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Peripheral blood stem cell mobilization: new regimens, new cells, where do we stand

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Abstract

Purpose of review—Granulocyte colony-stimulating factor-mobilized peripheral blood stem cells are widely used to reconstitute hematopoiesis; however, preclinical and clinical studies show that improvements to this mobilization can be achieved. We discuss the development of new mobilizing regimens and evaluation of new findings on mobilized stem cell populations that may improve the utility and convenience of peripheral blood stem cell transplant.

Recent findings—Chemokines and their receptors regulate leukocyte trafficking, and altering chemokine signaling pathways mobilizes stem cells. In recent trials, combination use of the chemokine (C-X-C motif) receptor 4 antagonist AMD3100 and granulocyte colony-stimulating factor mobilized more CD34⁺ cells in fewer days than granulocyte colony-stimulating factor alone and allowed more patients to proceed to autotransplant. In preclinical studies the chemokine GRO β synergizes with granulocyte colony-stimulating factor and when used alone or with granulocyte colony-stimulating factor mobilizes more primitive hematopoietic stem cells with less apoptosis, higher integrin activation, lower CD26 expression and enhanced marrow homing compared with granulocyte colony-stimulating factor. Hematopoietic stem cells mobilized by GRO β or AMD3100 demonstrate superior engraftment and contribution to chimerism in primary and secondary transplant studies in mice, and peripheral blood stem cells mobilized by AMD3100 and granulocyte colony-stimulating factor in patients demonstrate enhanced engraftment capabilities in immunodeficient mice.

Summary—Alternate regimens differentially mobilize stem cell populations with unique intrinsic properties with the potential to expand the utility of hematopoietic transplantation. Continued mechanistic evaluation will be critical to our understanding of mechanisms of mobilization and their use in regenerative medicine.

Keywords

hematopoietic transplantation; peripheral blood stem cell mobilization; stem cells

Introduction

Adult bone marrow is the primary source of stem cells that regenerate hematopoiesis. Bone marrow also harbors other stem and progenitor cells, including endothelial progenitor cells (EPCs) that can contribute to revascularization [1] and mesenchymal stem cells (MSCs), which can differentiate into adipocytes, chondrocytes and osteo-blasts [2–4]. Normally, most

hematopoietic stem cells (HSCs), EPCs and MSCs reside in marrow, but HSCs and EPCs also circulate in peripheral blood at low frequency. Early studies [5–7] showed that hematopoietic progenitor cells (HPCs) were elevated in blood of patients recovering from chemotherapy, which led to the realization that HSCs and HPCs could be induced to exit bone marrow, a phenomenon called ‘mobilization’, and that these mobilized cells can be collected and will re-home to marrow and repopulate hematopoiesis. Currently, mobilized peripheral blood is the primary source of hematopoietic cells used for hematopoietic transplantation [8]. In this review, new mobilizing regimens and studies demonstrating differential mobilization of stem cell populations with different quantitative and qualitative traits, and their potential to improve convenience, efficiency and outcome of peripheral blood stem cell transplantation will be discussed.

Peripheral blood stem cell mobilization by granulocyte colony-stimulating factor: the gold standard

Multiple agents induce peripheral blood stem cell mobilization, each with different kinetics and efficiencies [9–11] (Table 1), which suggests multiple mechanisms of action or multiple interventions along a common pathway. Combinations of agents can be additive or synergistic, and can produce grafts with quantitative and/or qualitative differences. Granulocyte colony-stimulating factor (G-CSF) is the predominant mobilizer used clinically. G-CSF-mobilized peripheral blood stem cells (PBSCs) engraft better than bone marrow or umbilical cord blood [12–15], with faster neutrophil and platelet recoveries, fewer platelet transfusions, faster lymphocyte reconstitution, fewer febrile episodes and lower regimen related mortality [12, 16–21]. Recovery of blood counts using chemotherapy-mobilized PBSC takes longer and febrile complications and transfusion requirements are higher than G-CSF-mobilized PBSC [22], and chemotherapy-based mobilization regimens are not viable for allogeneic transplantation. PBSC collection is less invasive than bone marrow harvest and avoids risks associated with general anesthesia. Target yields are usually achieved with 1–3 aphereses, which is adequate for human leukocyte antigen (HLA)-identical and matched-related transplant, but may be suboptimal in the haploidentical setting [23,24]. G-CSF-based mobilization is generally well tolerated, although rare cases of splenic rupture have been documented [25,26]. Most donors complete the procedure with collection of sufficient cells for transplantation. Although there is no clear minimum threshold of mobilized PBSC for successful transplantation, infusion below 2×10^6 CD34⁺ cells/kg may be associated with higher risk of graft failure. Higher CD34⁺ cell doses may negatively impact the rate of acute or chronic graft-versus-host disease (GVHD) [27–29] but positively impact overall patient survival [30–32]. Cellular subsets, particularly T cells and CD14⁺ monocytes, within the graft can impact outcome [30,33]. Overall, alterations in the quantitative and qualitative attributes of the PBSC graft can significantly impact engraftment and transplant outcome.

