Medicare allowable resource-based relative value scale to standardize costs across centers and reduce the need for disclosure of individual institutional costs.

Center-Specific Evaluations of Mobilization Strategies and Costs

Until PE data from larger trials are available, centers are encouraged to assess their own mobilization failure rates and costs to determine whether other mobilization methods may offer advantages. This can be done using a modified approach to health economic research analysis.

Step 1: Define the problem

Conduct a retrospective assessment of the institution's failure rate with current mobilization regimen(s).

Step 2: Identify the appropriate comparators

The institution's standard of care for mobilization should be compared to other methods (ie, up-front plerixafor, algorithms using plerixafor, chemotherapy, etc.).

Step 3: Identify the perspective

For most centers, the perspectives that will have the greatest impact on regimen choice will be those of the institution administrators, the healthcare practitioners, and the patient.

Step 4: Identify outcomes to Be measured

These should include failure rates, drug-related adverse events, and morbidities, such as infection rates, cytopenias requiring transfusions, and hospital admissions/readmissions.

Step 5: Identify relevant center-specific costs of current mobilization techniques

Assess the costs/charges associated with mobilization drug(s), apheresis, laboratory monitoring, stem cell processing and storage, physician service billing, and hospitalizations. The costs of failed mobilization attempts, in addition to those incurred during remobilization, should be included. In addition to monetary costs, consideration should be given to resource utilization, such as days of apheresis required.

Step 6: Implement the new approach

Prospectively collect data on costs, resource utilization, and mobilization outcomes associated with up-front plerixafor use.

Step 7: Compare mobilization strategies

After a predetermined number of patients have been mobilized, compare with the historical cohort mobilized with the standard regimen. Comparisons should be made regarding successful collection of predefined minimum and target cell yields, in addition to overall monetary cost of the mobilization attempts and resource utilization with each strategy evaluated.

Although mobilization techniques have not been shown to alter the clinical outcomes of patients undergoing aHSCT, available data suggest that effectiveness, QoL, and costs may differ significantly between strategies [18,19,21,24,62,63,68,74-78]. Prospective studies assessing QoL and PE endpoints are warranted.

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