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Review

Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations

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A B S T R A C T

Autologous hematopoietic stem cell transplantation (aHSCT) is a well-established treatment for malignancies such as multiple myeloma (MM) and lymphomas. Various changes in the field over the past decade, including the frequent use of tandem aHSCT in MM, the advent of novel therapies for the treatment of MM and lymphoma, and the addition of new stem cell mobilization techniques, have led to the need to reassess current stem cell mobilization strategies. Mobilization failures with traditional strategies are common and result in delays in treatment and increased cost and resource utilization. Recently, plerixafor-containing strategies have been shown to significantly reduce mobilization failure rates, but the ideal method to maximize stem cell yields and minimize costs associated with collection has not yet been determined. A panel of experts convened to discuss the currently available data on autologous hematopoietic stem cell mobilization and transplantation and to devise guidelines to optimize mobilization strategies. Herein is a summary of their discussion and consensus.

INTRODUCTION

Autologous hematopoietic stem cell transplantation (aHSCT) is used routinely in the treatment of multiple myeloma (MM) [1-8], non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma [9-11]. For patients with MM and relapsed chemosensitive NHL, aHSCT leads to improved progression-free survival and overall survival. Patients with MM achieve higher rates of complete remission with aHSCT than with chemotherapy alone.

Nearly 10,000 aHSCTs are performed in the United States annually, virtually all of them supported by peripheral blood stem cells (PBSCs) [12]. There are 2 general approaches to stem cell collection: cytokine mobilization using cytokines such as filgrastim (granulocyte-colony stimulating factor [G-CSF]), pegfilgrastim, or sargramostim (granulocyte macrophage-colony stimulating factor [GM-CSF]) alone or in combination, and chemomobilization (CM) using chemotherapy followed by cytokine administration. The published literature on these mobilization approaches is vast, but the relative efficacy, safety, and costs of each remain unclear owing to the paucity of high-quality randomized controlled trials comparing various mobilization strategies [13].

Historical Approaches to Stem Cell Mobilization

Following the observation that chemotherapy administration resulted in a temporary increase in circulation of stem cells during hematopoietic recovery, early stem cell mobilization techniques relied on chemotherapy alone

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[14,15]. The discovery and manufacture of hematopoietic cytokines further improved our ability to mobilize and collect PBSCs [16,17]. Currently, both steady-state and chemotherapy-based mobilization rely on the use of myeloid growth factors for the release of stem cells into the peripheral blood (PB). G-CSF, the most potent of the commercially available myeloid growth factors [18], works by inducing the release of various proteases into the marrow, which then cleave adhesion molecules such as SDF-1, releasing hematopoietic stem cells into the PB [19]. The use of chemotherapy before administration of high-dose myeloid growth factors generally produces higher stem cell yields [20-25], and in theory may reduce tumor contamination of the stem cell product, although data to confirm this are lacking.

Mobilization Beyond Myeloid Growth Factors

The biology of hematopoietic stem cell mobilization with agents other than G-CSF has been reviewed recently [26]. The novel stem cell mobilizing agent plerixafor has recently provided another mobilization option for the transplantation community. In 2008, plerixafor was approved for use in the United States in combination with G-CSF for the mobilization of hematopoietic stem cells in patients with NHL and MM undergoing high-dose chemotherapy followed by autologous stem cell rescue. Plerixafor is a reversible CXCR4 antagonist that allows the release of stem cells from the marrow by disrupting the interaction of CXCR4 with SDF-1. Administration of plerixafor in conjunction with G-CSF augments mobilization of $CD34^+$ cells into the PB, with a peak effect occurring 4-9 hours after administration but a much longer sustained effect, allowing for later initiation of apheresis [27].

The stem cell population mobilized by the combination of plerixafor and G-CSF differs from that mobilized by G-CSF alone. Plerixafor-mobilized PBSCs and/or apheresis products have higher proportions of cells in growth phase [28], primitive $CD34^+CD38^-$ progenitor cells [29], B and T lymphocytes [30-32], dendritic cells [33], and natural killer cells [30,32]. Stem cells mobilized by plerixafor also have increased expression of VLA-4 and CXCR4 [28], as well as of genes that promote cell adhesion, cell motility, the cell cycle, and antiapoptosis [34]. These characteristics suggest that plerixafor-mobilized cell products may have greater capacity to repopulate the marrow and reconstitute the immune system compared with grafts mobilized by G-CSF alone. These properties have been confirmed in mouse and primate models [35,36].

