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REVIEWS

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Harvesting Hematopoietic Progenitors: "Please Release Me, Let Me Go"

Randy A. Brown, John R. Wingard

For those who did not practice hematopoietic cell transplantation (HCT) at the time, it may be difficult to appreciate the impact that mobilized peripheral blood stem cells (PBSC) have had on the pace of hematologic recovery. In the days before mobilized PBSC, count recovery before day +21 was uncommon, and prolonged neutropenia resulted in a risk of death from infection that exceeded 5%.

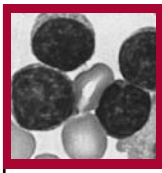
While the presence of hematopoietic progenitors in the blood had long been suspected, it was the work of Goodman and Hodgson that clearly demonstrated the presence in blood of pluripotent stem cells capable of restoring hematopoiesis when transplanted into lethally irradiated mice. These cells are present at such low levels, however, that collection of enough stem cells to do a transplantation is very difficult, generally requiring 5 or more apheresis. The demonstration by Duhrsen and others that granulocyte colony-stimulating factor (G-CSF) increases circulating progenitors 10- to 100-fold ushered in the modern era of PBSC mobilization and collection. Motivated primarily by rapid hematologic recovery, mobilized PBSC enumerated by CD34 determination has largely replaced bone marrow as a source of both autologous and allogeneic stem cells. Most centers use G-CSF at 10 μg/kg per day for 4 consecutive days, with apheresis commencing on day 5 and continuing until the CD34 target is reached.

Despite its effectiveness, the response to mobilization with G-CSF varies 2- to 3-fold even among normal donors. As a result, 10% to 20% of patients with myeloma or lymphoma fail to collect enough CD34+ cells to support a single transplantation (approximately 2×10^6 CD34+ cells/kg). Although multiple factors influence the success of mobilization, prior treatment with stem cell–damaging agents is perhaps the most important. Several approaches have been taken to improve mobilization in patients thought to be at risk for failure to mobilize. These approaches include G-CSF dose escalation and combinations of chemotherapy and G-CSF. Algorithms for predicting failure to mobilize are imperfect at best, however, and these approaches increase toxicity, risk, and cost.

Though the observation that G-CSF mobilizes stem cells was fortuitous, the rapid growth in knowledge of the adhesive molecules that anchor PBSC in marrow led to the rational development of plerixafor-a CXCR4 antagonist that, when combined with G-CSF, can lead to effective mobilization in at least half of patients who have failed a prior attempt.

Recent advances in our understanding of PBSC mobilization was the topic addressed in a satellite symposium held in February of 2011 at the BMT Tandem meeting in Honolulu, Hawaii. Dr. Waller addressed recent progress in our understanding of the basic science of stem cell mobilization. This discussion clearly indicates that new and possibly more effective mobilization strategies will be available in the near future. However, adhesive interactions also effect stem cell cycling, so careful attention will be needed to the "quality" of mobilized PBSC because this could influence the pace of both hematologic and immunologic recovery.

Because we must function in an environment of limited reimbursement, the additional cost of agents such as plerixafor is a major consideration. The presentations by Drs. McSweeney and Stuart are particularly relevant because they suggest strategies that could increase the proportion of patients who can successfully undergo harvesting without dramatically increasing cost.



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Blood and Marrow TRANSPLANTATION REVIEWS

Symposium Report

Graft Mobilization in Autologous and Allogeneic Hematopoietic Stem Cell Transplantation

Adapted from a continuing medical education symposium presented at the 2011 BMT Tandem Meetings on February 19, 2011, in Honolulu, Hawaii. This program is supported by an educational grant from Genzyme Corporation.

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Program Overview

Recent insights into the mechanistic underpinnings of hematopoietic stem and progenitor cell trafficking have paved the way for the development of novel agents to enhance the mobilization of cells capable of reconstituting hematopoiesis following autologous or allogeneic blood cell transplantation. For instance, a CXCR4 antagonist has recently been approved by the FDA for the mobilization of stem cells in patients with multiple myeloma and non-Hodgkin's lymphoma. Now that options for mobilization strategies have increased, the practicing physician is presented with a complex array of factors to consider when choosing a particular mobilization regimen. Costs, logistics, and efficacy are primary among these. Given the greater options for mobilization, strategies may now be more individualized based on patient and disease characteristics. Transplantation physicians are well advised to keep abreast of the latest developments in the stem cell mobilization field so they can offer their patients access to novel and potentially more effective therapies.

This symposium seeks to provide the audience with a state-of-the-art update on our current understanding of the mechanisms behind stem cell mobilization and will also provide practical insights into the factors that affect the decision to choose a particular mobilization strategy for any one individual.

Statement of Need

Transplantation physicians currently use mobilized peripheral blood to reconstitute hematopoiesis in nearly 100% of autologous transplantation recipients and now in more than 60% of allogeneic recipients. This lecture will be focused on transplantation physicians and their staff and will provide them with a clear understanding of the most current clinical information available in stem cell mobilization and will also highlight ongoing research into methods designed to enhance mobilization of stem cells and accessory cells in recipients of allogeneic and autologous transplantations. Many of these novel approaches have been based on recent mechanistic insights into stem cell trafficking. The audience will also be provided with an update on the basic biology of underlying stem cell mobilization. The audience will also read about practical issues that affect decisions to mobilize patients including the consideration of costs and logistics. A strategy for adapting or individualizing the mobilization regimen based on patient characteristics will be presented. Information presented should stimulate the audience to review their current practices and to consider alternative strategies designed to benefit their patients.

Target Audience

The program will be oriented to a targeted audience of physicians and medical care professionals specializing in oncology, hematology, immunology, and microbiology.

Learning Objectives

At the conclusion of this symposium participants should be able to:

- Review the current understanding of the mechanisms governing stem cell mobilization and to review how this knowledge may be exploited for clinical purposes.
- Discuss cost and other logistical factors that affect the choice of mobilization strategy.
- Assess the concept of individualizing or adapting the mobilization strategy for each patient as a means to enhance clinical outcomes.

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Robert K. Stuart, MD, does not have any relevant financial relationships with any commercial interests.

Luciano J. Costa, MD, PhD, discloses that he receives honoraria from Genzyme as a consultant and as a speaker.

Introduction

Peripheral blood progenitor cells are the most common graft source in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). According to data from the Center for International Blood & Marrow Transplant Research (CIBMTR), mobilized peripheral blood progenitor cells accounted for 91% of grafts in children and 98% of grafts in adults undergoing autologous HSCT during the period from 2004 to 2008 [1]. During the same period, peripheral blood accounted for 27% of allogeneic transplantations in children and more than 80% of allogeneic transplantations in adults [1].

Among many factors that can influence the success of HSCT, the dose of reinfused stem cells is critical. Higher stem cell doses are associated with faster platelet engraftment, faster neutrophil engraftment, and reduced need for prophylactic antibiotics and transfusion support. Current approaches to mobilizing peripheral blood stem cells for HSCT have different CD34+ cell yields, safety considerations, and costs. New insights into the mechanisms driving stem cell mobilization have revealed novel therapeutic approaches for enhancing stem cell mobilization and amplifying CD34+ cell yields in patients undergoing autologous HSCT. In addition, clinical decision-making models are being developed to guide the selection of patient-tailored mobilization strategies toward the most cost-effective care.

Understanding the Mechanisms Governing Stem Cell Mobilization

Edmund K. Waller, MD, PhD

Hematopoietic stem/progenitor cells (HSPCs) normally circulate between the bone marrow and the peripheral blood, with each distinct compartment maintaining a relatively constant proportion of CD34+ cells. The bone marrow is a rich source of hematopoietic progenitors. There, CD34+ cells comprise approximately 1% of all nucleated cells. By comparison, the blood is a poor source of hematopoietic stem cells during steady-state hemostasis. Under basal conditions, CD34+ cells account for only 0.02% of nucleated cells in the blood—an almost undetectable level. Thus, CD34+ cells must be mobilized to the peripheral blood to increase collection yields.

