

# Challenging the Current Concepts of Stem Cell Mobilization

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### Target Audience

The target audience for this program includes stem cell transplant physicians, hematologists, hematologist-oncologists, medical oncologists, oncology specialty pharmacists, and allied healthcare professionals charged with the care of patients undergoing stem cell transplant.

### Learning Objectives

Upon completion of this educational activity, participants should be better able to:

- Describe limitations of current stem cell mobilization techniques
- Analyze novel stem cell mobilization strategies and ongoing clinical trial designs for incorporating stem cell mobilization agents
- Identify patients at risk for poor mobilization and develop treatment plans to maximize stem cells collected during apheresis
- Discuss ongoing clinical trials and future directions in stem cell mobilization

### Statement of Need

A frequent approach to mobilizing stem cells for peripheral collection involves administering hematopoietic growth factors. Currently, granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are used in the autologous setting, while G-CSF is predominately used in the allogeneic setting. Growth factors are generally administered for 4-6 days prior to cell collection to allow adequate time for CD34+ cell mobilization from bone marrow to peripheral circulation. Chemotherapy administration prior to growth factor is a common approach that may increase peripheral blood stem cells (PBSC) 5-15 fold, but also introduces the risk of chemotherapy toxicity. In current clinical practice, patients who do not mobilize enough CD34+ cells for collection following multiple attempts at apheresis may require painful bone marrow harvest. Novel methods for obtaining the optimal dose of stem cells in the most efficient manner for transplant represent a significant medical need in autologous SCT. Furthermore, continuing clinical investigation in the allogeneic setting may demonstrate improved convenience for normal donors, and pharmacoeconomic analysis may indicate health-system cost savings. Healthcare professionals caring for patients requiring stem cell mobilization prior to SCT need to understand the basis for emerging therapeutic options, and the preclinical and clinical data supporting the development and integration of novel mobilization regimens into clinical practice. This live educational program will address optimal integration of emerging therapeutic strategies regarding stem cell mobilization, describe the means of optimizing stem cell mobilization while minimizing adverse events, and provide a perspective for directions in stem cell mobilization.

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## Introduction

The first hematopoietic stem cell transplant (HSCT) for malignant disease was reported in 1957.<sup>1</sup> Today more than 50,000 autologous (auto-SCT) and allogeneic (allo-SCT) stem cell transplants are performed annually for both malignant and non-malignant hematological disease.<sup>2</sup> Since that first report, marked improvements to the procedure have resulted in increased numbers of long-term survivors and decreased adverse effects. Modifications of the graft, both in what it is composed of and how it is obtained, are among the many changes that have taken place over the years. Current sources for HSCT grafts include bone marrow, mobilized peripheral blood stem cells (PBSC), and cord blood. Today, more than 90% of auto-SCT and 70% of allo-SCT in adults are conducted using mobilized PBSC (**Figure 1**).<sup>3</sup> The quality of the mobilized stem cell product, currently measured only by the quantity of CD34+ cells, is a critical factor for engraftment, and further optimization of the PBSC mobilization procedure may improve outcomes.<sup>4</sup> Therefore, a prestigious group of 16 stem cell transplant experts from top institutions around the nation joined chair, Sergio A. Giralt, MD of The University of Texas, MD Anderson Cancer Center, to discuss the history, current status, and future directions of hematopoietic stem cell mobilization.

**“Five years ago we had an advisory board, and people weren’t really excited about mobilization ... it seems like the winds are shifting, and there may be more interesting questions to ask about mobilization and what we should be looking at in the future.”**

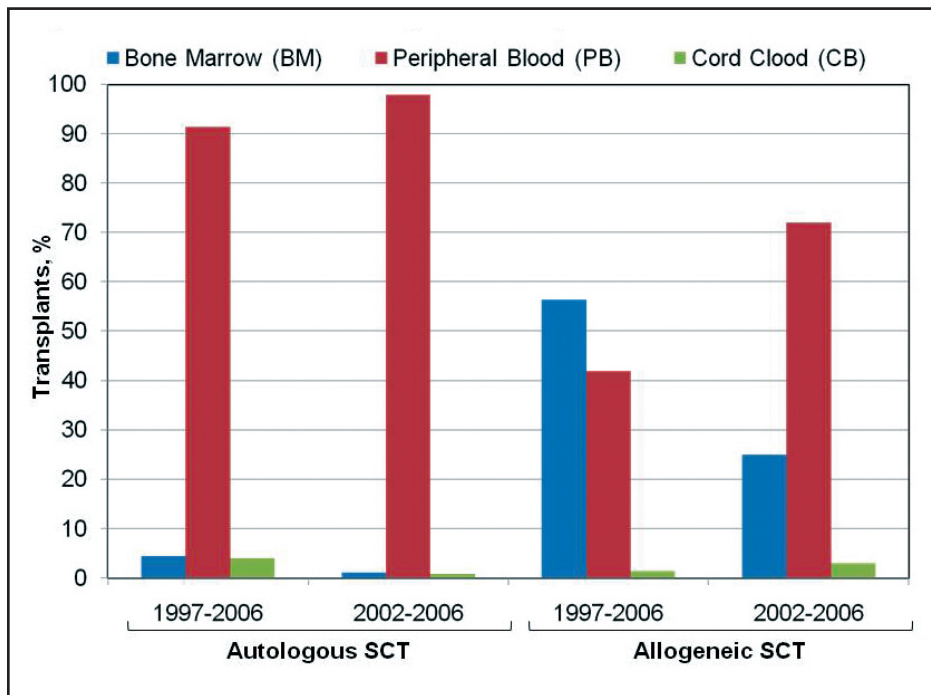
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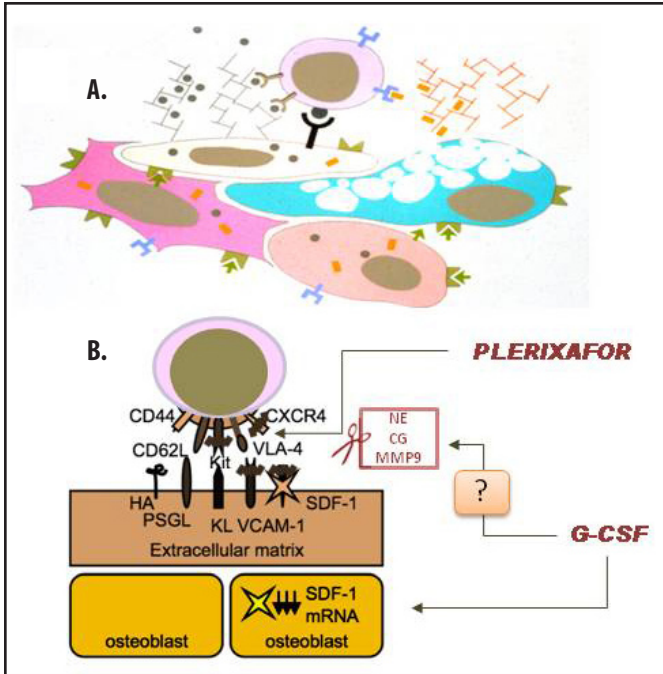
## Biology of Hematopoietic Stem Cell Mobilization