Shortly after the December 15, 2008, approval of plerixafor in the United States, guidelines and recommendations were published on the current status of stem cell collection and the role of plerixafor in patients with MM [37,38]. The consensus in these publications was that plerixafor, along with novel agents for treating MM, would change the standards of practice for aHSCT over the coming decade. Although the use of plerixafor for stem cell mobilization has become increasingly common since those first publications, the transplantation community at large has yet to determine its optimal role in mobilization not only in patients with MM and NHL, but also in patients with Hodgkin lymphoma and solid tumors. In October 2011, a panel of experts in stem cell mobilization and aHSCT was convened to review recently published mobilization and collection data and update the guidelines for maximizing mobilization outcomes.

Recommendations for Stem Cell Collection

Minimum and Target Cell Doses for aHSCT

The correlation between the number of stem cells infused for aHSCT and engraftment kinetics is well established. Administration of $CD34^+$ cell doses $<1.5\text{-}2.5 \times 10^6$/kg leads to delayed neutrophil recovery [39-43], and administration of doses $<1 \times 10^6$/kg has been associated with increased RBC transfusion requirements and even permanent loss of engraftment [42]. Significant delays in platelet recovery also have been seen with infusion of $<1.5\text{-}2.5 \times 10^6$ $CD34^+$ cells/kg [24,41-44], whereas infusion of $>3\text{-}5 \times 10^6$ cells/kg is associated with earlier neutrophil and platelet engraftment [39,41,45].

A recent post hoc analysis of the utility and added benefit of higher stem cell doses in patients undergoing aHSCT demonstrated that $CD34^+$ cell doses $>6 \times 10^6$/kg were associated with improved long-term platelet recovery and reduced blood transfusion requirements, although there was no significant difference in time to platelet recovery to 20×10^9/L [46]. $CD34^+$ cell doses $>10 \times 10^6$/kg have been associated with earlier neutrophil engraftment by 1 to 2 days and earlier platelet engraftment by 2 to 4 days compared with mid-range cell doses ($\sim 3\text{-}10 \times 10^6$/kg) [40,44]. One study found that $CD34^+$ cell doses $>15 \times 10^6$/kg eliminated the need for platelet transfusion support and significantly reduced the duration of thrombocytopenia $<50 \times 10^9$/L [47]. The data supporting the use of higher cell doses are not well controlled, however, and the higher collections attained for these transplants may be a surrogate for less heavily pretreated, lower-risk patients. More research is needed to determine the impact of higher cell doses on engraftment kinetics and to evaluate whether time to collection and stem cell quality, not simply quantity, may play an important role as well.

Recommendations for stem cell targets and doses

- The minimum recommended stem cell dose is 2×10^6 $CD34^+$ cells/kg.
- The decision to accept a collection yield of $1\text{-}2 \times 10^6$ $CD34^+$ cells/kg for aHSCT should be individualized to each patient's clinical parameters and circumstances; in some cases, the benefit of aHSCT may be sufficiently compelling to use doses in this range if absolutely necessary.
- Although minimum numbers are clear, the ideal target numbers are less clear. In general, higher target doses may result in faster engraftment times, but consideration should be given to the balance between targets and the number of apheresis sessions required to attain the target collection. The recommended stem cell collection target is $3\text{-}5 \times 10^6$ $CD34^+$ cells/kg, but in some cases it may be reasonable to accept a yield of 2.5×10^6 $CD34^+$ cells/kg in a single apheresis session rather than prolong the mobilization by several days to reach a target of 5×10^6 $CD34^+$ cells/kg.
- $CD34^+$ cell doses of 5×10^6 cells/kg may lead to improved platelet recovery and less resource utilization compared with doses of $\leq 3 \times 10^6$ cells/kg, provided that the higher target can be collected in a few apheresis sessions.
- Higher targets are necessary if multiple transplantations are planned. The collection target in this setting should be double the target used at the individual center for a single transplantation, to allow optimal cell doses for each transplantation [37].