Stem Cell Mobilization

Current approaches to harvesting HSPCs focus on moving CD34+ cells from the bone marrow to the peripheral blood, where they can be collected without the costs and potential complications of surgery. To induce this migration, mobilization techniques exploit the interactions between stem cells and cells of the bone marrow microenvironment, including stromal cells, endothelial cells, and osteoblasts.

In 2001, Wright and colleagues examined the kinetics of hematopoietic stem cell (HSC) recirculation between the bone marrow and peripheral blood in an elegant experiment using pairs of parabiotic mice [2]. The mice were genetically similar with the exception of a single locus (CD45) that marked the origin of HSCs. In the study, each mice pair was surgically conjoined and shared a common circulatory system. After the circulatory systems were connected, the pairs quickly established cross-engraftment of partner-derived HSCs, with blood chimerism reaching approximately 50% by days 7 to 10. Thereafter, blood chimerism was stable, with each mice pair maintaining partner-derived hematopoiesis even after being surgically separated [2]. These findings illustrate a pattern of continuous migration of HSCs between the peripheral blood and bone marrow, and confirm the role of blood-borne HSCs in the functional re-engraftment of unconditioned bone marrow.

In additional experiments, Wright and colleagues identified the specific molecular factors that regulate stem cell migration [3]. In a surprising finding, HSCs showed no migratory response to granulocyte colony-stimulating factor (G-CSF), a major cytokine used in current mobilization protocols, and no receptors for G-CSF on HSCs. Indeed, despite exposure to a diverse panel of cytokines and chemokines, HSCs migrated only in response to stromal derived factor-1 (SDF1), the ligand for the C-X-C type chemokine receptor 4 (CXCR4).

The highly specific responsiveness of HSCs to SDF1 (also called CXCL12) is unique among leukocytes, and proposed to be necessary for circulating HSCs to home to bone marrow. Specific responsiveness may also be required to maintain stem cells within the bone marrow microenvironment, where they are tethered to stromal cells via CXCR4 signaling. CXCR2 also binds to growth-related oncogene-beta (GRObeta), a chemokine ligand for the CXCR2 receptor. Through these interactions, CXCR4 and CXCR2 expression regulates the retention of stem cells in the bone marrow [3]. Accordingly, these chemokines and signaling pathways are attractive targets for therapeutic intervention.

Stem Cell Niches and Regulation of Mobilization

Stem cell niches are the highly specialized microenvironments where stem cell functions—including quiescence, self-renewal, differentiation, migration, and engraftment—are tightly controlled. The bone marrow microenvironment is a well-described niche harboring HSPCs. More recent evidence describes additional cell types that form similar niches to harbor dormant and self-renewing HSPCs during hemostasis and mobilize HSPCs in response to G-CSF and other molecular signals.

Role of CXCL12 Signaling

In 2011, Tzeng and colleagues examined the central role of CXCL12 in retaining HSCs in the bone marrow microenvironment by examining a murine model in which target genes were deleted at the adult stage [4]. In this model, CXCL12-deficient stromal cells were unable to support the population and quiescence of wild-type hematopoietic progenitor cells.

The investigators also examined the effects of CXCL12 depletion in 2 microenvironmental niches for bone marrow stem cells, including the endosteal (osteoblastic) and perivascular compartments. In the adult CXCL12-deficient mice, HSCs were absent in the endosteal niche, suggesting a defective osteoblastic environment. At the same time, the pool of hematopoietic progenitor cells in the perivascular niche increased, leading to enhanced recovery of progenitors and mature white blood cells when challenged with myelosuppression. The enhanced hematopoietic recovery in CXCL12-knockout mice was associated with a survival advantage compared with wild-type mice. Together, these findings suggest that CXCL12 expression is required as a stem cell chemoattractant. Stromal-derived CXCL12 also acts to maintain HSC quiescence, hematopoietic progenitor pool size, and niche functionality [4,5].

Macrophages and Monocytes

In another recent study of HSC migration, Link and colleagues described the underlying mechanisms by which G-CSF mobilizes stem cells [6]. As shown in a series of in vitro experiments, macrophages regulated the growth and behavior of osteoblasts in part via the production of osteocalcin, a bone marrow–forming protein. Osteoblasts produced significantly higher levels CXCL12 in cell cultures that also contained bone marrow macrophages than in cell cultures that lacked macrophages. The stimulatory effects of bone marrow macrophages on osteoblasts did not require cell-to-cell contact. Using an in vitro method that separated osteoblasts and macrophages with a permeable membrane, researchers showed that macrophages were still able to modulate the growth, survival, and CXCL12 expression of osteoblasts.

Link also evaluated the dynamics of CXCL12 expression in response to G-CSF in a population of transgenic mice. In some animals, G-CSF receptor (G-CSFR) expression had been knocked out entirely, while in others, G-CSFR expression had been reinstated only in cells of the monocyte-macrophage lineage. The relative levels of CXCL12 mRNA in the bone marrow were measured at baseline and after G-CSF treatment in these transgenic mice as well as in wild-type animals. Treatment with G-CSF decreased CXCL12 mRNA levels in wild-type animals, but had no effect on mRNA levels in animals that lacked all G-CSFR expression. In mice expressing G-CSF receptor only on the macrophage-monocyte lineage, treatment with G-CSF also significantly inhibited CXCL12 mRNA expression.

In 2011, Frenette and colleagues also examined the role of macrophages in HSC mobilization [7]. In animal studies, reductions in bone marrow mononuclear phagocytes led to the reduction of bone marrow CXCL12 levels, the down-regulation of genes associated with HSC retention, and movement of HSPCs into the peripheral blood. Macrophage depletion was also associated with enhanced mobilization in response to treatment with G-CSF or a CXCR4 antagonist [7]. These findings highlight the potential to target bone marrow macrophages as a method for improving stem cell yields in patients who mobilize poorly.

Ligands, Receptors, and Proteases

Thus multiple interactions involving ligands, receptors, and cellular proteases are involved in HSC homing and mobilization. Chief among these is the interaction between SDF-1 (CXCL12) and its receptor, CXCR4, which generates signals to regulate HSC trafficking in the bone marrow. Both SDF-1 and CXCR4 expression is required for the normal migration of HSCs from the fetal liver to the bone marrow, and for the retention of HSCs in the adult bone marrow [8]. Disruption of the CXCR4/CXCL12 signaling pathway appears to be the dominant mechanism of cytokine-induced HSPC mobilization. Treatment with small molecule CXCR4 antagonists such as plerixafor can selectively interfere with SDF-1/CXCR4 binding to induce rapid stem cell mobilization [9].

Several other factors may serve as future targets for intervention. Enhanced expression of CD45 on bone marrow leukocytes correlates with increased motility of hematopoietic progenitors in response to stress signals. Functional CD45 is needed for the development and activity of bone-resorbing osteoclasts, which indirectly affects HSPC behavior via interactions with bone and bone marrow stromal cells. This illustrates the importance of dynamic crosstalk between multiple components of the bone marrow microenvironment in regulating stem cell activity [10]. This crosstalk is seen in the endosteal stem cell niche, where expression of receptor activator of nuclear factor kappa-B ligand (RANKL) stimulates osteoclasts to release proteases that cleave adhesion molecules and promote progenitor mobilization. An influx of G-CSF induces proteases to cleave adhesion molecules, releasing stem cells into circulation [11].

Sympathetic Nervous System

Sympathetic nervous system (SNS) activation, particularly via beta-3 adrenergic receptors, plays a key role in stem cell mobilization. Recent evidence highlights the SNS and immune system as co-regulators of the bone marrow microenvironment [12]. During hemostasis, HSPCs are tethered to osteoclasts, endothelial cells, and reticular cells in the bone marrow microenvironment. As directed by signals in the highly innervated bone marrow microenvironment, HSPCs transiently enter the peripheral blood at very low levels [12].