The bone marrow (BM) microenvironment is comprised of a complex mixture of cells (mesenchymal cells [eg, fibroblasts, adipocytes, and smooth muscle], osteoblasts, and monocyte/macrophages) and extracellular matrix components (collagens, fibronectins, and proteoglycans).<sup>5,6</sup> Hematopoietic stem cells (HSC) reside in highly organized niches within the BM microenvironment and are anchored to the stroma by interactions between receptors and ligands expressed on the cell surface of HSC and stromal cells (**Figure 2A**). Adhesion molecules expressed by HSC include very late antigen-4 (VLA-4), the hyaluronan (HA) receptor, CD44, c-kit, the L-selectin CD62L, and the chemokine receptor CXCR4. BM stromal cells express cognate ligands for these receptors such as vascular cell adhesion molecule-1 (VCAM-1), kit ligand, P-selectin glycoprotein ligand (PSGL), HA, and stromal cell derived factor-1 (SDF-1).<sup>4,7</sup> Factors that alter the adhesion molecule expression profile change the HSC-stroma interaction and can result in HSC mobilization (**Figure 2B**).<sup>8</sup>



**Figure 1:** Stem cell sources in patients 20 years or older  
Pasquini M, Wang Z, Schneider L. *CIBMTR Newsletter*. 2007;12(2):5-8. Available at: <http://www.cibmtr.org/PUBLICATIONS/Newsletter/DOCS/2007Dec.pdf>.

Various hematopoietic growth factors, some chemokines, and cytotoxic chemotherapeutic agents induce HSC mobilization. In the 1980's it was demonstrated that autologous mobilized PBSC will reconstitute ablated bone marrow.<sup>9</sup> Since then, the use of mobilized PBSC has been shown to result in higher CD34+ content in grafts, shorter hospital stays, shorter engraftment times for neutrophils and platelets, improved immune reconstitution, and reduced morbidity.<sup>4,10,11</sup> Therefore, PBSC mobilization is attempted in nearly all adult auto-SCT and in the majority of allo-SCT.



**Figure 2:** (A) Depiction of the hematopoietic stem cell (HSC) anchored to the bone marrow stroma. Figure kindly provided by Beverly Torok-Storb, PhD. (B) Plerixafor and G-CSF disrupt adhesion between the HSC and stroma. Figure adapted from Nervi B, Link DC, DiPersio JF. Cytokines and hematopoietic stem cell mobilization. *J Cell Biochem.* 2006;99:690-705.

Granulocyte Colony Stimulating Factor (G-CSF) is the most widely utilized mobilizing agent.<sup>4</sup> The cytotoxic chemotherapeutic agents cyclophosphamide, paclitaxel, and etoposide are commonly used in combination with G-CSF for chemomobilization. In addition, the chemokine receptor inhibitor plerixafor (AMD3100) in combination with G-CSF and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) are FDA approved for stem cell mobilization (**Table 1**).<sup>12</sup>

G-CSF increases the number of granulocytes and granulocytic precursors in the microenvironment causing a release of neutrophil serine proteases, cathepsin G, neutrophil elastase, and matrix metalloproteinase-9 (MMP-9).<sup>13</sup> Increased concentration of these factors results in cleavage of VCAM-1, c-kit, CXCR4, and SDF-1. Compared to G-CSF, GM-CSF is a less potent mobilizing agent. However, GM-CSF does act synergistically with G-CSF and the combination is sometimes used as a salvage mobilization regimen.<sup>8,14</sup> Stem cells are also commonly mobilized during hematopoietic recovery after treatment with many myelosuppressive chemotherapeutic agents. Mobilization by chemotherapeutic agents is augmented by the addition of many cytokines such as G-CSF and GM-CSF.<sup>8,15</sup> Plerixafor is a reversible antagonist of CXCR4 that disrupts the CXCR4-SDF-1 interaction and downstream signaling, resulting in rapid HSC mobilization.<sup>16,17</sup>

## Defining a Successful Mobilization

Presented by Sergio A. Giralt, MD

The University of Texas, MD Anderson Cancer Center

The goal of peripheral blood mobilization is to produce a sufficient number of hematopoietic stem cells to achieve prompt and durable hematopoietic reconstitution after high-dose chemotherapy and HSCT. Current protocols use CD34+ as a surrogate marker for hematopoietic stem cells and define adequate engraftment as recovery of the absolute neutrophil count (ANC) to greater than  $0.5 \times 10^9/L$  in 10-14 days and platelet counts to more than  $20 \times 10^9$  platelets/L in 15-30 days post transplant with durable hematologic and immune system recovery.

