Optimizing Stem Cell Mobilization: Lessons Learned

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Abstract

Granulocyte colony-stimulating factor is the pivotal component of mobilization regimens and the growth factor most often used for peripheral blood progenitor cell collections. When used alone or after chemotherapy, products with adequate yields of CD34⁺ cells are obtained after leukapheresis, resulting in optimal blood count recovery after transplant. For patients who have had extensive prior treatment with chemotherapy and/or radiation, or treatment with specific agents, the yields may be limited. For these patients, plerixafor in combination with growth factor can be used to augment progenitor cell yield and ensure successful collection of target goals, with preservation of the integrity of the graft. Progenitor cells can similarly be collected by leukapheresis from patients for autologous use and from allogeneic donors, after a period of growth factor administration. Many chemotherapy regimens can be used before growth factor administration that serve a dual role of reducing tumor burden and enhancing the progenitor cell collection. Given modern methods, a high success rate exists for procurement of adequate stem cell products. (*J Natl Compr Canc Netw* 2014;12:1443–1449)

Introduction

Retention and Adhesion of Hematopoietic Stem Cells in the Bone Marrow Microenvironment

Hematopoietic stem cells (HSCs), capable of both self-renewal and reconstitution of the blood cell lineages after transplantation, reside in the bone marrow in an environment known as the stem cell niche. Key components of the niche include endosteal osteoblasts, bone

marrow endothelial cells, CXCL12 (formerly known as *stromal cell–derived factor 1* [SDF-1])–abundant reticular cells, mesenchymal stromal cells, and perivascular leptin receptor positive cells.^{1–3} HSCs express the chemokine receptor, CXCR4, the receptor for CXCL12, and this interaction is critical for retention of HSCs in the marrow.⁴ Other receptors, such as integrins (eg, VLA-4 interaction with VCAM-1)^{5,6} and CD44⁷, also play a role in the attachment within the marrow (Figure 1). HSCs exhibit physiologic circulation in the peripheral blood in small numbers, a process that can be augmented by pharmacologic dosing of cytokines and receptor antagonists. Granulocyte colony-stimulating factor (G-CSF) causes release of proteases, including neutrophil elastase, which cleaves CXCR4 and VCAM-1,^{8,9} and elevated levels of metalloproteinases, including MMP-2 (that may be produced by mesenchymal stromal cells),¹⁰ MMP-8,¹¹ and MMP-9,^{12–15} which contribute to the release of stem cells to the circulation. Other physiologic systems contribute to control HSC mobilization, including the fibrinolytic system,¹⁶ bone remodeling,¹⁷ the sympathetic nervous system,¹⁸ and circadian rhythms.¹⁹ The small molecule AMD3100 was developed as a specific antagonist for CXCR4, which is also the coreceptor for entry of HIV into host cells. It was found to mobilize HSCs in the laboratory and in human subjects, and is now FDA-approved as plerixafor for stem cell mobilization in non-Hodgkin's lymphoma (NHL) and multiple myeloma. Several agents have been shown to mobilize stem cells in the laboratory, including pegylated G-CSF, antibody to VLA-4 (natalizumab), thrombopoietin, stem cell factor (SCF), macrophage inhibitory protein 1 α , interleukin 8, and an CXCL12 analog, but only 3 drugs are FDA-approved for clinical use: G-CSF (filgrastim), granulocyte-macrophage colony-stimulating factor (GM-CSF; approved as sargramostim), and plerixafor.

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Dr. Becker has disclosed that she has received research support from Sanofi and Amgen.

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Figure 1 Stem cell mobilization. The hematopoietic stem cell resides in the endosteal niche, interacting with extracellular matrix components such as fibronectin (Fn), stromal cells, osteoblasts, and endothelial cells. Mobilization requires disruption of interactions, including integrins such as VLA-4 with ligands Fn or VCAM-1, CXCR4 migration toward CXCL12, c-kit with stem cell factor, and others, and then transendothelial migration to access the vasculature.