Under physiologically stressful conditions—including inflammation, injury, and treatment with G-CSF—several signals are sent to the bone marrow. Catecholamine signaling increases, SDF-1 levels decrease in the bone marrow and increase in the peripheral blood, and CXCR4 expression increases in the bone marrow. Together, these stress signals trigger the expansion and activation of osteoclasts, leading to the mobilization of HSPCs from the bone marrow to the peripheral blood to participate in host defense and tissue repair. In the absence of any other stimulus, the oscillation between steady-state homeostasis and physiologic stress also follows a diurnal pattern, with peak stress levels reached approximately 5 hours after sunrise [12]. Understanding the relationship between circadian rhythms and HSPC mobilization may have clinical implications regarding the optimal time of day for HSPC collection. Furthermore, these insights highlight the potential role of catecholamines for enhancing stem cell mobilization.

Epidermal Growth Factor Receptor

New evidence also suggests that the epidermal growth factor receptor (EGFR) plays a role in HSPC mobilization. In animal studies, treatment with EGF inhibited cytokine-mediated mobilization of stem cells from the bone marrow to the peripheral blood. Erlotinib is a tyrosine kinase inhibitor that targets the EGFR. Treatment with erlotinib suppressed EGFR activity and significantly enhanced the repopulating activity of the blood of G–CSF-treated mice compared with the blood of mice treated with G-CSF alone [13]. This research identifies the EGFR signaling pathway as another potential therapeutic target for improving HSPC mobilization.

Summary

With current techniques, mobilization of HSPCs from the bone marrow to the peripheral blood is mediated by induction of bone marrow proteases, attenuation of adhesion molecule function, and disruption of CXCL12/CXCR4 signaling in the bone marrow. Plerixafor, an antagonist of CXCR4, is an emerging option for increasing stem cell yields in patients who show poor mobilization in response to G-CSF alone. Future options for enhancing HSPC mobilization may exploit different signaling pathways and molecular targets. Erlotinib, an EGFR inhibitor, shows promise in enhancing stem cell mobilization. The SNS also harbors a range of diverse targets worthy of exploration with the goal of amplifying HSC mobilization.

The net effect of these strategies is to shift stem cells from the bone marrow compartment into the peripheral blood, where they can be collected by apheresis. With current strategies, the presence of CD34+ cells in the blood can be increased by approximately 0.5% [14]. The content of CD34+ cells in the blood correlates with the final CD34+ cell count in the apheresis product [14]. The ultimate goal is to mobilize enough HSCs into the peripheral blood to collect a cell dose sufficient for successful transplantation.

Cost and Logistical Considerations when Choosing a Mobilization Strategy

Peter A. McSweeney, MD

Several factors influence the quality of mobilization, which is critical to the success of an autologous stem cell transplantation (ASCT) procedure. The quality of the autologous stem cell graft a patient receives can affect their recovery from transplantation, future health, and future treatment options. Factors such as slow or repeat mobilizations, multiple apheresis sessions, and the use of expensive drugs and disposables can result in high costs of mobilization, and these costs can comprise a large part of the overall transplantation budget. The goal of limiting expenditures competes with the goal of optimizing stem cell collections because the most widely used surrogate for autograft quality is the number of CD34+ cells collected. Rational approaches to mobilization hold the promise of improving clinical outcomes and cutting costs associated with ASCT. To date, few studies have focused specifically on mobilization expenditures in patients undergoing ASCT. To fully evaluate mobilization costs in the context of achieving optimal quality autografts would require carefully planned prospective studies that account for both short-term expenditures and later costs that could be attributed to the autograft. This type of study has not been done yet.

From the many studies of different approaches for mobilizing autologous stem cells, 3 major approaches are currently used. (Figure 1). The first involves administering chemotherapy followed by a myeloid growth factor (chemomobilization) and exists in many variations. In general, chemomobilization involves intensive myelosuppressive chemotherapy with one or more agents, eg, cyclophosphamide, during the first day or 2 of the mobilization procedure, followed by growth factor administration until collections are completed. Apheresis is initiated when

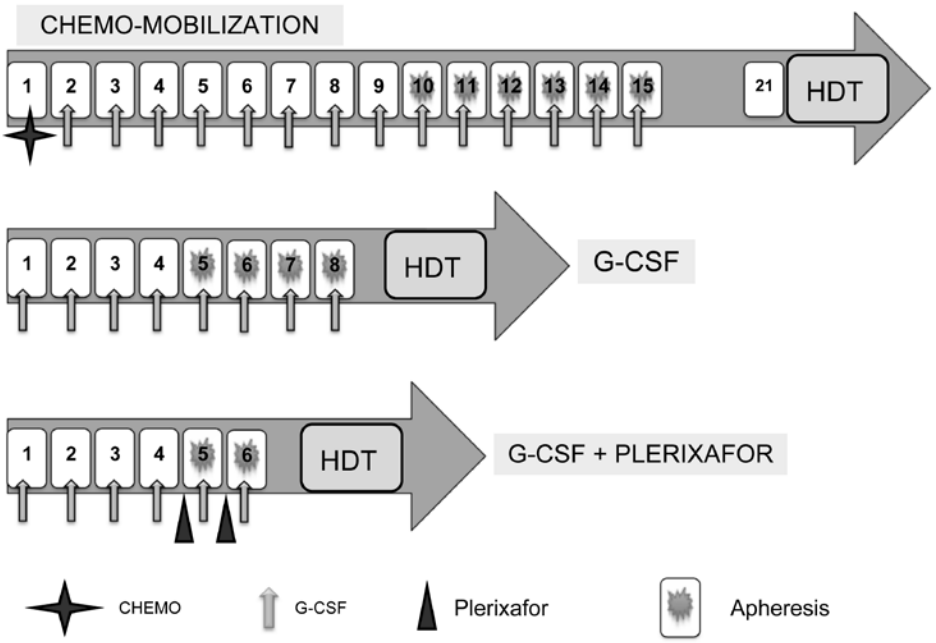

Figure 1. Options for hematopoietic stem/progenitor cell (HSPC) mobilization.

adequate progenitor cells can be measured in the peripheral blood, usually 10 or more days after the chemotherapy is administered. The timing and number of aphereses that may be required are unpredictable and depend largely on the timing and magnitude of progenitor cell mobilization. Typically the transplantation regimen is initiated approximately 3 weeks after the mobilization chemotherapy is administered, extending the overall treatment process by about 1 to 2 weeks over cytokine-based mobilization

The second major option for mobilization relies on the use of cytokines alone. In a typical protocol, hematopoietic growth factors, usually G-CSF, are administered for 4 days, and apheresis is performed on the fifth, sixth, and subsequent days as necessary. Chemomobilization and cytokine-induced mobilization have appeared comparable in the proportion of patients who mobilize sufficient progenitor cells to then proceed to transplantation. Thus although chemomobilization mobilizes a greater number of progenitors than cytokine-induced mobilization, the mobilization failure rates are similar between these mobilization approaches.

More recently, a third major option for stem cell mobilization has emerged that involves combining G-CSF and plerixafor. In a typical G-CSF and plerixafor protocol, G-CSF is administered for 5 days and daily thereafter as needed, with plerixafor administered on the evening of day 4 and subsequent evenings as needed. Apheresis is performed starting on day 5 and on subsequent days as needed. As a mobilizing regimen, plerixafor and G-CSF is superior to G-CSF alone. Plerixafor and G-CSF can be used as a first-line regimen in previously untreated patients and is effective as salvage therapy for patients who have failed other mobilization methods.

The Optimal Autologous Graft

In order to compare costs and logistics of different mobilization methods, it is important to define, if possible, the optimal autologous peripheral blood stem cell graft. Features of

an optimal graft are summarized in Table 1. Although the threshold of CD34+ cells to collect for optimal graft function is not well defined and may vary by patient, it has been reported that higher cell doses may improve survival after transplantation. Conversely, poor mobilization leads to a slower hematopoietic recovery and increased posttransplantation costs.

