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This activity is supported by an educational grant from Sanofi Genzyme.

Symposium Report

2018 BMT TANDEM MEETINGS

Optimal Use of Stem Cell Mobilization in Patients with Multiple Myeloma and Non-Hodgkin's Lymphoma

Adapted from a continuing medical satellite symposium presented at the 2018 BMT Tandem Meetings on February 23, 2018, in Salt Lake City, Utah.
This program is supported by an educational grant from Sanofi Genzyme.

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CME and Support Information

This continuing medical education activity is co-provided by The Medical College of Wisconsin and Carden Jennings Publishing Co, Ltd.

Program Overview

The goal of this educational program is to improve the treatment of patients with multiple myeloma (MM) and non-hodgkin lymphoma (NHL) through the dissemination of information about stem cell transplantation and mobilization for autologous hematopoietic cell transplantation. The data for stem cell transplantation in MM is rapidly changing. The techniques of mobilization are still evolving. There is considerable debate regarding the timing and number of transplants for MM and the indications for transplant in NHL. The optimal use of transplant in the disease course and appropriate

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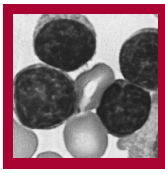

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continued from page 1

mobilization could drastically change the treatment of MM and NHL. This program serves as a medium to give physicians a chance to recognize these changes.

Learning Objectives

The following items are the learning objectives in CME format for this program. Upon completion of this program, participants will be able to:

- Identify existing and emerging strategies for optimizing stem cell transplantation in MM and NHL
- Evaluate current data on stem cell mobilization in patients with MM and Hodgkin's disease
- Determine the factors that affect and optimize the efficacy of stem cell mobilization

Target Audience

This activity has been developed and is intended for transplant specialists, oncologists, hematologists, and other healthcare professionals involved in the treatment of patients with hematologic malignancies.

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FROM THE EDITOR'S DESK

Optimizing Stem Cell Mobilization: Getting More for Less

Hemant Murthy, MD, Jack Hsu, MD, John R. Wingard, MD, University of Florida College of Medicine, Gainesville, FL

Autologous stem cell transplantation (ASCT) is an established standard of care treatment to improve survival in multiple myeloma and non-Hodgkin's lymphoma.

While much emphasis is placed on improving the efficacy of ASCT via disease specific interventions, the contribution of stem cell mobilization is often overlooked. The benefits of ASCT cannot be achieved without a successful stem cell mobilization, so efforts must also be focused on optimizing stem cell mobilization. With increasing demand for apheresis and limited budgets, it is important to find strategies to optimize mobilization in a cost-conscious manner. Ideally, the goal is that nobody will be denied a survival-enhancing transplant due to inadequate stem cell mobilization

Multiple approaches have been evaluated to optimize successful mobilization of stem cells and each strategy has its own unique set of benefits and pitfalls. The traditional approach of growth factors with or without chemotherapy can yield suboptimal collections in a significant number of patients, depending on disease type with failure rates of 9-18%. Chemomobilization, depending on the agent used, may be a more effective strategy from a standpoint of optimal stem cell collection, but has been limited by increased toxicities. Development of new mobilizing agents, such as plerixafor, have improved our ability to successfully mobilize patients, although cost poses a significant drawback. Alternatives to filgrastim, such as pegfilgrastim and TBO-filgrastim, may reduce costs or patient discomfort without altering mobilization effectiveness.

Fundamental questions still exist regarding goals and strategies on how to best mobilize patients. The optimal cell dose for a single autologous transplant is still an unanswered question. A particular mobilization strategy appropriate for a myeloma patient may not be optimal for a patient with lymphoma. Concerns about cost as well as availability of apheresis time also deserve consideration in choosing a mobilization regimen.

Efforts to optimize stem cell mobilization can be separated into two approaches, one being the development and validation of new agents for stem cell mobilization, such BL-8040. The other approach, and the focus of this review, is utilizing our current knowledge to construct decision algorithms to allow individualism of the best approach for each patient. Identifying optimal cell dose targets, recognizing risk factors for mobilization failures, and creating risk adapted approaches are just some of the strategies being developed based on our current knowledge.

This issue was developed from a symposium presented at the BMT Tandem Transplant meeting at Salt Lake City in February 2018. Dr. Luciano Costa discusses the mechanism of mobilization and various mobilization strategies, including benefits and risks, while also accounting for disease and other risks for mobilization failure. Dr. Parameswaran Hari details specific issues in patients with multiple myeloma and lymphoma as well as the issue of stem cell remobilization. Both discuss and detail consensus guidelines and considerations for stem cell mobilization in current day practice.

Determination of the optimal mobilization strategy for a patient can be complicated. Our challenge is to get the most stem cells possible for less: less expense, less chance for failure, less toxicity, less hassle.

Luciano J. Costa, MD, PhD

Introduction

Autologous stem cell transplantation (ASCT) is the established standard of care in the United States (US) for improving survival in patients with multiple myeloma and lymphoma. Successful transplant outcomes first requires successful stem cell mobilization. As researchers explore new mobilization strategies, best practices are taking shape in the multiple myeloma and lymphoma settings. This issue of *Blood and Marrow Transplantation Reviews* focuses on emerging strategies for optimizing stem cell mobilization outcomes in patients undergoing ASCT.

Optimal Mobilization Strategies

Luciano J. Costa, MD, PhD

Mechanisms of Mobilization

Hematopoietic stem cells (HSCs) reside in the bone marrow, where they express a wide range of adhesion molecules and interact with a diverse population of stromal cells in the extracellular matrix [1]. Multiple chemical signals are involved in breaking the adhesive interactions and trafficking the movement of HSCs from the extracellular matrix into the peripheral blood (PB). Key mediators promoting HSC mobilization include granulocyte-colony stimulating factor (G-CSF) and other growth factors (GFs), as well as various cytokines and chemokines. Manipulating the innate process of HSC mobilization enables the collection of stems cells via apheresis for both autologous and allogeneic transplantation [1].

Multiple approaches to inducing HSC mobilization have been evaluated [1]. Chemotherapeutic agents stimulate cell mobilization by inducing a state of severe neutropenia that triggers an influx of endogenous GFs. Exogenous GFs also degrade the links within the extracellular matrix that bind stem cells to the bone marrow. Plerixafor directly antagonizes CXCR4 to release HSCs from the bone marrow into the PB. When used concurrently, multiple mobilization agents act synergistically to break the links between stem cells and the bone marrow and to prevent their reattachment [1].