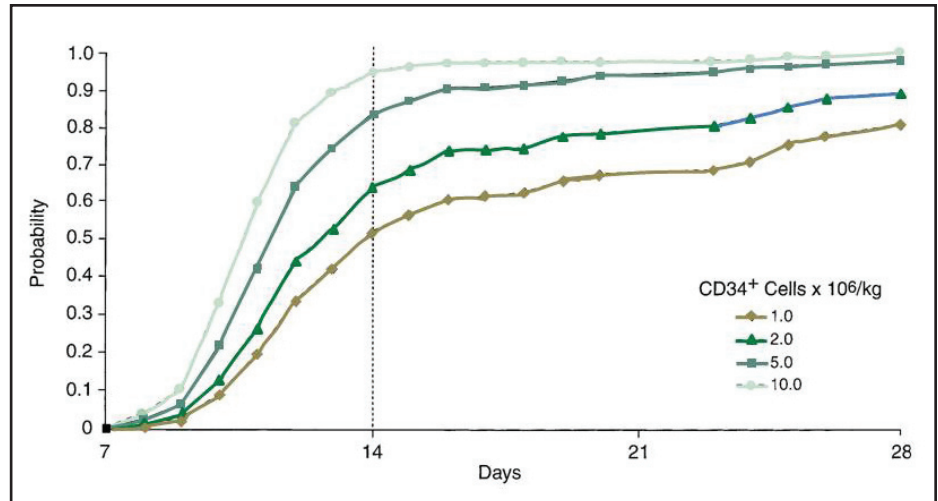
Auto-SCT is the standard of care for multiple myeloma (MM) and chemosensitive relapsed high or intermediate grade non-Hodgkin's lymphoma (NHL). Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) suggests that for MM patients undergoing auto-SCT in North America, 56% use growth factor plus chemotherapy mobilized product, 38% use growth factor only mobilized product, and 2% use chemotherapy alone mobilized product. For NHL, greater than 80% of transplants use chemo-mobilized product.

**Table 1: Commonly used mobilization agents for auto-SCT**

G-CSF	Most commonly used factor Granulocyte expansion/activation Protease release Cleavage of adhesion molecules
GM-CSF	Used in combination with G-CSF for salvage mobilization Stimulates production of granulocytes and macrophages
Plerixafor	Approved in combination with G-CSF for MM and relapsed NHL Disrupts CXCR4/SDF-1 interactions
Chemotherapeutic Agents -Cyclophosphamide -Paclitaxel -Etoposide	Used in combination with G-CSF Mechanisms not well understood Expansion and activation of granulocytes



The success of auto-SCT is dependent upon a number of factors including the dose of infused stem cells. Stem cell dose, as measured by CD34 expression, influences time to platelet and neutrophil engraftment and supportive care needs. In the United States, the average number of infused CD34+ cells per kg body weight is approximately  $3\text{-}5 \times 10^6$  cells. However, the optimum CD34+ cell dose is unknown, and there is no clear consensus on the minimum CD34+ cell dose needed for successful auto-SCT. When patients are given  $2 \times 10^6$  CD34+ cells/kg, 60% recover platelets by day 14. However, when  $10 \times 10^6$  CD34+ cells/kg are given, 90% of patients recover platelets by that time (**Figure 3**).<sup>18</sup> In addition, retrospective analysis suggests that the CD34+ cell dose may impact patient symptom burden. In one study, patients receiving  $10\text{-}15 \times 10^6$  cells peak symptom burden appear to be significantly less compared to those receiving  $4\text{-}6 \times 10^6$  cells (Giralt S., unpublished data).



**Figure 3:** Stem cell dose and platelet engraftment. Cox proportional hazards analysis for probability of platelet engraftment to  $20 \times 10^9$  platelets/L by CD34+ cell dose (n = 212). Glaspy EJ, Shpall CF, LeMaistre CF, et al. Peripheral blood progenitor cell mobilization using stem cell factor in combination with filgrastim in breast cancer patients. *Blood*. 1997;90(8):2939-2951.

Generally, patients who collect more than  $2 \times 10^6$  CD34+ cells/kg within 1-2 days are defined as “good” mobilizers. Patients who take longer or are unable to collect  $2 \times 10^6$  CD34+ cells/kg are considered “poor” mobilizers. Difficult mobilization has been shown to be a negative predictive factor in auto-SCT outcome.<sup>19-21</sup> In addition, retrospective analysis of 172 NHL patients treated with high-dose therapy and autologous PBSC transplantation found that the cost of transplant for “poor” mobilizers was significantly more than “good” mobilizers (\$80,833 versus \$140,264).<sup>22</sup>

While it is unclear precisely why some patients mobilize poorly, several factors have been identified that negatively impact stem cell collection from peripheral blood. For patients with MM, increased age and prior exposure to melphalan or lenalidomide are thought to negatively impact collection. While the use of melphalan prior to collection is rarely seen today, induction therapy with lenalidomide for MM is common. Although there are conflicting reports regarding the impact lenalidomide has on collection, several groups have reported that extended exposure of patients to lenalidomide negatively influences the number of peripheral blood CD34+ cells.<sup>23-26</sup> In general, NHL patient mobilization is more challenging. The number of prior therapies and platelet count are thought to correlate with differential ability to mobilize.<sup>27</sup>