Ideally, the optimal graft should not limit options for posttransplantation therapy. Increasingly patients are candidates for maintenance therapy or treatment with investigational posttransplantation protocols and require robust hematopoiesis to allow for these therapies. Over the longer term, maintaining good hematologic function is important especially for patients who ultimately relapse and require additional therapy. Ideally stem cells should be collected with the lowest toxicity to the patient. Chemomobilization is clearly more toxic than growth factor and plerixafor and hasn't been shown to improve outcomes of transplantation. Collecting a tumor-free or tumor-depleted graft may be important for improving transplantation outcomes. Given these considerations, it is clear that cost, logistical factors, and patient factors may all contribute to whether the grafts collected are optimal.

Specific targets for HSC mobilization have been defined in various reports. Hematopoietic progenitor cells mobilized to peripheral blood for apheresis contain distinct populations that include stem cells and other more differentiated progenitor cells. Given that the actual number of stem cells collected is not readily measured with current clinical methods, CD34+ cells are used as a surrogate marker for HSCs and as an indirect measure of stem cell graft quality. For a single transplantation, a minimum of 2×10^6 CD34+ cells/kg is usually required, but a more desirable dose is $> 5 \times 10^6$ CD34+ cells/kg. Factors such as patient age, prior chemotherapy, underlying disease, platelet count, and number of aphereses influence the likelihood of effective mobilization and the amount of progenitors that can be collected. Physician choice, local policies, and cost considerations also affect mobilization targets. It is unclear whether the targets for stem cell collection should be standardized across different mobilization procedures or modified to account for differences in mobilizing agents and techniques. To date, prospective studies have not determined whether current targets permit optimal long-term recovery and posttransplantation management.

Logistical Factors

Logistical factors may influence the cost of HSC collection. Depending on the mobilization method used, the timing of collection may be difficult to accurately predict. The number of aphereses required will depend on target cell doses and the efficacy of mobilization. Local operational factors, such as the availability of apheresis services and staff and the ability to perform weekend collections, also affect procedure cost. Some centers do not provide weekend collections, and others operate a fully staffed apheresis service 7 days per week. With these variables, CD34+ assays are critical for obtaining real-time data, planning collection times, and containing costs. Scheduling a collection procedure without knowing the pre-collection CD34+ count can result in a futile collection at substantial cost.

Some mobilization protocols call for growth factor and plerixafor injections later in the evening, after regular daytime working hours (ie, approximately 11 hours before the start of apheresis the following morning). This can cause further logistical challenges that also increase costs. More recently, studies have evaluated the safety and efficacy of earlier-evening plerixafor injection (ie, up to 17 hours prior to next-day apheresis). Adjusting the timing of drug administration to coincide with daytime shifts can reduce overall collection costs. Insurance constraints may dictate some decisions, such as the choice of mobilization agent or the ability to tie collections in to a previous chemotherapy cycle. An example of the potential influence of insurance reimbursement models comes from the Rocky Mountain Blood and Marrow Transplant Program and Colorado Blood Cancer Institute in Denver, Colorado, where 136 mobilization procedures for ASCT were performed over 12 months during 2009–2010 [15]. Of these procedures, 43% were considered "case-related" and were performed within strict cost constraints defined by a fixed reimbursement amount. The remaining mobilization procedures (57%) were "non–case-related" and were performed under different reimbursement models [15]. The effects of reimbursement models on costs of mobilization may vary considerably between different institutions in the USA and different health care systems worldwide, and these in turn influence what constitutes cost-effective mobilization at a local level. Further, no real accounting has been made in the cost evaluations performed so far as to the effects on patients and families of their costs, including the time involved undergoing treatment.

Consequences of Mobilization Failure

Failing to mobilize an adequate number of stem cells may lead to multiple subsequent attempts at stem cell mobilization and harvesting. Repeat attempts have substantial additional costs including further use of growth factors, plerixafor, mobilization chemotherapy, and management of any associated side effects. Mobilization failure rates and the consequences of mobilization failure likely vary from institution to institution and may depend on the patient mix by disease and age. In 2010, Gertz and colleagues described the outcomes of initial stem cell mobilization attempts performed at the Mayo Clinic in Rochester, Minnesota, from 2001 to 2007 [16]. During this 7-year period, a total of 2660 patients received growth factor therapy for HSC mobilization. Of these, 1775 patients were being treated for a hematologic malignancy, including Hodgkin's lymphoma (n = 93), non-Hodgkin's lymphoma (NHL) (n = 685), or multiple myeloma (n = 997) [16].

The goal for the initial mobilization attempt was to collect $> 5 \times 10^6$ CD34+ cells/kg, which they defined as the optimal autograft. The results of the CD34+ HSC collections varied across cancer types. Most patients with multiple myeloma (70%) reached this goal during collection, but only 43% of patients with Hodgkin's lymphoma and 29% of those with NHL had optimal HSC collections. For many patients the stem cell yield was low ($\geq 2 \times 10^6$ and $< 5 \times 10^6$ CD34+ cells/kg), but they underwent transplantation with the collected cells despite the suboptimal yield [16]. For a sizable minority of patients, the stem cell yield was poor ($< 2 \times 10^6$ CD34+ cells/kg) or the mobilization attempt failed altogether (< 10 CD34+ cells/μL). This was the case for 27% of patients with Hodgkin's lymphoma, 33% of those with NHL, and 14% of patients with multiple myeloma [16].

In the overall study population, 47% of patients had less-than-optimal initial mobilization attempts and stem cell collections. Management of these patients was associated with increased resource utilization in the form of increased growth factor and antibiotic use, subsequent chemotherapy mobilization attempts ("remobilizations"), increased transfusional support, additional apheresis procedures, and more frequent hospitalization during remobilization.

Several other trials have demonstrated better stem cell yields in patients with multiple

myeloma than in those with other hematologic malignancies [17,18]. In phase III studies evaluating the plerixafor and G-CSF mobilization regimen, mobilization efficacy was very different for patients with multiple myeloma compared to those with NHL. By day 4 of apheresis, 86.8% of patients with multiple myeloma achieved optimal stem cell collection (≥ 6 × 10^6 CD34+ cells/kg), and 90.9% of those with NHL reached only the minimum goal for collection (≥ 2 × 10^6 CD34+ cells/kg). In both studies, use of the plerixafor and G-CSF mobilization regimen increased the likelihood of reaching CD34+ cell/kg collection goals by approximately 2.5-fold compared with G-CSF alone (P < .0001) [17,18].

Table 1. Outcomes Following Autologous Hematopoietic Stem Cell Mobilization with Granulocyte-Colony Stimulating Factor (G-CSF) and Plerixafor Compared to G-CSF and Cyclophosphamide [23]

Outcomes	G-CSF Plus Plerixafor (n = 33)	Cyclophosphamide Plus G-CSF (n = 33)	*P*
Median apheresis days, n (range)	1 (1-4)	1 (1-4)	.45
Median CD34+ cells × 10^6/kg, n (range)	10.7 (3.5-37.9)	11.6 (2.1-69.3)	.5
Patients collecting ≥2 × 10^6 CD34+ cells/kg, n (%)	33 (100%)	33 (100%)	–
Patients collecting ≥5 × 10^6 CD34+ cells/kg, n (%)	31 (94%)	25 (76%)	.04
Initiating apheresis on scheduled day, n (%)	33 (100%)	29 (88%)	.04
Weekend apheresis, n (%)	0	16 (48%)	≤ .0001
G-CSF doses, n (range)	5 (4-8)	10 (6-17)	≤ .0001
Median days of stay for hospitalization, n (range)	0	1 (0-2)	≤ .0001
Transfusions during mobilitzation, n (%)	0	4 (12.1)	.06

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Costs of Mobilization

Few studies have examined the costs of HSC mobilization in patients undergoing autologous HSCT, and data from single-institution studies suggest wide variations in cost measured. In a study from the M.D. Anderson Cancer Center in Houston, Texas, the mean cost for initial stem cell mobilization and harvest for patients with NHL or Hodgkin's lymphoma was $9454 [19]. By comparison, the cost of remobilization in this patient population ranged from $25,076 to $44,216 [19].