Target Stem Cell Dosing

To understand the optimal number of cells needed for transplant, Glaspy and colleagues evaluated the relationship between CD34+ cell yield and engraftment in a study of 212 patients with high-risk breast cancer [2]. Up to a certain threshold, an increasing number of transplanted cells corresponded with an increasing likelihood of engraftment. For instance, infusion of 5 x 106 CD34+ cells/kg was associated with an 85% probability of platelet engraftment (defined as ≥20 x 109/L) by day 14 post-transplant, as well as a very low incidence of delayed platelet recovery beyond 28 days. Similarly, the probability of engraftment decreased with infusions of fewer cells. Among patients infused with 5 x 106 CD34+ cells/kg, the probability of engraftment was 65% by day 14, with approximately 10% of patients experiencing delayed platelet recovery.

In 2011, Stiff and colleagues examined the importance of CD34+ cell dose relative to long-term graft function measured at 12 months [3]. The post-hoc analysis of data from 2 multicenter phase III trials included 438 patients with NHL or multiple myeloma who underwent mobilization for ASCT. Patients were stratified according to the dose of CD34+ cells transplanted: 2-4 × 106 cells/kg, >4-6 × 106 cells/kg, and >6 × 106 cells/kg. In the NHL cohort, the was a statistically significant linear trend between increasing cell dose and increasingly likelihood of engraftment (P = .020 for trend). At 12 months, 56%, 81%, and 83% of patients with NHL, respectively, had platelet counts >150,000/μL. Among patients with multiple myeloma, the likelihood of engraftment was 74%, 83%, and 81% across dosing groups, respectively, and the trend did not reach statistical significance (P = .435). Together, these findings demonstrate a relationship between higher transplanted CD34+ cell dose and more favorable long-term platelet recovery following ASCT.

Despite evidence supporting higher CD34+ cell dosing, controversy persists regarding the optimal target number of HSCs for collection and transplant. Advocates in favor of collecting more stem cells list advantages such as faster engraftment, shorter hospital stays, fewer transfusions, reduced antimicrobial use, and the potential for better survival. Conversely, the limitations of collecting more cells include a higher number of apheresis procedures, higher costs and resource utilization, and potential tumor contamination. To provide guidance for the practice setting, Giralt and colleagues developed expert consensus recommendations for minimum and ideal target stem cell doses for a single autologous HSCT procedure (Table 1) [4]. Of note, increasing evidence suggests that patients with multiple myeloma may benefit from a second salvage transplant.

Current Options for Stem Cell Mobilization

As discussed, successful ASCT requires the collection and cryopreservation of hematopoietic progenitor cells (HPCs) to ensure safe engraftment. The most common approach to mobilization involves the use of hematopoietic GFs, such as

Table 1. Minimum and Ideal Target Stem Cell Doses for Autologous Hematopoietic Stem Cell Transplantation [4]

	Minimum Recommendation	Ideal Target
Stem cell dose	2 x 106 CD34+ cells/kg	3-5 x 106 CD34+ cells/kg
Additional considerations	· Use of collection yields of 1-2 x 106 CD34+ cells/kg for autologous HSCT should be individualized to each patient's clinical circumstances · Such doses may be used if needed and if benefit of autologous HSCT is compelling	· Yield of 2.5 x 106 CD34+ cells/kg in a single apheresis session may be reasonable to avoid prolonging mobilization by several days to reach ideal target dose · Higher targets necessary if multiple transplantations are planned

HSCT, hematopoietic stem cell transplantation.

G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF). Additional options have also been utilized to increase CD34+ cell yield and reduce the risk of mobilization failure.

Depending on the target patient population, each of the leading strategies for stem cell mobilization has distinct advantages and limitations (Table 2). The first strategy involves the use of cytokine mobilization agents alone, most commonly G-CSF. Other agents such as GM-CSF and pegylated filgrastim are also used. The second strategy, called chemomobilization, involves the combined use of cytokines (G-CSF of GM-CSF) plus chemotherapy to increase stem cell yield. Cyclophosphamide and etoposide are the most common chemotherapeutic agents used in current practice. Disease-specific regimens have been developed for patients with lymphoma and other tumor types. Third, the combination of cytokines plus plerixafor is also emerging as an important option for stem cell mobilization.

Mobilization Failure

In current practice, failed attempts at stem cell mobilization are not uncommon. In 2010, Gertz and colleagues described the natural history of initial stem cell mobilization attempts performed at the Mayo Clinic in Rochester, Minnesota, from 2001 to 2007 [5]. During this 7-year period, a total of 2,660 patients received GF therapy for HSC mobilization. Of these, 1,775 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).

For the initial mobilization attempt, the collection goal was ≥5 x 106 CD34+ cells/kg. Results of the CD34+ HSC collections varied across cancer types (Table 3) [5]. The majority of patients with multiple myeloma (70%) reached this goal during collection. By comparison, only 43% of patients with Hodgkin's lymphoma and 29% of those with NHL had optimal HSC collections. For many, the stem cell yield was low (≥ 2 x 106 and <5 x 106 CD34+ cells/kg), but patients underwent transplant with the collected cells despite the suboptimal yield. For a sizable minority of patients, the stem cell yield was poor (< 2 x 106 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.

In the overall study population, 47% of patients had less-than-optimal initial mobilization attempts and stem cell collections [5]. Management of these patients was associated with increased resource utilization in the form of increased GF and antibiotic use, subsequent chemotherapy mobilization attempts ('remobilizations'), increased transfusional support, additional apheresis procedures, and more frequent hospitalization during remobilization. The Mayo Clinic experience highlights the ongoing challenges of stem cell mobilization.

Predicting Mobilization Failure

Given the potential limitations of each mobilization strategy, it is important to identify patients who are most likely to benefit from GF alone, GF plus chemotherapy, or GF plus plerixafor. Several factors are associated with poor mobilization, including increasing age, history of diabetes or smoking, and lower steady-state platelet count. In general, patients with lymphoma are typical worse mobilizers than patients with multiple myeloma. Treatment history can jeopardize mobilization, including prior exposure to lenalidomide (>4 cycles), fludarabine, or bendamustine, extensive radiation, and radioimmunotherapy. Delayed recovery from prior chemotherapy also predicts poor mobilization.