For patients who fail to mobilize, options include repeat mobilization with G-CSF, alternative cytokine regimens (increased dosing of G-CSF or combining G-CSF and GM-CSF), addition of chemotherapeutic agents, bone marrow collection via a traditional harvest, or the addition of plerixafor. All options are associated with increased costs. In addition, repeat mobilization with G-CSF adds additional product volume (when combined with previous collections), yields higher morbidity rates, and has high associated failure rates.<sup>28</sup> Alternative cytokine regimens and the addition of chemotherapy are associated with added toxicity and the efficacy rates are generally low. For bone marrow harvests, patients must be put under general anesthesia, which is associated with higher rates of morbidity. Successful remobilization with plerixafor after failed chemotherapy or cytokine mobilization was reported to be greater than 70% in one study.<sup>29</sup> However, the plerixafor-induced grafts differ in composition<sup>30</sup> and long-term studies have not been performed. Side effects associated with plerixafor are generally mild and include pain at the injection site, lightheadedness, bloating, flatulence, perioral paresthesias, diarrhea, and headache.<sup>31,32</sup> The addition of plerixafor to the mobilization armamentarium has raised several new questions regarding the optimal mobilization strategy.

### Roundtable Discussion

A number of key topics, such as the minimum and target CD34+ cell numbers, quality of the graft, and incorporation of plerixafor into their individual treatment algorithms, were discussed during the roundtable. The faculty agreed that  $2 \times 10^6$  CD34+ cells/kg

body weight is the minimum target for an auto-SCT. Some of the faculty would transplant patients who had between 1 and 2 million CD34+ cells, but only after multiple mobilization attempts and only on a case by case basis. “Our target is 2 million. We will do 1.9 and 1.8 ... but if we get below 1.5 or 1.6, we will make a second attempt. That second attempt will either be salvage with plerixafor or sometimes a bone marrow harvest,” said Robert J. Soiffer, MD of the Dana-Farber Cancer Institute. Concerns about using less than 2 million cells included delayed engraftment and higher treatment-related mortality.<sup>33</sup> Jayesh Mehta, MD of Northwestern University added, “we could do with less than 2 million ... if there is absolutely no other option, but we would typically have made at least 2 and usually 3 mobilization attempts by that time ... below 2 million the engraftment times get prohibitively high and treatment-related mortality does go up.”



When asked for their optimum target CD34+ cell number, answers from the faculty varied. For lymphoma, the optimum ranged from 4-10 million. For MM the range was 4-20 million. While higher cell dose does lead to more rapid engraftment,<sup>4</sup> it is unknown whether more rapid engraftment translates to improved long-term survival. “We don’t have data beyond hematopoietic engraftment, so does the higher dose lead to better immune reconstitution? Does it lead to improved survival? Is there less myelodysplasia? ... We need better data ... looking at endpoints other than hematopoietic recovery as the goal of the transplant,” said Richard Champlin, MD of MD Anderson Cancer Center. However, until a prospective randomized study comparing cell dose is undertaken and completed, it is difficult to set an optimal target. When asked if he thought that study should be done, Dr Soiffer answered, “I’m not sure that it’s worth our resources to do that question, but I think it’s an interesting question. If a group or company wanted to do that kind of a trial, I think it would be a very interesting one to do. It might advance the field.”

Whether the target number of CD34+ cells should include enough cells for future use, was another area of debate. Dr Mehta said, “One of the reasons we try to collect 10 million in lymphoma is not to give all 10 million. We actually withhold 5 million in reserve, because all of these patients relapse. When they get chemotherapy for relapse, their bone marrow often burns out and we use the stem cells to reconstitute hematopoiesis. We do the same thing with the myelomas. In myeloma, not only do we want 20 million, but we want them aliquoted in at least 4 different bags, where each bag should be sufficient to reconstitute hematopoiesis.” Others agreed that their optimum target included enough cells for storage. Shaji Kumar, MD from the Mayo Clinic would attempt to collect enough cells for storage for future salvage transplant in patients younger than 65 years. Some faculty, however, raised concerns about the cost-effectiveness of collecting cells for storage if they may not be used.

Quality of the mobilized product is also critical, but graft quality is much more difficult to assess. Moreover, the composition of an ideal graft is currently unknown. In addition, the effects of  $2 \times 10^6$  cells collected in a single day has not been compared directly to a greater number of cells collected over a longer period of time. “The quality of 2 million cells collected in 1 day is significantly different than 2 million cells collected over 5, 6, 7 or however many days you collected” said Jeffrey R. Schriber, MD, FACP from the City of Hope. He also described an institutional retrospective analysis comparing  $2 \times 10^6$  cells collected in 1-2 days to  $2 \times 10^6$  cells collected over a longer period of time.<sup>34</sup> “There was a difference in engraftment. There are real differences,” said Dr Schriber. Another area of concern with multiple apheresis is tumor cell contamination. “If you are doing multiple collections over a long period of time ... we would worry about if you are gradually getting a higher number of malignant cells and there might be some threshold effect there that would lead to an adverse outcome. The relationship of the mobilizing regimen in tumor cell contamination is still debated,” said Dr Champlin. Concerns regarding quality of the graft are valid and important; however, until the optimum graft is defined and easily assessed, surrogate markers such as CD34+ numbers will continue to guide therapy.