In 2010, Pusic and colleagues described the health economics of stem cell mobilization in patients undergoing ASCT at Washington University School of Medicine. The mean costs for initial mobilization procedures were $12,458 for patients who received G-CSF alone and $17,932 for those who received both plerixafor and G-CSF. All patients initially treated with plerixafor and G-CSF (n = 21) achieved mobilization goals of ≥ 2 × 10^6 CD34+ cells/kg and proceeded to transplantation. Of 20 patients initially treated with G-CSF alone, 8 failed to achieve minimum CD34+/kg goals, and 6 underwent remobilization. The estimated cost of remobilization with plerixafor and G-CSF was $17,376 [20].

Another retrospective analysis examined first-line mobilization costs by regimen in patients with NHL who were undergoing ASCT at the University of Arizona [21]. Mean mobilization costs were $20,965 for patients treated with cyclophosphamide and G-CSF (n = 34) and $19,523 for those treated with plerixafor and G-CSF (n = 8). Fewer patients in the cyclophosphamide/G-CSF group (70.6%) than in the plerixafor/G-CSF group (87.5%) achieved mobilization targets [21].

Clinical and financial consequences of failed first-line mobilization can be severe. Researchers at Stanford University School of Medicine in Stanford, California, evaluated outcomes of high-dose chemotherapy and ASCT in patients who were unable to mobilize sufficient progenitor cells to allow for rapid HSC engraftment following transplantation [22]. In the analysis of 172 consecutive patients with NHL, 80% were considered "good" mobilizers according to their stem cell yields (≥ 2 × 10^6 CD34+ cells/kg), and 20% were considered "poor" mobilizers (< 2 × 10^6 CD34+ cells/kg). After a median follow-up of 3.5 years, event-free survival, overall survival, and risk of relapse were similar between groups. In the economic analysis, however, the poor mobilizers had significantly higher costs for total transplantation care than good mobilizers ($140,262 versus $80,833, respectively; P < .001), in part due to longer hospital stays (30.5 versus 19 days, respectively; P = .02) [22]. These findings suggest higher costs of posttransplantation care among patients who fail to achieve CD34+ cells/kg targets with first-line mobilization. This also indicates that the nature of the patient population being treated may substantially influence the cost of transplantation and whether reimbursement covers the cost of the procedure.

A Multicenter Analysis of Mobilization Costs and Outcomes

In 2011, Shaughnessy and colleagues described outcomes from a 2-center study of G-CSF and plerixafor compared with G-CSF and cyclophosphamide for the frontline mobilization and collection of peripheral blood stem cells for ASCT in patients with NHL, Hodgkin's lymphoma, and multiple myeloma [23]. The study population included 33 patients who were participating in the expanded access program (EAP)—a database of patients who were treated with plerixafor-based mobilization regimens across multiple transplant centers—as well as 33 controls with NHL or multiple myeloma. The EAP and control patients were well matched for age, sex, disease, disease stage at time of transplantation, and number of prior therapies.

The chemomobilization regimen included treatment with cyclophosphamide 3 to 5 g/m^2 on day 1 and G-CSF 10 µg/kg per day on days 2 to 15. Apheresis was started when the peripheral blood CD34+ cell count reached ≥ 10 cells/µL. In the G-CSF and plerixafor group, patients were treated with G-CSF 10 µg/kg per day on days 1 to 8. Plerixafor 0.24 mg/kg was administered on the evening of day 4, 11 hours before apheresis was initiated on day 5. The mobilization targets were defined as ≥ 5 × 10^6 CD34+ cells/kg for patients with lymphoma and ≥ 6 × 10^6 CD34+ cells/kg for those with multiple myeloma [23].

The economic analysis was designed to estimate the true costs of mobilization by capturing all related expenditures, including medical procedures, resource utilization, and medication use. To avoid potential bias related to institution-specific charges, the investigators evaluated costs using the Centers for Medicare & Medicaid Services (CMS) schedule of reimbursement rates for mobilization procedures, hospitalization,

provider visits, apheresis, CD34+ cell processing, and cryopreservation. Additional costs not in the CMS database were extrapolated from another recent economic analysis of stem cell mobilization [19]. Procedural costs were also evaluated on the basis of average sale price for medications related to mobilization, including G-CSF, plerixafor, cyclophosphamide, mesna, antiemetics, and antimicrobials. Costs related to transplantation were not included in the study, and mobilization failures were not included in the study [23].

Mobilization Efficacy

An efficacy analysis showed some potentially important differences in outcomes between the mobilization regimens (Table 2). Although patients in both groups completed apheresis in a median of 1 day, those in the G-CSF plus plerixafor group were more likely than those in the G-CSF plus cyclophosphamide group to collect at least 5×10^6 CD34+ cells /kg (94% versus 76%; $P = .04$). Treatment with plerixafor also reduced the G-CSF dosing requirements by half compared with the chemotherapy-based regimen (5 versus 10; $P \leq .0001$) [23].

Scheduling outcomes favored the G-CSF plus plerixafor regimen, suggesting greater convenience for patients and staff. All patients in the G-CSF plus plerixafor group were able to initiate apheresis on the originally scheduled day, compared with 88% of those in the G-CSF plus cyclophosphamide group ($P = .04$). Moreover, no patients in the G-CSF plus plerixafor group required weekend apheresis, compared with almost half (48%) of patients in the G-CSF plus cyclophosphamide group ($P \leq .0001$) [23].

Treatment with plerixafor plus G-CSF reduced hospitalizations and the risk of complications associated with mobilization. More than half of patients who received G-CSF plus cyclophosphamide (58%) required hospitalization, compared with no patients in the G-CSF plus plerixafor group ($P \leq .0001$). In addition, 12.1% of patients in the G-CSF plus cyclophosphamide group required transfusion support during mobilization, compared with no patients in the G-CSF plus plerixafor group ($P \leq .0001$) [23].

Mobilization Costs

Overall, the total estimated expenditures associated with stem cell mobilization were similar in the G-CSF plus plerixafor and G-CSF plus cyclophosphamide groups, whether measured as mean costs ($20,298 versus $19,173; $P = .57$) or median costs ($14,224 versus $18,824; $P = .45$). However, when mobilization costs were calculated by day of apheresis, a different pattern emerged (Figure 2). Most patients in the G-CSF group (69%) finished apheresis in 1 day, compared with 39% of those in the G-CSF plus cyclophosphamide group. During this first apheresis day, the median total cost of mobilization was lower in the G-CSF plus plerixafor group. The balance shifted on the second and subsequent days of apheresis, when the median total cost of mobilization was higher in the G-CSF plus plerixafor group due to the added cost of plerixafor on those days. This suggests that the acquisition costs of plerixafor in the G-CSF plus plerixafor group were offset by reductions in other resource utilization in the G-CSF plus cyclophosphamide group. Applying these findings to clinical practice, the need for repeated plerixafor dosing, especially the use of more than two doses, can be expected to push total mobilization costs higher than those of other regimens that do not incorporate plerixafor [23].

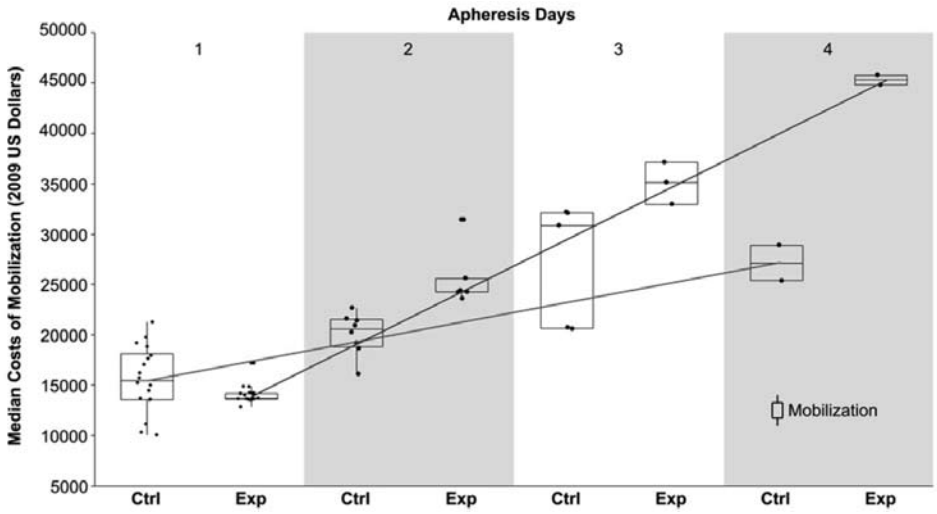

Figure 2. Mobilization costs by regimen on successive days of apheresis. Reprinted with permission from Elsevier [23].