Based on known risk factors for impaired mobilization, Costa and colleagues evaluated whether a prediction

Table 2. Advantages and Limitations of Mobilization Strategies

Regimen	Advantages	Limitations
Growth factor	· Simple · Low toxicity · Less expensive	· High risk of failures · Low cell yields
Growth factor plus chemotherapy	· Possible "anti-tumor" effects · High cell yields	· Toxicity · High cost · Risk of failure
Growth factor plus plerixafor	· Low toxicity · Low risk of failure · High cell yields	· Cost · Plerixafor-specific toxicity

Table 3. Stem Cell Mobilization Outcomes by Tumor Type [5]

Collection Goal	HL (n = 93)	NHL (n = 685)	MM (n = 997)
Optimal ≥5 x 106 CD34+ cells/kg	40 (43%)	199 (29%)	699 (70%)
Low ≥2 ≤5 x 106 CD34+ cells/kg	28 (30%)	262 (38%)	162 (16%)
Poor <2 x 106 CD34+ cells/kg	8 (9%)	119 (17%)	48 (5%)
Failed PB CD34+ cells <10/μL	17 (18%)	105 (15%)	88 (9%)

HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PB, peripheral blood.

model could be developed to direct mobilization strategies [4]. In the multicenter retrospective study of 477 patients with multiple myeloma undergoing first autologous mobilization with GF, investigators included 2 definitions of poor mobilization: <20/mm3 PB-CD34+ cells and <10/mm3 PB-CD34+ cells at day 4 after GF initiation. A predictive model incorporating known clinical risk factors performed poorly in identifying the <20/mm3 and <10/mm3 thresholds for poor mobilization, with areas under the curve of 0.710 and 0.747, respectively. Further, a multiple regression analysis showed no correlations between either threshold and any other clinical characteristics at the time of mobilization, including treating institution, patient gender, time between diagnosis and mobilization, or plasma cells in the bone marrow. Therefore, clinical characteristics were not useful for developing a predictive model to stratify patients for different mobilization regimens. Moreover, relying solely on clinical characteristics may lead to mobilization failures in some patients and overtreatment in others.

Chemomobilization Strategies

Several trials have examined the safety and efficacy of adding chemotherapeutic agents to G-CSF during stem cell mobilization. The most commonly used agent is cyclophosphamide, which is given at doses ranging from 1.5 g/m2 to 7 g/m2. Cyclophosphamide is associated with a 30% risk of infection and a failure rate of 5% to 20%, depending on the treatment setting. Another option for chemotherapy is vinorelbine 35 mg/m2, which is associated with a 95% success rate in patients with multiple myeloma [6]. Treatment with vinorelbine is generally well tolerated, with a low rate of hospital admissions (1.5%) and an infrequent need for transfusion support [6].

Lastly, etoposide chemomobilization is also associated with high rates of success in patients with lymphoma (94%) and multiple myeloma (100%) [7; 8]. The standard regimen of etoposide 375 mg/m2 on days 1 and 2 added to G-CSF, however, is associated with a frequent need for blood products and a higher rate of hospitalization for the management of febrile neutropenia (6% to 17%) [7; 8].

Preemptive Plerixafor

The strategy of preemptive plerixafor was designed to minimize the costs of treatment and the risk of adverse events for patients undergoing ASCT. Using this approach, patients are treated with standard G-CSF for 4 days. If the CD34+ cell yield is sufficient on day 4, patients proceed to immediate apheresis. Otherwise, evening plerixafor is given in preparation for next-day apheresis.

The preemptive plerixafor approach is feasible given that the concentration of CD34+ cells measured in the peripheral blood (PB-CD34+ cells/mm3) strongly predicts the apheresis yield (CD34+ cells/kg) (r2, 0.899; $P < .01$) [9]. Centers can predict the effects of adding plerixafor prior to apheresis based on data showing that plerixafor increases the CD34+ cell yield by 3-5-fold [10]. Based on this experience, Costa and colleagues developed and validated a decision-support algorithm for identifying which patients are most likely to benefit from the addition of plerixafor prior to apheresis [9]. For a given collection target (e.g., ≥6 x 106 CD34+ cells/kg), the algorithm identifies the threshold of PB-CD34+ cells on day 4 (e.g., 25 cells/mm3) that favors G-CSF alone versus G-CSF plus plerixafor for the most cost-effective mobilization.

As applied in clinical practice, the algorithm recommends plerixafor use for approximately 68% of patients [9]. On average, the apheresis product is 103% of the predicted yield, enabling 94% of patients to meet their mobilization target. Only 3% of patients require remobilization. The mean interval between mobilization and transplantation is 14 days.

Chemotherapy-Based Mobilization

Many centers favor chemotherapy-based mobilization protocols to prepare patients for ASCT. In a retrospective analysis, Shaugnessy and colleagues examined mobilization outcomes among patients treated with plerixafor plus G-CSF (n = 33) or chemotherapy plus G-CSF (n = 33) [11]. The median total yield of CD34+ cells was similar in the chemotherapy and plerixafor groups (11.6 versus 10.7 x 106/kg; $P = .50$), as was the likelihood of collecting ≥6 x 106 CD34+ cells/kg (90% versus 100%; $P = .49$). By comparison, there were more weekend apheresis procedures in the chemotherapy group than the plerixafor group (19 versus 0; $P \leq .0001$), underscoring the decreased predictability of chemotherapy-based mobilization. In addition, patients in the chemotherapy were more likely than those in the plerixafor group to require mobilization-related hospitalization (58% versus 0%; $P \leq .0001$), suggesting increased toxicity. All patients proceeded to autologous HSCT, with no difference between the chemotherapy and plerixafor groups in engraftment outcomes. The median total costs of mobilization were similar in the chemotherapy and plerixafor groups ($18,824 versus $14,244, respectively; $P = .45$).

Some evidence suggests that chemotherapy-based mobilization may increase the risk of mobilization failure. Another retrospective study evaluated outcomes in 50 patients managed with preemptive plerixafor, as guided via a mobilization decision-support algorithm, and 81 patients from an historic cohort treated with chemotherapy plus G-CSF and GM-CSF [12]. The mobilization failure rate was 2% among those managed with the plerixafor-based mobilization algorithm, compared with 22% who were treated with chemotherapy ($P < .01$). In addition, 2% of patients in the preemptive plerixafor group developed complications requiring hospitalization, compared with 30% in the chemotherapy group ($P < .01$).