Progenitor Cell Mobilization for Hematopoietic Cell Transplantation

In the 1990s, the field of bone marrow transplantation shifted from use of bone marrow cells to mobilized peripheral blood progenitor cells (PBPCs). PBPC products contain HSCs, as proven by their ability to regenerate blood cell production after myeloablative chemoradiotherapy. Advantages of the mobilized cell products include ease of collection compared with operative procedures under anesthesia, more rapid recovery of blood counts after transplant, and more rapid immune recovery. In the allogeneic setting, the risk of chronic graft-versus-host disease (GVHD) is increased, but no difference in survival is associated with the use of PBPCs versus bone marrow.²⁰ Appreciable data and algorithms now exist to optimize PBPC collections in both the autologous and allogeneic settings.²¹ Both growth factors, G-CSF and GM-CSF, can be used to mobilize stem cell products, and have also been used in combination with each other and with chemotherapy; pegfilgrastim also results in successful mobilization, although it is not currently approved for this indication. The advent of the use of plerixafor has markedly improved collections for patients with limited stem cell reserve.²² The potential side effects of the procedures associated with stem cell collec-

tions have been thoroughly analyzed and catalogued, and their safety has been accepted. Lastly, the high number of successful PBPC transplants performed worldwide attests to the successful refinement of the procurement procedures and their standardization.

Autologous Stem Cell Mobilization

Mobilization can be performed after myelosuppressive chemotherapy regimens and growth factor administration or with growth factor alone.^{23,24} Both G-CSF and GM-CSF are FDA-approved for this indication, but G-CSF is more widely used. A target yield of CD34⁺ cells in the progenitor cell product of 2.0 to 5.0 × 10⁶ per kilogram weight of the recipient is the range that has been shown to result in adequate and prompt blood cell recovery. Several studies showed delayed neutrophil and platelet recovery if less than 2.0 or 2.5 × 10⁶ CD34⁺ cells/kg were infused, with increased platelet and red cell transfusion requirements.^{25–30} The usual dosing of G-CSF is in the range of 10 to 32 mcg/kg/d in single or divided twice-daily doses (Table 1). Apheresis collections begin on day 4 or 5 when G-CSF is used as a single agent.^{23,31}

Comparable yields of CD34⁺ cells were obtained when high-dose G-CSF was used at 12 mcg/kg/d, or Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine, and melphalan) followed by G-CSF was used as the regimen for mobilization, with an average yield of 5.3 versus 5.1 × 10⁶ CD34⁺ cells/kg, respectively, and a median of 2 collections for each.²⁴ “Mega” doses of progenitor cells (for patients who collected and received infusions of >8 × 10⁶ CD34⁺ cells/kg) may confer an advantage, because “super mobilizers” were associated with a superior survival after (autologous) transplant for lymphoid malignancy in retrospective multivariate analysis,³² and more rapid engraftment of neutrophils and platelets. Improved relapse-free survival was seen, but the mechanism could not be elucidated. GM-CSF may also be used for mobilization, typically at a dose of 250 mcg/m²/d, and has been used alone or sequentially daily for 3 days before G-CSF.²¹

Pegfilgrastim (polyethylene glycol-linked G-CSF, or pegylated G-CSF), which has a longer half-life than G-CSF, has also been studied in clinical trials and comparable cell yields have been obtained,^{33,34} but mobilization is currently not an approved use.

Table 1 Essentials of Stem Cell Mobilization: Typical Dosing

Type of Donor	Drug and Dose
Standard autologous patient	G-CSF alone: 10 mcg/kg/d (up to 32 mcg/kg/d) via subcutaneous injection, daily or twice daily schedule; start to collect day 4 or 5. G-CSF is continued up to and including the day of leukapheresis Chemotherapy (several regimens, depending on diagnosis and disease burden) + G-CSF: chemotherapy regimen then approximately 1 day after chemotherapy, start daily G-CSF at dose specified above until WBC count increases and CD34 ⁺ /mCL target is achieved, then start leukapheresis
Poor autologous mobilizers (actual or predicted)	High-dose G-CSF (20–32 mcg/kg/d on twice-daily schedule) Chemotherapy + G-CSF (several regimens) G-CSF + GM-CSF Plerixafor + G-CSF (twice-daily schedule) with addition of plerixafor 0.24 mg/kg via subcutaneous injection (if CrCl >50 mL/min, maximum dose 40 mg), 11 hours before collection (eg, start on day 4 of G-CSF) May give plerixafor daily for up to 4 consecutive days “Just in time” in the case of a low CD34 ⁺ cell count: add plerixafor 0.24 mg/kg (if CrCl >50 mL/min maximum dose 40 mg) 11 hours before collection time with continued G-CSF
Standard allogeneic donor	G-CSF 10 mcg/kg/d (range, 10–16 mcg/kg/d) via subcutaneous injection, start to collect day 4 or 5