The majority of faculty agreed that the addition of plerixafor to the mobilization armamentarium has affected patient transplants, but the faculty differed on how it affected them. Some faculty felt that patients are now being transplanted who would not have been before the availability of plerixafor. John M. McCarty, MD of Massey Cancer Center found that in a retrospective analysis plerixafor was responsible for 74 auto-SCT that would not have been performed based on failure to mobilize 10 CD34+ cells/ $\mu$ L or collect at least  $2 \times 10^6$  cell/kg in 4 apheresis attempts (McCarty JM, unpublished

**“I don’t think plerixafor has changed how many people we bring to transplant. It’s just changed how they get to transplant ... you can get it done much faster and it’s easier on everyone if you have plerixafor, then you don’t have to go to the OR. You don’t have to do multiple different strategies of mobilization.”**

*Robert J. Soiffer, MD*

Harvard Medical School, Dana-Farber Cancer Institute



data). Madan Jagasia, MBBS, MS from Vanderbilt University agreed saying, "10% of myeloma patients don't mobilize with chemo and G-CSF. Around 15% to 20% of the lymphoma patients don't mobilize. I think if 70% of these patients can be salvaged with plerixafor, I think it's going to lead to that many more transplants." However, Nelson J. Chao, MD, MBA from Duke University felt plerixafor would salvage only those patients for whom bone marrow could not be harvested. Other faculty stated that plerixafor hasn't changed the number of patients getting transplants, but it has changed how they get to transplant. Finn Bo Petersen, MD from Salt Lake City said, because of very aggressive protocols, his group has been successful in attaining the minimum number of cells for the vast majority of patients. In his case, the change has been in how the patient gets to transplant, "I think what plerixafor has meant for us is a lot less patient suffering to get there and higher CD34 numbers to transplant," he said. This was echoed by several faculty, stating that, prior to plerixafor, they would perform numerous apheresis, aggressive mobilization protocols, or bone marrow harvests. "These same patients that we would have predicted a long apheresis period and prolonged engraftment, now mobilize with plerixafor, we haven't seen delayed engraftment," said Michael W. Schuster, MD from Cornell University. Although most of the faculty agreed with this assertion, there has not been a randomized study on the subject.



**Summary I**



	Myeloma	Lymphoma
Minimum threshold:	2 x 10 <sup>6</sup> CD34+ cells/kg	2 x 10 <sup>6</sup> CD34+ cells/kg
Target:	6-10 x 10 <sup>6</sup> CD34+ cells/kg, divided into 2 collections	5 x 10 <sup>6</sup> CD34+ cells/kg
Predictors of poor mobilization:	Age, melphalan exposure, lenalidomide exposure	Number of prior regimens, CBC, low platelet count, fludarabine exposure

**Rationale for Current Mobilization Regimens**

**Presented by Steven M. Devine, MD, The Ohio State University**

Currently, the availability of data on mobilization from randomized controlled studies is limited. Therefore, a great deal of discussion is generated from anecdotes and clinical impressions. The transplant team at The Ohio State University has developed a practical approach to mobilization. However, this approach, which is intended to utilize the available biologic and clinical data, still includes biases. Dr Devine attempted to explain these biases and the rationale used to develop the Ohio State approach. Cost, resource utilization, safety, and efficacy are among the key factors that affected the decision making process. In addition, practical issues, such as predictability of mobilization, were also incorporated.

At The Ohio State University, most patients receive their salvage chemotherapy or myeloma-induction therapy from the referring physicians. Patients are often referred to Ohio State after the fact, when it is too late to incorporate mobilization into the final chemotherapy cycle. In addition, there is currently no data available comparing chemomobilization to G-CSF in terms of disease-free or overall survival. The kinetics of CD34+ cells are also less predictable with chemomobilization compared to G-CSF, and toxicity is increased. When the data at Ohio State and Washington University were analyzed, there was approximately a 10-20% admission rate for febrile neutropenia and a higher likelihood of central line infections with chemotherapy-based mobilization. In addition, total transplant charges at Ohio State are approximately 50% less with G-CSF alone compared to chemotherapy (Devine SM, unpublished data). Therefore, chemotherapy-based mobilization is generally not used in the Ohio State mobilization algorithm.

The Ohio State mobilization regimen for Hodgkin's Disease (HD), NHL, and MM uses 10 µg/kg G-CSF. On day 5 a peripheral blood CD34+ cell count is performed. If the count is greater than 10 CD34+ cells/µL, cells are collected. The cutoff of 10 CD34+ cells/µL was used because approximately 95% of collections at The Ohio State University with a COBE Spectra at 4 times blood volume yielded at least 1 x 10<sup>6</sup> CD34+ cells/kg. Below 10 cell/µL the variability increases (Devine SM, unpublished data). The goal is to collect at least 5 x 10<sup>6</sup> CD34+ cells/kg in up

**Table 2: The Ohio State University historical mobilization failure rates using G-CSF alone**

Patients	Percent Failing to Mobilize*
Total	17.3%
Lymphoma	38.5%
Multiple Myeloma	10.7%

\*Failure defined as peripheral absolute CD34+ cell count ≥ 10. Devine SM, unpublished data.