Table 4. Mobilization Outcomes Following Filgrastim or TBO-Filgrastim [13]

Outcome	TBO-Filgrastim (n = 99)	Filgrastim (n = 86)	P Value
Median CD34+ cells on day 4	12.5 cells/μL	12.5 cells/μL	.78
Median plerixafor utilization	66%	60%	.61
Mean plerixafor doses, n	.96	1.06	.31
Mean total collection days	1.57 days	1.65 days	.24
Median CD34+ cells/μL on day 5	50 cells/μL	43 cells/μL	.15
Median total collected CD34+ cells	5.85 x 106 cells/kg	5.56 x 106 cells/kg	.59

Table 5. Mobilization Outcomes Following Filgrastim or Pegfilgrastim [14]

Characteristic	Filgrastim (n = 74)	Pegfilgrastim (n = 57)	P Value
Median PB-CD34+ cells on day 4	18.1 cells/μL	28.7 cells/μL	.01
Patients requiring plerixafor	67.5%	45.6%	.01
Mean days of apheresis, n	1.62 days	1.68 days	.6
Mean number of injections, n	13.12	2.68	< .001
Median total CD34+ cells collected	7.26 x 106 cells/kg	7.54 x 106 cells/kg	.6
Patients not meeting mobilization target, %	8.1%	8.8%	1
Mobilization failures (<2 x 106 CD43+ cells/kg), %	1.3%	1.7%	1

PB, peripheral blood.

Table 6. Consensus Recommendations for Remobilization [4]

Consideration	Recommendation/Comments
Cytokine-alone strategies	· Do not use for remobilization
Plerixafor	· Include in remobilization regimens for patients failing a non-plerixafor-containing mobilization attempt · May be effective in patients who have failed previous plerixafor-based mobilization · Options include plerixafor + G-CSF and chemotherapy + G-CSF + plerixafor · Addition of plerixafor to chemotherapy for remobilization should be explored in prospective trials
Chemotherapy-based remobilization	· Acceptable strategy for patients who have failed cytokine-only mobilization
Bone marrow harvest	· Third-line approach in patients who are ineligible for mobilization clinical trials and in whom the benefit of autologous HSCT is sufficiently compelling to outweigh the potential drawbacks

G-CSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplantation; PB, peripheral blood.

The cost-effectiveness analysis also favored plerixafor. The estimated cost per patient of successfully completing mobilization was lower in the plerixafor group than in the chemotherapy group ($23,893 versus $29,423, respectively), before accounting for costs associated with multiple mobilization attempts. Given the higher rate of subsequent mobilization attempts following chemotherapy, the true difference in total costs between the plerixafor and chemotherapy groups may be greater.

Emerging G-CSF Alternatives

Alternatives to standard G-CSF agents provide more options for patients undergoing mobilization. TBO-filgrastim is a recombinant G-CSF agent that was initially approved as a biosimilar to filgrastim in Europe and subsequently approved as biologic agent in the US. By comparison, pegfilgrastim is a pegylated form of filgrastim, the recombinant form of G-CSF.

Experience to date supports the use of these G-CSF alternatives in appropriate patients and experienced centers [13-15]. In 2015, Elayan and colleagues described outcomes among 185 patients with lymphoma or plasma cell disorders treated with filgrastim (n = 86) or TBO-filgrastim (n = 99), with or without plerixafor [13]. Compared with filgrastim, TBO-filgrastim showed identical performance across all measures of mobilization, including median CD34+ cell yield, total collection days, and plerixafor utilization. Further, TBO-filgrastim demonstrated an average cost savings of $964.25 per patient relative to filgrastim (Table 4).

Pegfilgrastim, which is commonly used for the prevention of neutropenia and fever following outpatient chemotherapy, has also been evaluated as a mobilization agent. In a retrospective study of 131 patients with lymphoma or multiple myeloma, pegfilgrastim significantly increased the median PB-CD34+ cell yield on day 4 compared with filgrastim (P = 0.01) (Table 5) [14]. Pegfilgrastim was also associated with a subsequent reduction in plerixafor utilization (P = .01), as well as a significant decrease in total number of injections (P < .001). Investigators concluded that the single administration of pegfilgrastim 12 mg represented improved convenience for patients, compared with the filgrastim dosing schedule of 10 μg/kg/day continuing until the completion of collection.

To further optimize the use of pegfilgrastim, centers are now evaluating new mobilization protocols. At the University of Alabama at Birmingham, one investigational regimen involves the use upfront pegfilgrastim (6 mg flat dose) on day 1, plerixafor 240 μg/kg on day 3, and collection by apheresis on day 4. If CD34+ cell collection goals are not met with the first apheresis, patients are treated with additional cycles of evening plerixafor 240 μg/kg in preparation for next-day apheresis, for a maximum of 3 collections [15]. Preliminary results in 235 patients suggest that this is a feasible

mobilization strategy. Overall, 83% of patients were able to reach the collection targets of 3 x 106 CD34+ cells/kg (for lymphoma) or 6 x 106 CD34+ cells/kg (for multiple myeloma), and patients had a median of 2 collections. In addition, 95% of patients were able to collect the minimum target of 2 x 106 CD34+ cells/kg. Accounting for the procedure success rate and the costs of repeat mobilization attempts, a cost-effectiveness analysis favored pegfilgrastim over filgrastim [15].

Consensus Recommendations

The 2014 consensus recommendations for stem cell mobilization provide additional guidance for treatment selection [4]. Specific strategies should be selected for individual patients based on 3 central goals: to reduce the overall mobilization failure rate to <5%; to minimize mobilization-related complications; and to optimize resource utilization.

In general, pre-apheresis PB-CD34+ cell-count monitoring is recommended to identify poor mobilizers prior to mobilization failure. The use of preemptive plerixafor, based on PB-CD34+ cell-count monitoring, appears to prevent mobilization failure. Additional consensus recommendations outline best practices specific to stem cell remobilization (Table 6). To offset the need for remobilization, consider upfront stead-state mobilization with plerixafor plus G-CSF in select patients. Emerging strategies such as chemotherapy plus plerixafor plus G-CSF merit further evaluation in prospective trials [4].

Mobilization for Myeloma and Lymphoma

Parameswaran Hari, MD, MS

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) suggest a steady increase in the number of patients undergoing ASCT each year in the U.S. over the past few decades, reflecting a rise in autologous transplantation worldwide [16]. Most of the growth in autologous HCT since 2000 has occurred in patients between the ages of 60 to 69 years, although the number of patients aged 70 years and older receiving autologous transplant has also been increasing since approximately 2010. This trend illustrates the demographic changes within the aging transplant patient population, as well as advances in supportive care that have made autologous HCT a very safe procedure.