Abbreviations: CrCl, creatinine clearance; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Mobilization using a combination of chemotherapy and growth factor provides the advantage of reducing tumor burden before transplant in addition to resulting in high yield and reduction of contamination of the progenitor cell product. The single chemotherapy drugs used in combination with G-CSF are most often high-dose cyclophosphamide^{35,36} or high-dose etoposide.³⁷ Combinations of these 2 agents,²² or other pairs of agents such as high-dose etoposide and high-dose cytarabine,³⁸ have also been used for mobilization. In addition, the more aggressive multiagent regimens, such as DHAP (dexamethasone, high-dose cytarabine, and cisplatin) and R-ICE (rituximab, ifosfamide, etoposide, and carboplatin) for lymphoma,³⁹ or VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) for multiple myeloma,⁴⁰ and others can be adapted through the addition of daily G-CSF and used for chemomobilization and reduction of residual disease. The timing of collection after chemotherapy plus growth factor is delayed, usually until approximately day 11 or 12 or later, depending on the increase of the white blood count and the circulating CD34 cell count. Target CD34 cell concentrations may be used to ensure an adequate collection, and institutional variation exists regarding when the collection will begin, usually

in the range of 5 to 20 CD34⁺ cells/ μ L. One formula that can predict the expected number of CD34⁺ cells that may be collected is the following: blood volume processed (L) $\times$ (CD34⁺ cells/ μ L $\times$ machine collection efficiency)/patient weight (kg).⁵

Strategy for Low-Yield Collection

The minimum target number of CD34⁺ cells/kg is 2×10^6 /kg,²⁶ below which sustained recovery of all blood counts may not occur. Certain factors, such as pretreatment with lenalidomide or fludarabine-containing regimens,^{41,42} or extensive pretreatment with chemoradiotherapy (eg, >10 cycles of chemotherapy or radiation to bone marrow-containing regions), can interfere with the ability to obtain sufficient progenitor cell collections, possibly related to stem cell depletion or damage to the bone marrow microenvironment. A retrospective study at Memorial Sloan Kettering Cancer Center showed that 13% of patients with multiple myeloma did not meet the target of 5×10^6 CD34⁺ cells/kg,⁴³ which was correlated with older age, lower platelet count, and use of single-agent G-CSF. Other studies have shown that as many as 18% to 26% of patients who undergo autologous transplant after mobilization with G-CSF alone do not reach target cell doses,^{27,28,44} and 17% to 47% of those who undergo mobilization with chemotherapy plus G-CSF do not achieve goals of col-

lection.^{28–30} For many years, patients who had insufficient progenitor cell collections needed to undergo repeat mobilization with growth factor and/or chemotherapy and growth factor, and, if this failed, undergo bone marrow harvest. For example, high-dose G-CSF at 20 mcg/kg/d and then 32 mcg/kg/d in split dosing could salvage 88% of patients to a target yield of 2.5×10^6 CD34⁺ cells/kg.⁴⁵ Moreover, a combination of G-CSF (10 mcg/kg/d) plus GM-CSF (5 mcg/kg/d) was comparable with 32 mcg/kg/d of G-CSF, and resulted in 93% of patients achieving sufficient cell yield at a reduced cost.⁴⁶