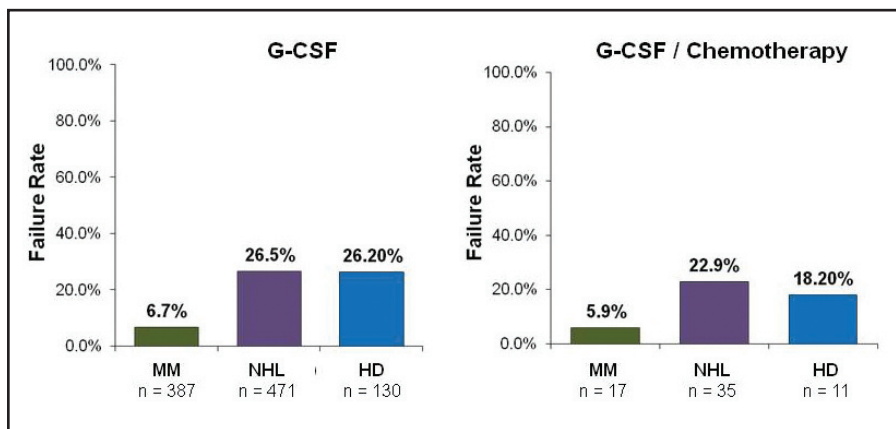
to 4 collections. The minimum to proceed to transplant is  $2 \times 10^6$  CD34+ cells/kg. When more than  $2 \times 10^6$  CD34+ cells/kg are collected, apheresis is discontinued and patients are transplanted. The mean number of collections at Ohio State is 2.25, and approximately 17% of patients do not yield  $2 \times 10^6$  CD34+ cells/kg. The mobilization failure rate for lymphoma patients is higher than for MM patients (38.5% lymphoma versus 10.7% MM) (Devine SM, unpublished data) (Table 2). However, although no formal study has been conducted, the percent of MM patients failing mobilization appears to be increasing as more patients are exposed to longer durations of lenalidomide-based therapy.

**“It is key to try to make that first mobilization attempt work.”**

*Steven M. Devine, MD*  
The Ohio State University

Data from the Washington University database suggests that the probability of converting a poor mobilizer to a good mobilizer is similar between G-CSF and G-CSF plus chemotherapy. According to these data, the failure rate with G-CSF alone or G-CSF with chemotherapy is approximately 20% (Figure 4).<sup>35</sup> However, the database included only a small number of patients and may be biased because patients who received chemotherapy plus G-CSF may have been selected based on their likelihood to mobilize poorly.

At The Ohio State University, enough CD34+ cells were obtained in 51% of patients re-mobilized with chemomobilization after failure with G-CSF alone. Another 10% were remobilized with G-CSF plus plerixafor and all were successful. Overall, approximately 31% of patients who failed to mobilize after the first attempt never made it to the autograft (Devine SM, unpublished data). Because of concerns of slower engraftment, increased platelet transfusions, and more transplant-related morbidity, bone marrow was not harvested from any patient. Overall, 30% of patients who failed initial mobilization failed remobilization. These data suggest that a successful first mobilization is critical.



**Figure 4:** First mobilization failure rates\* for MM, NHL, and HD<sup>†</sup>

\*Failure Rates defined as  $< 2 \times 10^6$  CD34+ /kg after 5 days of apheresis.

<sup>†</sup>MM, multiple myeloma; NHL, non-Hodgkin’s lymphoma; HD, Hodgkin’s disease; G-CSF, granulocyte colony stimulating factor. Pusic I, Jiang SY, Landua S, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. *Biol Blood Marrow Transplant.* 2008;14(9):1045-1056.

Clearly there is a need for more effective and predictable PBSC mobilization strategies. Currently mobilization failure rates are high and result in increased cost, time to engraftment, and patient burden. The criteria currently used to recognize poor mobilizers is neither sensitive nor specific. Patients with risk factors for poor mobilization who are treated at Ohio State are pre-approved for plerixafor. On day 4 or 5 a peripheral blood CD34+ count is performed. If the cell count is less than  $10 \text{ CD34+ cells}/\mu\text{L}$ , plerixafor is administered in the evening and cells are harvested the next day. For patients who must obtain plerixafor from an outside pharmacy, a pre-planned dose of plerixafor is given on day 5. This strategy is based on the idea that it is better for patients to collect in their first attempt and move to transplant, although this approach has not been validated in a randomized study.

## Roundtable Discussion

While the Ohio State Mobilization protocol has not been tested in a randomized trial, it has resulted in mobilization. “You are giving the drug in a way that is consistent with a labeled indication and if it works, that’s clinical validation,” said Edmund K. Waller, MD, PhD, FACP from Emory University School of Medicine. However, Dr Soiffer said, “It would be nice to have a trial to document that.” His institution is planning a retrospective analysis to determine how many patients can be successfully mobilized using a threshold peripheral CD34+ strategy. Mitchell E. Horwitz, MD from Duke University also discussed a planned study that will use a peripheral CD34+ threshold of  $7 \text{ cells}/\mu\text{L}$ . For that study patients will be pre-approved for plerixafor, and a dose will be given on day 5 if the peripheral counts are below the threshold.



The benefits and drawbacks of a pre-planned dose of plerixafor based on peripheral CD34+ cell counts versus a salvage mobilization were discussed. “We think it is a good idea because it makes sense in terms of what’s happening biologically. In the absence of a good prospective trial, we know that these patients are likely to have to undergo a second strategy because if they are less than 10 or less than 5 on day 5, those patients typically don’t do well,” said Dr Devine. Dr McCarty felt that using plerixafor as a salvage regimen is also a viable option. “A significant portion of patients were able to be mobilized subsequently with the use of G plus plerixafor,” he said. However, Melissa Alsina, MD from the H. Lee Moffitt Cancer Center brought up that engraftment would be delayed. She emphasized that the question is whether or not there is a difference in outcomes between patients undergoing a planned plerixafor dose based on peripheral CD34+ counts or patients going through with collection, stopping, and then trying to remobilize a week later with plerixafor and G-CSF. This is especially critical for lymphoma patients, given that extended durations off of chemotherapy have a negative impact on outcomes.<sup>36</sup>