Transplant centers are feeling the pressure of the evolving transplant landscape. Centers are providing autologous transplant services for an ever-growing number of patients. Moreover, with an increasing number of patients who achieve remission after an initial transplant, more patients are returning for second transplant procedures. With the recent development of chimeric antigen receptor (CAR) T-cell therapy, which involves lymphocyte apheresis, the limited resources of many transplant centers are stretched further.

Multiple myeloma and NHL and the two major indications for ASCT [17]. With roughly 9,000 patients with multiple myeloma and 4,000 patients with NHL undergoing autologous HCT each year, a total of 15,000 patients will require stem cell mobilization. Specific considerations for stem cell mobilization in patients with multiple myeloma and NHL are discussed in the next sections.

Mobilization in Multiple Myeloma

Stem Cell Mobilization

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702) StaMINA trial is one of the largest recent clinical trials of transplantation in multiple myeloma in the U.S.[18]. The phase III randomized trial enrolled 758 patients aged ≤70 years with multiple myeloma. After undergoing autologous transplantation, patients were randomly assigned to 1 of 3 treatment arms before continuing with lenalidomide maintenance 10 mg/day: consolidation with lenalidomide, bortezomib and dexamethasone (RVD) for 4 cycles; no consolidation; or a second autologous transplant.

Primary results from the StaMINA trial presented at the 2016 American Society of Hematology (ASH) annual meeting showed no difference in progression-free survival or overall survival across the 3 treatment arms [19]. For this discussion, however, one of the most notable aspects of the StaMINA trial involves its study design. As with most multiple myeloma trials in the U.S., the induction therapy regimen was not specified. Moreover, patients were required to have an autograft of ≥ 4 × 106 CD34+ cell/kg, but the mobilization approach was not specified [18].

In contrast to StaMINA, several recent European trials demonstrated a consistent benefit with upfront autologous transplant relative to comparator arms in patients with multiple myeloma (Table 7).[20-23] One of the major differences between U.S. and European study designs involves the specification of the induction and mobilization regimens in the European trials. In each European trial, patients have undergone stem cell mobilization with cyclophosphamide. Some experts attribute the progression-free and overall survival benefits observed with upfront ASCT in the European trials at least in part to the cyclophosphamide mobilization strategy.

Additional trials have also provided insight into the potential therapeutic role

Table 7. Recent Studies of Upfront Transplantation or Novel Agent-Based Regimens in Newly Diagnosed Multiple Myeloma [20-23]

Group/Trial (Patients)	Induction	Comparison	Response ≥VGPR	PFS	OS	Mobilization
GIMEMA 2014 (N = 402)	RD x 4	MPR x 6 ASCT x 2	63% 59%	Median: 22 mos 43 mos*	At 4 years: 65% 81%*	Cyclophosphamide
Gay et al Multicenter Trial (n = 389)	RD x 4	CRD x 6 ASCT x 2	50% 54%	Median: 29 mos 43 mos*	At 4 years: 86% 73%*	Cyclophosphamide
IFM/DFCI 2009 (N = 700)	VRD x 3	VRD x 5 ASCT + VRD x 2	78% 88%*	Median: 34 mos 43 mos*	At 4 years: 83% 81%	Cyclophosphamide
EMN02/ H095 MM (N = 1192)	VCD x 3-4	VMP x4 ASCT 1 or 2	74% 85%*	At 3 years: 57% 65%*	NS; short follow-up	Cyclophosphamide

*Statistically significant (P < .05).

ASCT, autologous stem cell transplant; CDR, cyclophosphamide, lenalidomide, and dexamethasone; EMN, European Myeloma Network; GIMEMA, Italian Group for Hematologic Diseases in Adults; IFM/DCFI, Intergroupe Francophone Du Myelome/Dana-Farber Cancer Institute; MPR, melphalan, prednisone, and lenalidomide; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; RD, lenalidomide plus dexamethasone; VCD, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

of the mobilization regimen. In a recent German study, Oyekunle and colleagues reviewed outcomes among 236 patients with multiple myeloma who underwent ASCT following chemotherapy-based stem cell mobilization [24]. Most patients were treated with novel induction regimens that contained bortezomib (n = 223) and/or lenalidomide (n = 19), and 89.5% achieved at least partial remission following induction. Stem cells were then mobilized with regimens containing cyclophosphamide (93.4%) or etoposide (6.6%). According to an analysis of changes in intact Ig and free light chain (FLC) levels before and after chemomobilization, only 3% of patients experienced a significant improvement in remission status. However, chemomobilization was associated with adverse events (AEs) in 28.4% of patients, including infection in 23% of patients and AEs requiring hospitalization in 3.8%. These findings suggest that chemotherapy-based mobilization causes substantial morbidity without improving remission status.

In a retrospective analysis from the CIBMTR database, Uy and colleagues evaluated mobilization strategies among 968 patients with multiple myeloma who underwent ASCT between 2007 and 2012 [25]. The mobilization regimens were GF alone in 519 patients and GF plus chemotherapy in 449 patients. Platelet engraftment was slightly faster among patients treated with GF plus chemotherapy compared with those treated with GF alone (19 days versus 18 days, respectively; P = .006). However, the estimated 3-year progression-free survival was similar for patients treated with GF with or without chemotherapy (40% versus 43%; P = .33) The estimated 3-year overall survival was also comparable among those treated with GF with or without chemotherapy prior to transplantation (80% versus 82%; P = .43). In a multivariate analysis, the mobilization strategy predicted neither progression-free survival (P = .93) nor overall survival (P = .27). Together, these findings do not support the use of chemotherapy-based mobilization as a strategy for preventing disease progression or prolonging survival in patients with multiple myeloma [24; 25].

Stem Cell Collection Targets

Several factors must be considered to determine the optimal target for stem cell mobilization. First, it is important to consider how many transplant procedures might be required. As multiple myeloma increasingly resembles a chronic disease, more patients are now eligible for a second transplant at the time of salvage therapy. Tandem transplantation is also an emerging strategy for achieving minimal residual disease (MRD) negativity in select patients with multiple myeloma. Therefore, consistent with a "more is better" philosophy, it is appropriate to collect sufficient stem cells to plan for 2 or more transplants over the patient's lifetime.

Preparing for multiple transplants requires allocating sufficient cells to multiple bags for cryopreservation (i.e., ≥2 x 106 CD34+ cells/kg per bag). The desired targets are a minimum collection of 2-4 x 106 CD34+ cells/kg for a single transplant, and an ideal collection of 8-10 x 106 CD34+ cells/kg for multiple transplants. In addition to being available for a second transplant, these cryopreserved cells can be can be used to improve blood counts after repeated chemotherapy in the relapsed setting. This enables patients who would otherwise be excluded from clinical trials due to thrombocytopenia to enroll in a clinical trial and access promising investigational therapies. Thus, having stem cells in the freezer is an important asset for patients with multiple myeloma.