The CXCR4-CXCL12 chemotactic pathway is central to normal HSC homing and retention in the marrow. Plerixafor is a small molecule inhibitor of CXCR4, initially developed to block cellular entry of HIV1 and also shown to inhibit CXCR4 binding to CXCL12.⁴⁷ It was later studied in healthy volunteers to demonstrate safety and efficacy in mobilizing hematopoietic progenitor cells.⁴⁸ The side effects noted in this study included injection site symptoms (69%), headache (27%), perioral paresthesias (31%), nausea (38%), and sensation of abdominal distention (19%).⁴⁸ When used in combination with G-CSF, plerixafor could improve the yield of autologous stem cell collections in patients with NHL⁴⁹ or multiple myeloma,⁵⁰ and it was FDA-approved for this indication. For example, addition of plerixafor to G-CSF was compared with placebo plus G-CSF after a rest period of 7 days from initial failed mobilization in NHL. Only 7% of those who received plerixafor versus 38% of those who received placebo failed this remobilization, as defined as less than 0.8×10^6 CD34⁺ cells/kg in 2 days or less than 2×10^6 CD34⁺ cells/kg in 4 days.⁵¹ The dosing guideline recommends that it be administered 11 hours before the collection, but study of other administration times has shown satisfactory collections of 6×10^6 or more CD34⁺ cells/kg in 90% of patients with 1 day of apheresis when it is administered at 17 hours before collection.⁵² This earlier time would allow administration within the normal business day before the next day's collection. Plerixafor is always used in combination with growth factor. The dose is 0.24 mg/kg via subcutaneous injection for creatinine clearance (CrCl) greater than 50 mL/min, with a maximum dose of 40 mg/d, and for CrCl of 50 mL/min or less, the dose is 0.16 mg/kg, with a maximum dose of 27 mg/d. Doses may be given for up to 4 consecutive days.⁵³

Considerable effort has been made to study what factors would predict a low stem cell yield, so that plerixafor could be added “on demand,” “just in time,” or as a “rescue.” For example, one group correlated the peripheral blood CD34 cell count on day 4 or 5 of growth factor with the yield of progenitor cells after leukapheresis.⁵⁴ A count of 11, 17, 21, or 28/mcL corresponded with yields of 2, 4, 8, or 12×10^6 CD34⁺ cells/kg, respectively, in patients with multiple myeloma and 6 or 15/mcL corresponded to yields of 2 or 4×10^6 CD34⁺ cells/kg in patients with NHL. Furthermore, a first-day yield of less than 0.8×10^6 CD34⁺ cells/kg was correlated with an ultimate yield of less than 2×10^6 CD34⁺ cells/kg. These types of correlations have led to institutional standards regarding when to use plerixafor in a risk-based approach; for instance, if the CD34⁺ cell count is less than 10/mcL with a target of greater than 2.5×10^6 CD34⁺ cells/kg, then add plerixafor.⁵⁵ Using this same count of less than 10/mcL, Gopal et al²² showed that 87% of patients with lymphoma or myeloma achieved a target yield of progenitor cells with the addition of plerixafor. A retrospective comparison of G-CSF plus plerixafor versus chemotherapy plus G-CSF versus G-CSF plus GM-CSF as a remobilization regimen demonstrated the following success rates: 84%, 60%, and 79%, respectively, with the ability to collect 53%, 20%, and 28%, respectively, in a single day.⁵⁶ The relative total costs of drugs plus leukapheresis for these 3 approaches revealed that the total costs were comparable for G-CSF plus plerixafor versus chemotherapy plus G-CSF, but the cost was approximately 40% less for G-CSF plus GM-CSF ($P < .01$). An extensive cost-effectiveness analysis of many studies by a panel of experts revealed differences in effectiveness, quality of life, and cost among many regimens and algorithms, and the conclusion was to propose a more uniform center-specific prospective approach to examine these issues.⁵⁷ Lastly, it has been shown that even after a prior mobilization attempt with plerixafor, repeat mobilization with plerixafor can be successful.⁵⁸

Allogeneic Donor Stem Cell Mobilization

The most common method for mobilization of normal donors is G-CSF at doses in the range of 10 to 16 mcg/kg/d via subcutaneous administration followed by leukapheresis beginning on day 4 or 5.^{31,59,60}

Approximately 80% of allogeneic donors are able to achieve target cell doses with mobilization.⁶¹ GM-CSF has also been shown to be effective,⁶² as has a tandem combination of GM-CSF followed by G-CSF.⁶³ Typically, 1 or 2 apheresis procedures are sufficient, but occasionally inadequate collections occur for several reasons, such as larger size of recipient, high cell number needed for graft manipulation, or missed doses of G-CSF. Plerixafor also augments stem cell mobilization in healthy donors, although this is currently not an approved indication.⁶⁴