For lymphoma, collection can often be coordinated off of a planned salvage chemotherapy regimen. When the chemotherapy is being done in-house, there is more control. Dr Schuster said that at his institution, this works well because the therapy is already being performed in-house. “We have much more control over it. This is a planned salvage regimen anyway. We are getting 2 bangs for the buck. We are giving them the salvage regimen and we are collecting off of that salvage regimen,” he said. It is more challenging if the chemotherapy is being performed by a referring physician. Dr Horwitz said, “We collect off salvage regimens, oftentimes by the referring physician ... It takes a lot of work. There’s no question, but we have the referring physician give the chemotherapy. They get their counts checked. The counts are faxed to us. We call them as soon as we think it is their time.” However, to coordinate this, there is a full-time position dedicated to coordinating and scheduling the mobilization with the referring physician.

Many MM patients are mobilized with G-CSF alone, but a number of the faculty stated that they use chemomobilization for the majority of their auto-SCT (whether it is off of a salvage regimen or not or in a MM or NHL patient). Some are incorporating plerixafor into their mobilization algorithm, and improving mobilization. Dr Soiffer said that more than 90% of his patients receive chemotherapy plus G-CSF. Plerixafor is administered when threshold CD34+ numbers are not met. Currently, there is very little data available with chemomobilization and plerixafor.

As the mobilization algorithm is changed, many institutions are planning or in the process of performing pharmacoeconomic analysis. There are many factors to consider. There are numerous tangible and intangible associated costs, especially for patients who don’t readily mobilize. Tangible costs for bone marrow harvests include operating room costs. For remobilization, there are additional apheresis. For plerixafor, there are additional drug costs. If a patient is not given enough cells up front, then the probability of a longer time to engraftment increases which translates into longer recovery time and more platelet transfusions, all of which add cost to the transplant. Even harder to assess are additional missed work days for the patient, and the cost to benefit if the cells are needed at a later time and not available. Other factors include the pay structure, how plerixafor is obtained (outside pharmacy, in-house), patient out of pocket costs, and quality of life. “You have to figure out what question you are trying to ask yourself. Much of it depends on your patient population ... you have to ask yourself at your own individual institution based on the numbers you pick and the patient population, etc. I’m not sure there is only one answer, but I think the studies that are being done will be very helpful,” said Dr Schriber.

Dr Jagasia and Dr Waller both discussed the pharmacoeconomic analysis done at their institutions. Dr Jagasia has analyzed 250 patients at Vanderbilt University. An ideal mobilization using chemotherapy plus G-CSF was defined as the collection of  $2 \times 10^6$  CD34+ cells on the planned day of pheresis in one apheresis without any negative clinical events. They found this to be achieved (using  $3 \text{ g/m}^2$  cyclophosphamide and G-CSF) only 25% of the time. Although detailed analyses are pending, Dr Jagasia said that from a pharmacoeconomic standpoint, when an ideal collection is achieved, the mobilization appears to be more cost effective with G-CSF and cyclophosphamide compared to when plerixafor is added. However, the majority of patients require additional days of collection, have a negative clinical event, or require G-CSF dose escalation. The cost-effective edge of G-CSF and cyclophosphamide is lost when the mobilization becomes more complicated.

**“Cost-effectiveness can be looked at in so many ways. What’s really going to matter is toxicity to the patient, convenience to the patient, and convenience to the transplant center.”**

*Koen van Besien, MD, PhD*  
University of Chicago



Dr Waller discussed cost effectiveness analysis at Emory Healthcare. According to Dr Waller, the largest cost associated with stem cell collection is cryopreserving the cells. Cryopreservation accounts for approximately 50% of the overall cost, apheresis is 35%, and thawing cells is 15%. For chemomobilization, 50% of patients collect the target in 1 day, 25% collect in 2 days, and the remainders are considered “slow-mobilizers.” The average cost for chemomobilization is approximately \$15,000-\$16,000. The addition of plerixafor makes the mobilization cost more, but because it increases the fraction of people collecting in 1 day the average cost worked out to be approximately \$1,000-\$2,000 more per case (Waller EK, unpublished data).

Most faculty agreed that the key to optimizing cost to benefit with plerixafor is to identify which patients will need it and optimize when to use it. “The trick is can you identify the outlier patients. Can you predict your hard to mobilize patients, and, in those patients, come up with a creative regimen where you can collect them is 1 goal,” said Dr Jagasia. Dr Petersen agreed with this saying, “We had an equation where we felt we could identify lymphoma patients and myeloma patients at high risk for failing mobilization. We put them on what we call a hard-to-mobilize protocol with increased doses of G and GM. When plerixafor became approved, we looked at the cost of the hard-to-mobilize protocol patients, which was a hard protocol for them and not infrequently required hospital admissions ... it was clear to us that both from a patient convenience point and from a cost point going to the plerixafor was an advantage.”