In 2009, DiPersio and colleagues published a landmark phase III trial examining the role of plerixafor as a mobilization agent in patients with multiple myeloma undergoing ASCT (N = 302) [10]. Compared with G-CSF alone, adding plerixafor on day 4 of G-CSF treatment led to a significant 3-5-fold increase in the yield of CD34+ cells on day 1 of apheresis. In total, 71.6% of patients in the plerixafor plus G-CSF group achieved the primary endpoint of collecting ≥6 x 106 CD34+ cells/kg in ≤2 aphereses, compared with 34.4% of patients in the placebo plus G-CSF group (P < .001) (Table 8). Furthermore, 54% of patients in the plerixafor group reached the target mobilization after 1 apheresis, whereas 56% of patients in the placebo group required at least 4 aphereses to reach the target CD34+ cell yield.

Table 8. Mobilization with or without Plerixafor in Patients with Multiple Myeloma [10]

Results	Apheresis Day				Hazard Ratio	P Value
	Day 1	Day 2	Day 3	Day 4		
Patients reaching ≥6 x 106 CD34+ cells/kg						
Plerixafor + G-CSF	54.2%	77.9%	86.8%	86.8%	2.54	< .0001
Placebo + G-CSF	17.3%	35.3%	49.0%	55.9%		

G-CSF, granulocyte-colony stimulating factor.

Stem Cell Remobilization

Salvage transplant is an increasingly available option for patients with hematologic malignancies. According to data from CIBMTR, more than 500 salvage autologous transplants are currently performed each year in the US [17][17][17]. Further, with treatment advances allowing more patients to achieve MRD-negative status, more patients are expected to be eligible for transplant at relapse.

The phase III British Society for Blood and Marrow Transplantation/UK Myeloma Forum (BSBMT/UKMF) Myeloma X trial evaluated the effect of salvage autologous HSCT in patients with relapsed multiple myeloma across 51 centers in the UK [26]. In total, 174 patients with multiple myeloma who relapsed after their first transplant were re-induced with 2 to 4 cycles of bortezomib, doxorubicin and dexamethasone (PAD). Patients were then randomly assigned to high-dose melphalan and salvage autologous HSCT or weekly cyclophosphamide. Compared with chemotherapy maintenance, salvage autologous transplantation significantly improved OS by 42% (HR, 0.58; 95% CI, 0.37-0.93; P = .022).

In another analysis of the Myeloma X trial, investigators examined the safety, efficacy, and feasibility of remobilization after re-induction with PAD [27]. In total, 110 patients who were initially randomized to the transplant arm in the Myeloma X trial underwent at least 1 remobilization. Of these, 32 patients and 4 patients, respectively, underwent second and third remobilization attempts. The overall success rate was 49.1%, including adequate cell collection among 37.3%, 31.3%, and 75% of patients after the first, second, and third attempts, respectively. Accounting for both previously stored and reharvested cells, 70 patients (63.6%) were able to proceed to randomization. Therefore, findings from the Myeloma X trial demonstrate that remobilization after relapse is possible for patients who did not have adequate numbers of stem cells harvested at the time of their first autologous transplant.

Lenalidomide Exposure and Mobilization

Prior exposure to lenalidomide is associated with suboptimal mobilization of CD34+ cells [28; 29]. In 2008, Paripati and colleagues reported findings from a retrospective review of 61 patients undergoing stem cell mobilization after induction therapy with lenalidomide and dexamethasone (n = 20) or other regimens (n = 41) [28]. Compared with other induction regimens, lenalidomide was associated with significantly worse mobilization outcomes, including lower mean peripheral blood CD34+ count (P = .002), a lower total number of CD34+ cells collected (P = .0025), a higher rate of failure after the first collection attempt (P = .0011), and a trend toward increased mean days of collection (P = .07). Moreover, the likelihood of having a successful collection decreased with an increasing duration and/or number of cycles of lenalidomide, indicating that collection earlier during the course of lenalidomide induction (i.e., within the first 4 cycles) was preferable.

Another analysis from Costa and colleagues in 2012 focused on the effects of lenalidomide exposure on mobilization in 89 patients with multiple myeloma [29]. Those exposed to more cycles of prior lenalidomide (> 4 cycles) experienced significantly worse CD34+ cell mobilization than patients exposed fewer cycles of lenalidomide (1-4 cycles) or those with no history of lenalidomide treatment (P < .001 for trend). Increased lenalidomide exposure was also associated with an increase in the number of apheresis sessions required to achieve the mobilization target (P = .008). Despite these challenges, GF mobilization with preemptive plerixafor was ultimately successful in these patients, with no patients failing mobilization or requiring remobilization prior to transplantation.

In 2014, Giralt and colleagues published consensus guidelines that include recommendations for ASCT following lenalidomide [4]. Ideally, early collection (between the second and fourth cycles of lenalidomide) should be performed whenever possible. In addition, a washout period of 2-4 weeks between the last lenalidomide dose and the start of apheresis is recommended. Although evidence supporting a single mobilization strategy in patients with lenalidomide exposure is limited, a combined approach including plerixafor plus G-CSF and chemomobilization may be effective in this setting. Of note, mobilization with G-CSF alone is insufficient in patients with extensive lenalidomide pretreatment (i.e., more than 4 to 6 cycles) and should be avoided.

Other Mobilization Strategies

Another chemomobilization approach involves the use of etoposide added to G-CSF. In 2011, Wood and colleagues reported their institutional experience with this regimen at the University of North Carolina (UNC) in a review of 152 patients with multiple myeloma undergoing ASCT [8]. Patients were treated with etoposide 375 mg/m2 on days 1 and 2 and filgrastim 5 mcg/kg twice daily from day 3 through the final day of collection. With this protocol, 99% of patients were able to collect at least 5 x 106 cells/kg in 1 to 2 days of apheresis. The median total number of CD34+ cells collected

Table 9. General Considerations for Mobilization in Multiple Myeloma [4]

	Recommendation/Comments
Goals of mobilization	· Reduction of overall failure rates to <5% · Minimize mobilization-related complications · Optimize resource utilization
Monitoring	· Pre-apheresis peripheral blood CD34+ cell count monitoring to identify poor mobilizers before failure
Preemptive plerixafor	· Preemptive plerixafor use based on peripheral blood CD34+ cell count monitoring appears to prevent mobilization failure
Upfront plerixafor + G-CSF	· Consider upfront steady-state mobilization with plerixafor and G-CSF to offset the need for remobilization
Future approaches	· The combination of chemomobilization, plerixafor, and G-CSF merits further evaluation in prospective trials

G-CSF, granulocyte-colony stimulating factor.