Summary

Cost-effectiveness research related to stem cell mobilization is young, but has already revealed some options for minimizing the total economic burden of mobilization. Successful initial mobilization avoids the need for remobilization and minimizes the number of total procedures required. To accomplish this, it is important to set appropriate target cell doses for single and tandem transplantations, to plan procedures on a schedule that uses staff time efficiently, and to monitor CD34+ cell counts in the peripheral blood, proceeding to apheresis only in cases of adequate mobilization.

With stem cell collection algorithms, clinicians can identify likely "good" and "poor" mobilizers prospectively. Though G-CSF plus plerixafor is more effective than G-CSF alone for mobilization, it is possible to identify patients who mobilize adequately without plerixafor. As a result some mobilization algorithms omit plerixafor if the day 4 CD34+ cell counts meet mobilization targets. If after an apheresis CD34+ cell collections are near target, it may be reasonable to collect without plerixafor use before the final apheresis. These decisions are further complicated by data suggesting that performing transplantations on patients with lower doses of CD34+ cells may increase overall transplantation costs and compromise future therapies. While more CD34+ cells may be better, the value of specific target doses > 5 million per kg have not been well defined. Lastly, from a cost-containment perspective it may be important to plan mobilization on a patient by patient basis within the knowledge of each patient's insurance coverage plan and whether drug reimbursement programs are available for patients without full transplantation coverage.

Should Mobilization Strategy Be Adapted to Each Patient?

Robert K. Stuart, MD
Luciano J. Costa, MD, PhD

Autologous HSCT is the current standard of care for select patients with multiple myeloma and chemosensitive, relapsed, intermediate- or high-grade NHL. New approaches to stem cell mobilization for these patients include individualized mobilization regimens that account for variables such as target apheresis yields, risk for mobilization failure, and cost-effectiveness of treatment. Dual approaches to improving the cost-effectiveness of stem cell mobilization include maximizing the likelihood of successful mobilization while minimizing mobilization-related costs. Containing procedural costs associated with mobilization can bolster the long-term viability of autologous HSCT programs. Several cost-containing strategies related to the selective use of plerixafor have been proposed.

Cost-Lowering Strategies

Plerixafor for Mobilization Failures

One strategy for lowering mobilization costs calls for the use of plerixafor only in patients who have already failed upfront mobilization with G-CSF alone. This approach would substantially lower plerixafor use to approximately 20% of current rates, resulting in a corresponding decrease in medication costs.

To compensate for this change in protocol, patients who failed first-line mobilization and then required remobilization with plerixafor would endure longer wait times to transplantation. Remobilization is also associated with higher overall growth factor cost, higher apheresis cost, and greater unpredictability. This approach, which would likely increase the number of first-line failures, would also disrupt the normal flow of patients through the transplantation center.

Plerixafor for Patients at Risk of Mobilization Failure

Another strategy involves the use of plerixafor as part of first-line mobilization regimens only in patients who are at risk for mobilization failure. In this model, plerixafor would be available to approximately 30% to 40% of patients who undergo stem cell mobilization. Compared to the first model, which restricted plerixafor use to mobilization failures only, this approach would reduce the need for remobilization and provide greater predictability.

The main drawback of this approach is the requirement that clinicians identify patients who are at increased risk of mobilization failure. Current models for prediction of mobilization failure are imperfect, and clinical decisions based on flawed models may lead to the exclusion of patients who are appropriate candidates for plerixafor. Furthermore, this approach does not provide an option for using plerixafor to correct "slow" and "inadequate" collections in patients who are not at risk for mobilization failure. The residual need for remobilizations in patients who do not receive first-line plerixafor will also lead to high growth factor and apheresis costs.

Plerixafor Given According to Day 4 Mobilization Results

In this model, the decision to administer plerixafor is based on real-time mobilization results after 4 days of treatment with G-CSF. This algorithm offers several advantages, including greater predictability, a lower number of apheresis sessions, and a very low need for remobilization. Accordingly, costs for growth factor, apheresis, and cryopreservation are lower, and transplant center flow is improved. This approach also provides a mechanism for avoiding unnecessary plerixafor use in patients with adequate mobilization after G-CSF alone.

As a potential disadvantage, this approach may reduce the use of plerixafor in first-line mobilization regimens only modestly, to 40% to 70% of current utilization rates. In addition, this approach requires the availability of real-time CD34+ cell count assays, which will incur their own added costs.

This algorithm assumes that patients with extremely low CD34+ cell counts in the peripheral blood on day 4 are destined to fail and therefore require plerixafor. On the other extreme, patients with extremely high CD34+ cell counts are destined to reach mobilization targets without plerixafor, and do not require additional mobilization agents. Patients with intermediate CD34+ cell counts should be evaluated in context with other factors, including the costs of additional therapy and the proximity of cell-count targets.

At the 2010 American Society for Blood and Marrow Transplantation (ASMBT) annual meeting, DiPersio and colleagues described the feasibility of using the threshold of ≤ 10 CD34+ cells/μL in the peripheral blood to trigger the addition of plerixafor to a mobilization regimen [24]. The post-hoc analysis included 142 patients with NHL who were mobilized with G-CSF alone (10 μg/kg for up to 8 doses). CD34+ cells were measured on the morning of day 4, approximately 24 hours prior to the scheduled start of apheresis. The CD34+ cell counts on day 4 were then compared with apheresis yields.

Among the 124 patients with evaluable peripheral blood CD34+ cell counts at day 4, 60% had cell counts of ≤ 10 cells/μL and 40% had cell counts of > 10 cells/μL. The median CD34+ cell yields increased between day 2 and day 4 of apheresis in both groups (Table 2). In the subgroup of patients with > 10 CD34+ cells/μL after 4 days of G-CSF mobilization, 20.4% failed to collect the minimal cell dose (≥ 2 × 10^6 CD34+ cells/kg) and 59.2% failed to

Table 2. Apheresis Outcomes According to Proposed Mobilization Thresholds [24]

	Proposed Threshold for Mobilization	
Outcome	**≤ 10 CD34+ cells/μL**	**> 10 CD34+ cells/μL**
After 2 Apheresis Days		
Median yield, CD34+ cells/kg x 10^6 (range)	0.97 (0.06 - 9.16)	3.30 (0.46 - 12.00)
Patients achieving ≥2 × 10^6 CD34+ cells/kg, %	22.7	65.3
Patients achieving ≥5 × 10^6 CD34+ cells/kg, %	5.3	30.6
After 4 Apheresis Days		
Median yield, CD34+ cells/kg x 10^6 (range)	1.31 (0.06 - 10.58)	4.52 (0.46 - 15.00)
Patients achieving ≥2 × 10^6 CD34+ cells/kg, %	34.7	79.6
Patients achieving ≥5 × 10^6 CD34+ cells/kg, %	10.7	40.8

collect the optimal cell dose (≥ 6 × 10^6 CD34+ cells/kg) after 4 days of apheresis. On the basis of these findings, the authors concluded that using a threshold of > 10 CD34+ cells/μL for stem cell collection does not ensure adequate yields for patients with NHL who are mobilized with G-CSF alone. They recommended that mobilization algorithms incorporate higher CD34+ cell count thresholds to facilitate sufficient stem cell collection for patients proceeding to autologous HSCT [24].

In the subgroup of patients with > 10 CD34+ cells/μL after 4 days of G-CSF mobilization, 20.4% failed to collect the minimal cell dose (≥ 2 × 10^6 CD34+ cells/kg), and 59.2% failed to collect the optimal cell dose (≥ 6 × 10^6 CD34+ cells/kg) after 4 days of apheresis. On the basis of these findings, the authors concluded that using a threshold of > 10 CD34+ cells/μL for stem cell collection does not ensure adequate yields for patients with NHL who are mobilized with G-CSF alone. They recommended that mobilization algorithms incorporate higher CD34+ cell count thresholds to facilitate sufficient stem cell collection for patients proceeding to autologous HSCT [24].