The donor cell product is known to have a higher number of T lymphocytes when harvested from a leukapheresis collection compared with a bone marrow harvest, and a theoretical concern existed regarding which product might be superior in the unrelated donor setting, where the risk of GVHD might be increased. Therefore, a randomized trial compared the outcomes for PBPCs versus bone marrow as the source for patients undergoing unrelated donor transplantation.²⁰ No differences in overall survival rate at 2 years (51% vs 46%, respectively) or the incidence of acute GVHD were seen. However, differences were noted in the incidence of graft failure (3% vs 9%, respectively; $P=.002$) and chronic GVHD at 2 years (53% vs 41%; $P=.01$).²⁰ Thus, these differences in graft failure and chronic GVHD are balanced by the advantages of PBPCs, so that there is no difference in overall survival.

Contamination of Mobilized Products by Tumor Cells

Tumor cells have been identified in mobilized stem cell products, with wide variability from 0.01% to greater than 10%.⁶⁵ The kinetics of mobilization are also variable, and some reports have shown the tumor cells to be mobilized with the same kinetics as the hematopoietic progenitors, and others have reported that there are different peaks of mobilization. One study showed that contamination was predictive of overall survival in multiple myeloma.⁶⁶ Contamination by tumor has been a major problem for neuroblastoma, and was able to be reduced from 50% to no contamination by CD34 selection.⁶⁷ Given the historical high rates of tumor contamination with G-CSF mobilization, it is intriguing that a study of cell products mobilized by G-CSF and plerixafor showed that no contamination by myeloma cells occurred.⁵⁰

Adverse Events Associated With Mobilization

The most common side effect of G-CSF is bone pain, with a reported incidence of 61% in patients²⁵ and 97% in normal donors.⁶⁸ Other issues include inflammation at the injection site, exacerbation of rheumatologic disorders, and sickle cell crisis, including fatal consequences. Several case reports exist of splenic rupture after growth factor administration in allogeneic donors, but a prospective study of 309 normal donors did not encounter splenic rupture, although reversible enlargement of the spleen to an average of 1.5 times (range, 0.6–2.6) the pretreatment size was seen on ultrasound.⁶⁹ A case of pulmonary hemorrhage was also reported in a normal donor.⁷⁰ Another theoretical concern has been the possible contribution of G-CSF to the development of hematologic malignancies, and large studies of normal donors have not revealed a definitive risk. One group prospectively examined for chromosomal instability in normal donors who received G-CSF and found no abnormalities.⁷¹

Biosimilars

Tbo-filgrastim, originally designated XM02, is another recombinant G-CSF that gained FDA approval in August 2012 based on conventional phase III trials demonstrating efficacy, and not according to the regulations permitting approval of biosimilars. Tbo-filgrastim is indicated to reduce the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy drugs associated with a clinically significant incidence of febrile neutropenia. Tbo-filgrastim is approved as a biosimilar G-CSF (Ratiograstim or Tevagrastim) in Europe, and has been shown in clinical trials overseas to be effective in mobilizing progenitor cells in patients⁷² and healthy donors,⁷³ but it is not approved for this indication in the United States. In the future, as biosimilars become common, they may effectively reduce the cost of mobilization. However, given the relatively short experience with biosimilar drugs, the World Marrow Donor Association currently cautions against the use of biosimilars for unrelated donors unless this use is part of a clinical trial assessing safety.⁷⁴

Conclusions

Strategies for hematopoietic progenitor cell collection from patients and donors are highly successful,

albeit very costly. Which patients might benefit most from plerixafor, or who may even use the agent in a rescue strategy, can now be predicted, thus optimizing the cost-effectiveness. The role of biosimilar myeloid growth factors in mobilization has yet to be defined. Novel growth factors and small molecule inhibitors, and combinations of these agents, continue to be studied in the laboratory and clinical trials. The ideal strategy will result in a high stem/progenitor cell yield with minimal toxicity during procurement, a product with reduced tumor cell contamination, and enhanced graft-versus-tumor effect with minimal GVHD. Recently published consensus guidelines for stem cell mobilization⁷⁵ can serve as an additional resource.

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