Table 10. Mobilization with or without Plerixafor in Patients with Non-Hodgkin Lymphoma [32]

Collection Goal	Apheresis Day			
	Day 1	Day 2	Day 3	Day 4
≥ 2 x 106 CD34+ cells/kg				
Plerixafor + G-CSF	56.5%	81.0%	87.9%	90.9%
G-CSF alone	20.4%	35.3%	56.9%	59.8%
HR (95% CI)	2.50 (1.86-3.36); P < .0001			
≥ 5 x 106 CD34+ cells/kg				
Plerixafor + G-CSF	27.9%	49.1%	57.7%	65.6%
G-CSF alone	4.2%	14.2%	21.6%	24.2%
HR (95% CI)	3.64 (2.39-5.45); P < .0001			

CI, confidence interval; G-CSF, granulocyte-colony stimulating factor; HR, hazard ratio.

among all patients was 12 x 106 cells/kg. In the safety analysis, 20% of patients required supportive transfusions and 17% of patients required hospitalization for fever and/or neutropenia.

Selecting the appropriate mobilization strategy is critical for safe and effective outcomes in select patient groups. For instance, patients with amyloid light-chain (AL) amyloidosis have a high risk of perimobilization morbidity and mortality. In an institutional review of 49 patients with AL amyloidosis, Dhakal and colleagues compared 2 mobilization strategies: G-CSF alone administered at 10 mcg/kg daily (n = 25), or a protocol to reduce G-CSF exposure by adding plerixafor 0.24 mg/kg starting on day 3 (n = 24) [30]. Compared with C-CSF alone, the addition of plerixafor was associated with a significant reduction in weight gain (P = .001), a predictive marker of fluid overload and increased cardiovascular risk. Other outcomes, including number of apheresis sessions, number of hospitalization days, transfusions, and use of antibiotics, were similar in both treatment groups. These findings favor the upfront use of plerixafor plus G-CSF in patients with AL amyloidosis.

Current ongoing trials from the CIBMTR and other groups are examining chemomobilization strategies with the goal of identifying the optimal balance between safety and efficacy for patients undergoing ASCT.

Consensus Recommendations on Mobilization in Multiple Myeloma

The 2014 consensus guidelines outline the goals of mobilization, the selection and timing of mobilization, recommendations for monitoring, and future strategies (Table 9) [4]. Each institution should take a customized approach to optimizing resource utilization, tailored to local considerations and the unique patient population being served.

Of note, steady-state mobilization with G-CSF alone (10-16 mcg/kg daily) should be limited to patients with multiple myeloma with ≤1 previous line of therapy, no previous melphalan exposure, and exposure to <4 cycles of lenalidomide. In such patients, peripheral blood CD34+ cell count monitoring and preemptive plerixafor will allow for successful collection [4].

Mobilization in Lymphoma

Challenge of Poor Mobilization in NHL

Approximately 10%-20% of patients do not collect adequate numbers of CD34+ cells to proceed to high-dose chemotherapy and ASCT [5; 31]. Failure rates tend to be higher in patients with NHL than among those with multiple myeloma, possibly due to the heavier reliance on myelosuppressive chemotherapy in NHL relative to the increased use of novel agents in multiple myeloma [31]. In one analysis of 1,040 patients undergoing mobilization for ASCT, 19% of patients collected <2 x 106 CD34+ cells/kg after a maximum of 5 aphereses [31]. Depending on the regimen, the first mobilization failure rates were 5.9% to 6.3% for patients with multiple myeloma and 22.9% to 26.8% for those with NHL. In another study of 328 patients with NHL undergoing mobilization, the failure rate was 19% [5].

Effective mobilization regimens are critical for achieving collection goals. In a phase III trial, DiPersio and colleagues compared the rates of successful mobilization using different collection targets among 298 patients with NHL who received G-CSF alone or G-CSF plus plerixafor [32]. By day 4 of apheresis, patients in the plerixafor group were more than twice as likely as those mobilized with G-CSF alone to achieve the collection goals defined as optimal (≥ 5 x 106 CD34+ cells/kg) and minimal (≥ 2 x 106 CD34+ cells/kg) (Table 10). In a

long-term follow-up analysis, the addition to plerixafor to G-CSF for stem cell mobilization had no effect on 5-year survival outcomes in patients with lymphoma or multiple myeloma [33].

The Study Group Indolent Lymphomas (StiL) trial examined the potential implications of bendamustine exposure on stem cell mobilization for ASCT [34]. In the phase III, multicenter, noninferiority trial, 549 patients with follicular lymphoma (55%), mantle cell lymphoma (19%), and other NHL subtypes (26%) were randomly assigned to first-line treatment with rituximab plus bendamustine (R-B) or standard R-CHOP induction therapy. In total, 46 patients underwent mobilization with G-CSF with or without high-dose cyclophosphamide. Bone marrow involvement was observed in 17 of 23 patients (74%) undergoing mobilization in the R-B arm, and in 14 of 23 patients (61%) undergoing mobilization in the R-CHOP arm. The median number of CD34+ cells collected in the R-B and R-CHOP arms were 4.55 x 106 cells/kg and 6.17 x 106 cells/kg, respectively. Therefore, findings from the StiL trial demonstrate the feasibility of collecting sufficient numbers of peripheral blood stem cells following upfront treatment with bendamustine.

Table 11. Peripheral CD34+ Cell Counts with Plerixafor or Placebo Added to G-CSF [10]

	Plerixafor (n = 130)	Placebo (n = 124)	P Value
Pre-mobilization†			
Mean	12.1 ± 12.2 cells/mL	12.5 ± 18.5 cells/mL	.81
Median	7.6 cells/mL	7.9 cells/mL	
Post-mobilization‡			
Mean	53.5 ± 47.5 cells/mL	19.2 ± 23.7 cells/mL	< .001
Median	36.0 cells/mL	13.0 cells/mL	
Fold increase			
Mean	6.2 ± 5.4	1.9 ± 1.5	< .001
Median	5.0	1.4	

†Pre-mobilization = after G-CSF treatment and prior to plerixafor or placebo.
‡Post-mobilization = 10-11 hours after plerixafor or placebo treatment.
G-CSF, granulocyte-colony stimulating factor.