Mobilization Decision-Making Algorithms

Adding plerixafor to current mobilization regimens for all patients undergoing autologous HSCT is impractical and unnecessary. Mobilization algorithms guide the use of plerixafor to ensure better stem cell collection yields in patients who need it, while maintaining the cost-effectiveness of therapy and optimizing the utilization of available resources.

Algorithm Development and Validation

At the Medical University of South Carolina (MUSC) in Charleston, South Carolina, Costa and colleagues developed a decision-making algorithm that uses the peripheral blood CD34+ cell count on day 4 of G-CSF administration to decide between continuing G-CSF only or adding plerixafor to the mobilization regimen. The goal of the algorithm was to identify which mobilization approach would ensure adequate stem cell collection at the lowest estimated cost [25].

The MUSC algorithm was built on the assumption, based on historical data, that adding plerixafor to the mobilization regimen on day 4 of mobilization provided a 3-fold increase in CD34+ cell count on the first day of apheresis. To provide flexibility in its clinical application, the algorithm allowed users to evaluate different collection targets. For instance, collection targets at MUSC are ≥ 6 × 10^6 CD34+ cells/kg for patients with multiple myeloma who are planning up to 2 transplantations, and ≥ 3 × 10^6 CD34+ cells/kg for all other patients with hematologic malignancies. For each collection target, the algorithm was able to determine the maximum peripheral blood CD34+ cell count for which the plerixafor and G-CSF approach remained cost-effective (Figure 3) [25].

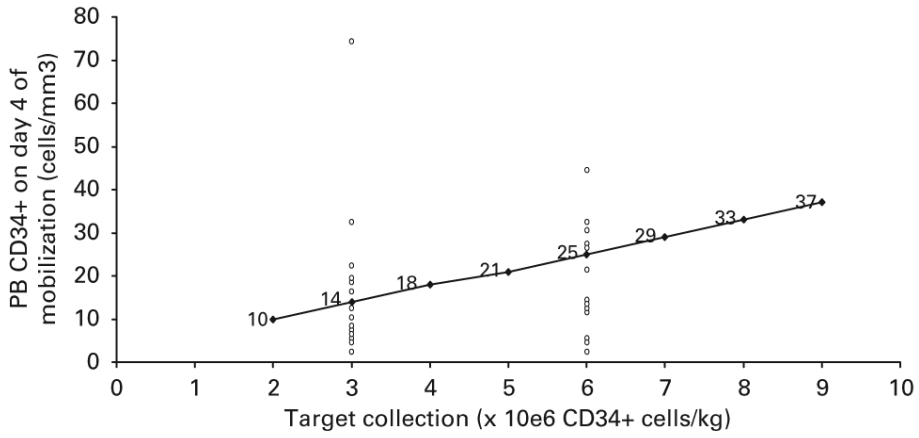

Figure 3. Medical University of South Carolina (MUSC) mobilization algorithm [25]. For a given stem cell collection target, plerixafor should added to the mobilization regimen unless the peripheral blood CD34+ cell count (cells/mm^3) on day 4 of mobilization exceed the number displayed on the continuous line. Reprinted with permission from Elsevier [25].

The MUSC algorithm was validated in a cohort of 34 patients who completed HSC mobilization, including 24 patients (71%) with multiple myeloma and 10 patients (29%) with lymphoma. Of note, more than half of the patients with multiple myeloma (58%) had received prior treatment with lenalidomide. On the basis of day 4 peripheral blood CD34+ cell counts and individual collection targets, 11 patients (32%) were mobilized with G-CSF alone and 23 patients (68%) were mobilized with plerixafor and G-CSF. Overall, 33 patients (97%) reached their prespecified collection targets with the algorithm-guided regimen. Indeed, the median stem cell collection was 129% of prespecified targets in the G-CSF group and 166% of prespecified targets in the G-CSF plus plerixafor group (P = .22). Moreover, 94% of all patients were able to complete their stem cell collection within the predicted number of apheresis sessions. This included 81.9% of patients in the G-CSF group and 95.7% of patients in the G-CSF plus plerixafor group (P = .18) [25].

Mobilization Algorithm versus Chemotherapy Mobilization

In another recent study, Costa and colleagues compared the safety and efficacy of chemotherapy mobilization versus mobilization guided by the MUSC algorithm [26]. The chemotherapy cohort included 81 patients who were mobilized at MUSC prior to November 2008. In this historical cohort, patients were treated with cyclophosphamide 2000 mg/m^2 followed by G-CSF 5 μg/kg per day and GM-CSF 5 μg/kg per day. Apheresis was started when peripheral blood CD34+ cell counts reached 10 cells/mm^3 and was continued until collection targets were met.

After the MUSC mobilization algorithm was developed and validated, it became the preferred method for mobilization at MUSC beginning in January 2009. In the current study, the MUSC algorithm (MA) cohort included 50 patients who were mobilized as directed by the MUSC algorithm. The MA cohort included a greater proportion of patients with multiple myeloma than the chemotherapy cohort (64% versus 41%; P = .01) and a corresponding lower proportion of patients with lymphoma (36% versus 59%). Among patients with multiple myeloma, those in the MA cohort were more likely than those

Table 3. Comparison of Engraftment Kinetics by Mobilization Method [27]*

	Mobilization Method			
Peripheral Blood Stem Cell Products	**G-CSF (n = 26)**	**G-CSF Plus Perixafor (n = 32)**	**Cyclophosphamide Plus G-CSF and GM-CSF (n = 38)**	***P***
CD34+ cells, × 10^6/kg (range)	4.21 (3.35-4.81)	4.11 (3.41-6.36)	4.67 (4.17-5.34)	.433
Mononuclear cells, × 10^8/kg (range)	5.62 (4.08-7.65)	6.54 (5.11-10.10)	3.55 (1.76-6.65)	< .001
CFU-GM, × 10^5/kg (range)	9.08 (7.58-11.42)	7.41 (5.89-12.63)	10.88 (7.27-18.30)	.081
CFU-GM/CD34+ ratio	0.22 (0.19-0.29)	0.19 (0.14-0.23)	0.24 (0.18-0.37)	.008

*G-CSF indicates granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; CFU-GM, colony-forming units–granulocyte-macrophage. Reprinted with permission from John Wiley and Sons [27].

in the chemotherapy cohort to have received prior treatment with lenalidomide (59% versus 71%; P = .02). These differences reflect the changing standards of multiple myeloma care within the past several years [26].

In the efficacy analysis, all but 1 patient in the MA group (98%) successfully completed mobilization and stem cell collection, compared with 78% in the chemotherapy group (P < .01). Of the 18 patients who failed upfront mobilization with cyclophosphamide and growth factor support, 10 patients (12.3%) completed stem cell collection in a subsequent mobilization attempt, and 8 patients (10%) failed a second mobilization attempt and could not undergo autologous HSCT [26].

Patients completing stem cell collection had a median of 1 day of apheresis, regardless of treatment group. All patients in the MA group, however, achieved collection targets within 3 sessions, but patients in the chemotherapy cohort required up to 5 apheresis sessions. The median apheresis yield was 7 × 10^6 CD34+ cells/kg in the MA group and 7.74 × 10^6 CD34+ cells/kg in the chemotherapy group (P = .08) [26].

Use of the MUSC algorithm decreased time from mobilization to transplantation, benefiting patients and allowing better use of resources. The median time from mobilization to transplantation was 14 days in the MA group and 43 days in the chemotherapy cohort (P < .01) [26].

Complication rates were also lower when mobilization was guided by the MUSC algorithm. One patient in the MA group and 24 patients in the chemotherapy group had complications requiring hospitalization for neutropenic fever during mobilization (2% versus 30%; P < .01). The estimated mean cost per patient who successfully completed mobilization was lower in the MA group ($23,893) than in the chemotherapy group ($29,423), not including costs associated with subsequent mobilization attempts [26].