### Summary II



- Initiation of apheresis is often based on a peripheral blood CD34+ count of 5-10 cells/ $\mu$ L
- Some patients can be identified as “hard-to-mobilize”
- Mobilization attempts are generally made in “hard-to-mobilize” patients
- Plerixafor use has been incorporated into the patient algorithms for many institutions and is often based on:
  - CD34+ cell threshold or
  - “Hard-to-mobilize” identification
- Pharmacoeconomic issues still need to be determined
  - Many institutions have pharmacoeconomic analysis planned or underway
- The long-term impact of plerixafor on disease-free or overall survival is unknown

### Future Directions for Stem Cell Mobilization

**Presented by Edmund K. Waller, MD, PhD, FACP, Emory University**

Mobilization is a complex process that is not fully understood. CD44 is a key factor tethering the HSC stem cell to the microenvironment niche. The binding of CD44 to ligands on the surface of endothelial cells is potentially degraded by metalloproteases. In addition, there are inhibitors of matrix metalloproteases (MMP) expressed on the cell surface. More recently it has been demonstrated that G-CSF acts through phosphoinositide-3 kinase and AKT, downregulating the membrane-bound MMP neutralizing molecule, RECK, and upregulating metalloproteases.<sup>37</sup> As this complex process becomes better defined, one can easily imagine that robust mobilization targets, other than inhibitors of cell adhesion, could be identified. Small molecule inhibitors that act at the level of signaling are one possibility. Mobilization using small molecule inhibitors of the VLA-4/VCAM interaction were recently demonstrated.<sup>38</sup> Future mobilizations may include combinations of small molecules that interfere with both ligand/receptor interactions between the HSC and the stroma and intracellular signaling of metalloproteases and their inhibitors.

Clearly, it is not one size fits all. Biological differences likely account for some of the variability in patient mobilization. In an effort to model mobilization in vitro, cytokines were used to mobilize CD34+ cells from bone fragments in culture. The number of CD34+ cells that moved from the bone to the supernatant was measured over time. CD34+ cells moved from the bone to the supernatant in time and factor dependent fashion (Waller EK, unpublished data). This type of methodology could eventually be developed into a high-throughput screen whereby various agents are tested on individuals and the best mobilizing regimen is selected from the in vitro data.

However, there is still a great deal that needs to be optimized with the currently available agents and regimens. It has been demonstrated that CD34+ cell dose from bone marrow grafts significantly impact long-term survival. However, a clear impact of



CD34+ dose on long-term survival from the PBSC graft has not been demonstrated in both the allogeneic and autologous setting. The integrity of the graft, as measured by thrombopoiesis, significantly impacts survival and emphasizes the importance of graft quality.<sup>39</sup> Quality of the stem cells and composition of the optimal graft, not just the number of CD34+ cells being transplanted, are critical and must be better defined. ))

Further optimization of the integration of plerixafor into clinical protocols is needed. When to use plerixafor, how to use it, and precisely who to use it on needs to be further characterized. Currently at Emory, circulating CD34+ cells are measured and plerixafor is administered only when the numbers are suboptimal. A phase II prospective, single arm clinical trial is planned to determine if the addition of plerixafor to all chemomobilized patients will improve the number of patients who mobilize in a single day. Plerixafor will be administered on the evening after the patient's ANC is greater than 1500. Apheresis will start the next morning. The study is powered to detect an increase in the number of patients who mobilize on day 1 from 50% to 75%. The target collection number is  $10 \times 10^6$  CD34+ cells/kg for MM patients and  $5 \times 10^6$  CD34+ cells/kg for NHL patients. ))

Once mobilization is optimized for allo-SCT and auto-SCT for malignant conditions, mobilization strategies may be used to treat other conditions. Mobilization of HSC for auto-SCT in patients after myocardial infarction is one area where studies are being initiated. Another area is for patients with peripheral vascular disease. Finally, the ability to mobilize or chemosensitize malignant stem cells is also under investigation, and would open an entirely new therapeutic realm for mobilizing agents.

**Roundtable Discussion**

The faculty finished the roundtable by discussing how optimization of HSC mobilization should proceed. Integration of plerixafor clearly needs to be better defined. Even the optimal mode of administration is currently unknown. All faculty at the roundtable administer plerixafor subcutaneously, but preliminary data suggest that intravenous administration of plerixafor may be more robust, safe, and well-tolerated.<sup>40</sup>

The faculty were asked what study they would most like to see performed in the near future. The majority of faculty wanted a comprehensive, all inclusive study on the "just-in-time" protocol where circulating CD34+ cells are measured and plerixafor is administered only in patients who have not met a threshold cell number, ideally compared to a protocol where every patient gets plerixafor. Other selected studies included the correlation of graft quality and composition with reconstitution and outcomes, a validated model for up-front prediction of poor mobilizers, determination of the impact of plerixafor on long-term survival, defining the optimal number of CD34+ cells for infusion, pharmacoeconomic analysis and cost/benefit of plerixafor, and intent to mobilize analysis to determine if more patients are getting to transplant because of plerixafor availability.

**"I strongly feel we need a just-in-time study ... this is the type of question we can answer now."**  
*Robert J. Soiffer, MD*  
 Harvard Medical School, Dana-Farber Cancer Institute

Beyond the role of plerixafor as a mobilizing agent, future roles, either alone or in combination with other factors, may include the ability to chemosensitize or mobilize malignant stem cells. Dr Schuster concluded saying, "a far bigger homerun would be an enhanced ability to destroy malignant hematologic stem cells." ))

The entire Broadcast of the educational roundtable, Challenging the Current Concepts of Stem Cell Mobilization, can be found at [www.educationalconcepts.net/Webcast/MTH029AE1/index.html](http://www.educationalconcepts.net/Webcast/MTH029AE1/index.html).

**Summary III** ))

- Important studies for the future of mobilization:**
- "Just in time" with plerixafor
  - Graft composition and quality correlated with outcome
  - Differential mobilization of normal and malignant cells
  - Validated model for up-front prediction of poor mobilizers
  - Impact of plerixafor on long-term survival
  - Optimal CD34+ cell dose
  - Pharmacoeconomic and cost/benefit analysis
  - Intent to mobilize analysis

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