Table 12. General Mobilization Recommendations for Patients with Non-Hodgkin Lymphoma [4]

Criteria	Recommendation/Comments
CM vs steady-state cytokine mobilization	· Ongoing debate (head-to-head data are equivocal) · Varying response to mobilization regimens between patients with myeloma and NHL · Growth factor alone often adequate for patients with early-stage myeloma, suboptimal for those with late stage multiple myeloma and NHL · Stand-alone CM can be a successful strategy but is associated with toxicity and higher cost
Stand-alone CM	· Limit to patients who have not responded optimally to salvage therapy or in patients who have failed other strategies
Use of higher cyclophosphamide doses (>4 g/m2)	· Supporting data are limited
Upfront plerixafor	Suitable option for all patients particularly in the following circumstances: · If goal is highest possible CD34+ cell collection yield · If real-time PB CD34+ cell counts are not available · If fewer apheresis days is the top priority · Preemptive use of plerixafor based on PB CD34+ measurements is reasonable in other cases
Use of CM vs plerixafor + G-CSF	· Firm recommendations cannot be made (lack of data) · Controlled prospective trials comparing the 2 strategies should be considered

CM, chemomobilization; G-CSF, granulocyte-colony stimulating factor; NHL, non-Hodgkin lymphoma.

Considerations During and After Chemomobilization

Recent evidence suggests that the development of neutropenic fever in the perimobilization period reduces stem cell yield. Khouri and colleagues evaluated outcomes in a study of 554 patients who underwent mobilization with etoposide and G-CSF [35]. During mobilization, 24% of patients were hospitalized for neutropenic fever. Most patients (90%) had no identified infection source, while 6% had bacteremia, 3% had pneumonia, and <1% had herpes simplex. In total, 93% of patients proceeded to transplant. Patients who developed neutropenic fever, however, had a significantly lower likelihood of proceeding to transplant than those who did not develop neutropenic fever (86% versus 96%; P < .001). Neutropenic fever was also associated with a lower cell dose collection (P = .002) and an increased likelihood of requiring more than 4 days of apheresis (P < .001).

Recent studies have focused on immune reconstitution in patients undergoing autologous transplantation. Immune reconstitution appears to occur gradually, with substantial variations across types of immune cells. Whereas natural killer cells and dendritic cells appear to recover within 1 to 3 months, respectively, B cell and T cell recovery may take more than 12 months. [36; 37]

One of the major complications of delayed reconstitution involves disease relapse, most likely associated with residual disease after transplant.[36; 38] In a recent review of lymphoma studies, Sauter and colleagues demonstrated identified a statistically significant link between higher CD34+ dose and greater survival benefit in patients undergoing ASCT [39]. These findings support a possible mechanistic relationship between early

lymphocyte recovery and long-term transplant outcomes. To explore whether this relationship can be exploited to improve PFS, investigators at Memorial Sloan Kettering Cancer Center are comparing the standard of care versus higher CD34+ cell dosing (≥ 7 x 106 CD34+ cells/kg) in a randomized trial of patients with relapsed/refractory diffuse large B-cell lymphoma (NCT02570542).

In current practice, the most common approach to stem cell mobilization involves adding plerixafor to G-CSF in patients who do not appear to be mobilizing sufficient CD34+ cells with G-CSF alone. In the pivotal phase III trial, adding a single dose of plerixafor resulted in a 5-fold increase in the median number of circulating peripheral CD34+ cells (Table 11) [10]. Many centers use the threshold of <10 cells/μL as an indication for adding plerixafor. Ongoing research is focused on new mobilization strategies, such as the use of intravenous plerixafor, the role of other emerging and investigational agents, and individualized approaches for patients with conditions that limit mobilization, such as diabetes.

In summary, consensus guidelines provide an evidence-based framework for stem cell mobilization in patients with NHL (Table 12) [4]. Steady-state mobilization with G-CSF alone (10-16 mcg/kg/d) appears to increase the risk of failure in some patients. Due to low toxicity and ease of scheduling, however, this approach remains reasonable when limited to patients at low risk of mobilization failure. In addition, peripheral blood CD34+ cell count monitoring with preemptive just-in-time plerixafor when indicated will allow for successful stem cell collection in most patients.

Summary

The development of several novel mobilization regimens has improved access to ASCT for patients with multiple myeloma and lymphoma by increasing stem cell yield and decreasing the need for remobilization. Each mobilization strategy is associated with advantages and limitations, and therefore treatment must be individualized for each patient. Consensuses recommendations are available to guide the selection of an optimal mobilization strategy in patients with multiple myeloma, lymphoma, and other hematologic malignancies who are candidates for autologous HSCT.

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1. Which of the following best describes the recommended minimum and ideal doses of CD34+ cells for autologous transplant?
- A. Minimum dose is 1 x 106 CD34+ cells/kg; ideal dose is 2-3 x 106 CD34+ cells/kg
- B. Minimum dose is 2 x 106 CD34+ cells/kg; ideal dose is 3-5 x 106 CD34+ cells/kg
- C. Minimum dose is 3 x 106 CD34+ cells/kg; ideal dose is 6-9 x 106 CD34+ cells/kg
- D. Minimum dose is 5 x 106 CD34+ cells/kg; ideal dose is 7-10 x 106 CD34+ cells/kg

2. Which of the following best describes the implications of higher CD34+ cell dosing in patients undergoing autologous transplant?
- A. Higher cell dose is associated with a longer hospital stay
- B. Higher cell dose is associated with lower cost
- C. Higher cell dose is associated with more apheresis
- D. Higher cell dose is associated with slower engraftment

3. Cytokine-alone protocols are not recommended for remobilization
- A. True for all patients
- B. True only for patients with multiple myeloma
- C. True only for patients with lymphoma
- D. False for all patients

4. In current clinical practice, approximately what percentage of patients with lymphoma fail to collect adequate numbers of CD34+ cells to proceed to high-dose chemotherapy and ASCT?
- A. <5%
- B. 10% to 20%
- C. 30% to 40%
- D. 50% to 60%

5. Which of the following differentiates European and US trials of ASCT in multiple myeloma?
- A. US trials are more likely to specify the induction regimen
- B. US trials are more likely to specify the mobilization strategy
- C. European trials are more likely to specify mobilization with cytokines alone
- D. European trials are more likely to specify mobilization with cyclophosphamide