These findings demonstrate that the MUSC algorithm carries a mobilization success rate of nearly 100%. MA-directed mobilization is also safer, more predictable, and likely to be more cost effective than chemotherapy mobilization in patients with multiple myeloma or lymphoma [26].

Mobilization and Engraftment Outcomes

To date, most studies comparing mobilization regimens focus on apheresis yields, collection times, and mobilization failure rates. The next step is comparing engraftment outcomes associated with different mobilization regimens. In 2011, Alexander and colleagues retrospectively evaluated the engraftment kinetics in patients mobilized with G-CSF alone (n = 26), G-CSF plus plerixafor (n = 32), and cyclophosphamide plus G-CSF and GM-CSF (n = 38) [27].

All patients received autologous HSCT with comparable CD34+ cell doses, regardless of mobilization method (Table 3). Mononuclear cells were present in greater numbers in the G-CSF plus plerixafor group compared with other groups, but there was a trend toward fewer colony-forming unit–granulocyte-macrophage (CFU-GM) colonies in the G-CSF plus plerixafor group. This resulted in a significantly lower ratio of CFU-GM colonies to CD34+ cells in the G-CSF plus plerixafor group, suggesting the possibility of delay in engraftment. By day 100, however, there were no differences in graft function across groups, as measured by white blood count (P = .172), absolute neutrophil count (P = .117), and platelet count (P = .947) [27]. These findings demonstrate that hematopoietic graft function at day 100 is not affected by mobilization regimen.

Summary

Methods for HSPC mobilization are shifting from uniform protocols to patient-tailored algorithms that account for apheresis targets, real-time efficacy of G-CSF–induced mobilization, and cost considerations. Compared with historical data, mobilization with G-CSF or G-CSF plus plerixafor, as guided by decision-making algorithms, improves a range of outcomes for patients undergoing mobilization for autologous HSCT. Individualized mobilization strategies are associated with more predictable apheresis, more successful mobilization, lower complication rates, and shorter time to transplantation, without an increase in mobilization-related costs. Additional refinements in mobilization strategies and novel mobilization regimens may provide even greater stem cell yields while minimizing adverse events and preserving the cost-effectiveness of treatment.

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ASBMT News

2012 BMT Tandem Meetings will be Feb. 1-5 in San Diego

The combined 2012 annual meetings of ASBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR) will be Feb. 1-5 at the Manchester Grand Hyatt in San Diego, California.

Recent advances in the broad field of cellular therapy and blood and marrow transplantation will be addressed in plenary sessions, concurrent sessions, oral abstracts, workshops, poster sessions, and symposia.

The scientific program chair for ASBMT is John E. Levine, MD, MS, of the University of Michigan, Ann Arbor, and the chair for CIBMTR is Stella M. Davies, MBBS, PhD, of the Cincinnati Children's Hospital, Cincinnati.

In addition to the five days of scientific sessions for BMT clinicians and investigators, there will be other related conferences and sessions:

- FACT Workshops for Applicant Preparation and Inspector Training – Jan. 31
- BMT CTN Steering Committee Meeting – Jan. 31
- Clinical Research Professionals / Data Managers – Jan. 31-Feb. 1
- BMT CTN Coordinators – Feb. 1-2
- Pediatric BMT – Feb. 2
- BMT Center Administrators – Feb. 2-3
- Clinical Practice Forum – Feb. 3
- BMT Pharmacists – Feb. 3-4
- Transplant Nursing – Feb. 3-5
- Advanced Practice Professionals – Feb. 4
- Medical Directors – February 4

The deadline for early registration and for abstract submission is Oct. 13. Online meeting registration, housing, and abstract submission can be accessed at both the ASBMT website, www.asbmt.org, and the CIBMTR website, www.cibmtr.org. Information is updated continuously.

Graft Mobilization in Autologous and Allogeneic Hematopoietic Stem Cell Transplantation

CME Assessment Test

1. **What is widely considered to be the minimum CD34+ threshold for autologous hematopoietic stem cell transplant (HSCT)?**
   A. $\geq 1 \times 10^6$ CD34+ cells/kg
   B. $\geq 2 \times 10^6$ CD34+ cells/kg
   C. $\geq 5 \times 10^6$ CD34+ cells/kg
   D. $\geq 10 \times 10^6$ CD34+ cells/kg

2. **What is widely considered to be the optimal CD34+ threshold for autologous HSCT?**
   A. $\geq 1 \times 10^6$ CD34+ cells/kg
   B. $\geq 2 \times 10^6$ CD34+ cells/kg
   C. $\geq 5 \times 10^6$ CD34+ cells/kg
   D. $\geq 10 \times 10^6$ CD34+ cells/kg

3. **What is the dominant mechanism of cytokine-induced hematopoietic stem/progenitor cells (HSPC) mobilization?**
   A. Down-regulation of granulocyte colony-stimulating factor (G-CSF) receptor expression in HSCPs
   B. Disruption of the CXCR4/CXCL12 signaling pathway
   C. Inhibition of epidermal growth factor receptor (EGFR) expression in HSPSs
   D. Differentiation of circulating monocytes to macrophages

4. **Which of the following variables is included in current algorithms designed to guide decision-making regarding optimal mobilization strategies?**
   A. Peripheral blood CD34+ cell count on day 1 of apheresis
   B. Peripheral blood CD34+ cell count on day 2 of apheresis
   C. Peripheral blood CD34+ cell count on day 3 of apheresis
   D. Peripheral blood CD34+ cell count on day 4 of apheresis

5. **Compared with chemomobilization with cyclophosphamide and G-CSF, mobilization with G-CSF plus plerixafor is associated with which of the following outcomes?**
   A. Higher median CD34+ cell yield with apheresis
   B. More patients reaching the minimal CD34+ cell collection threshold
   C. More patients reaching the optimal CD34+ cell collection threshold
   D. Greater demand for weekend apheresis

6. **Mobilization with G-CSF or G-CSF plus plerixafor, as guided by the Medical University of South Carolina (MUSC) algorithm, is associated with which of the following outcomes compared with chemomobilization?**
   A. Fewer median days of apheresis
   B. Shorter time from mobilization to autologous HSCT
   C. Similar rate of hospitalization due to neutropenic fever
   D. Higher estimated mean mobilization cost per patient

CME Evaluation Form

Please evaluate the effectiveness of this CME activity on a scale of 1 to 5, with 5 being the highest, by circling your choice. Fax *with the Answer Sheet* to the Office of Continuing and Professional Education, 414-456-6623, or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 10000 Innovation Drive, Milwaukee, WI 53226.

Overall Quality of the CME Activity	1	2	3	4	5
Articles in the publication were presented in a clear and effective manner.	1	2	3	4	5
The material presented was current and clinically relevant.	1	2	3	4	5
Educational objectives were achieved.	1	2	3	4	5
The CME activity provided a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias.	1	2	3	4	5

How will you change your treatment based on this CME activity?

Would you benefit from additional CME programs on this topic? Yes No

I have read these articles on Graft Mobilization in Autologous and Allogeneic Hematopoietic Stem Cell Transplantation, published in *Blood and Marrow Transplantation Reviews*, and have answered the CME test questions and completed the Evaluation Form for this activity.

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CME Assessment Test Answer Sheet – Program ID #11136

Release Date: August 15, 2011
Last Review Date: August 15, 2011
Expiration Date: August 15, 2012

Instructions

(1) Read the articles in the publication carefully. (2) Circle the correct response to each question on the Answer Sheet. (3) Complete the Evaluation Form. (4) To receive CME credit, fax the completed Answer Sheet and Evaluation Form to the Office of Continuing and Professional Education (414-456-6623) or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 10000 Innovation Drive, Milwaukee, WI 53226. No processing fee is required.

1.	A	B	C	D	**3.**	A	B	C	D	**5.**	A	B	C	D
2.	A	B	C	D	**4.**	A	B	C	D	**6.**	A	B	C	D

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