Poor mobilization to G-CSF occurs in 25% of patients, particularly in those with lymphomas [34,35], multiple myeloma [36,37] and acute leukemia [38–40], and in 10–20% of normal volunteers [41,42], requiring extended aphereses [43]. Poor mobilization is also seen in heavily treated cancer patients [44,45] and genetic disorders, such as Fanconi's anemia [46]. In a recent study [47**] of the feasibility of PBSC mobilization and autologous transplant in recovered aplastic anemia patients, PBSC collection using G-CSF was feasible in only a small percentage of patients. There is a broad individual variability in mobilization responsiveness of donors and patients to G-CSF [48–50]. Expanded application of allogeneic transplantation, particularly to patients with malignant disease receiving matched-unrelated grafts, or to patients receiving tolerizing grafts for organ transplant or for treatment of genetic disorders that do not require lethal conditioning, will require larger doses of mobilized cells to overcome HLA barriers and provide durable engraftment, acceptable leukocyte recovery kinetics and low incidence of GVHD [23,24,51]. Thus despite the success of G-CSF, there are areas for

improvement that can have significant clinical impact: specifically, multiple dosing, variable and suboptimal mobilization in some groups, number of aphereses, inability to predict optimal mobilization times and graft composition.

Alternative mobilization strategies

Clinical trials continue to affirm the use and benefit of G-CSF-mobilized PBSC. Longer acting G-CSF, Pegfilgrastim, may address the multidosing requirement of conventional G-CSF. In patients with multiple myeloma [52,53], aggressive lymphoma [54] and previously treated lymphoma patients [55,56], a single dose of Pegfilgrastim in combination with chemotherapy was as effective as G-CSF in mobilizing sufficient CD34⁺ cells for auto-transplant, with sustained engraftment and rapid absolute neutrophil count (ANC) recovery. In patients with multiple myeloma, Pegfilgrastim used alone was effective in mobilizing adequate PBSCs with efficacy and toxicities similar to a standard G-CSF regimen [57]. Similar to G-CSF, splenic rupture in a patient following Pegfilgrastim mobilization has been reported [58]. In the allogeneic setting, there is little information available for Pegfilgrastim mobilization. In one study in normal donors [59], 80% achieved target CD34⁺ cell counts in one apheresis with a single Pegfilgrastim dose, and increased leukocytosis was demonstrated in a pharmacokinetic/pharmacodynamic study in normal volunteers [60]. Although Pegfilgrastim studies are at early stages, it appears that it may address shortcomings of the multiday G-CSF regimen. Poor mobilization response in some patients and donors, however, remains an area of unmet medical need.

Other agents have been used to try to enhance the G-CSF-induced peripheral blood stem cell mobilization (PBSCM) response, including stem cell factor (SCF) and thrombopoietin, the respective ligands for the c-kit and c-mpl receptors expressed on HSCs and HPCs; however, lack of efficacy or toxicity has prevented their development [34,61,62]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is approved for PBSCM; however, it mobilizes less CD34⁺ cells than G-CSF [22,63] and little overall benefit was seen in combination trials [37,64].

Chemokines and their receptors direct leukocyte movement, including HSCs [65–67], and have been implicated in PBSCM. Macrophage inflammatory protein-1 α (MIP1 α /CCL3) mobilizes HPCs and short-term repopulating cells and shows greater than additive effect with G-CSF [68–70,71*]. The chemokine (C-X-C motif) receptor 2 (CXCR2) ligands GRO β and GRO β Δ ₄ [70,72,73] and interleukin-8 (IL-8) [74] mobilize HSCs and HPCs and synergize with G-CSF [70,72]. Stromal cell derived factor-1 α [SDF-1 α /chemokine (C-X-C motif) receptor 12 (CXCL12)] and its receptor chemokine (C-X-C motif) receptor 4 (CXCR4) are an important axis for movement into and retention in the marrow [75]. Mobilization is observed using SDF-1 α peptide analogs, CTCE-0021 and CTCE-0214 [76,77], the CXCR4 antagonist AMD3100 [78,79] and the SDF1 analog Met-SDF-1 β [80], suggesting that altering SDF-1/CXCR4 signaling produces the mobilization response, most likely by CXCR4 receptor down modulation [47**,77,80].

The bicyclam AMD3100 induces HSC and HPC mobilization in mice [78], dogs [81], monkeys [82] and humans [78,79,83,84] and synergizes with G-CSF [71*,78,85,86**,87]. In a phase II trial, AMD3100 and G-CSF mobilized more CD34⁺ cells than G-CSF in 84% of patients with multiple myeloma and non-Hodgkin's lymphoma with a higher yield of CD34⁺ cells [86**]. In two recent randomized placebo-controlled phase III trials, AMD3100 (plerixafor) and G-CSF mobilized more CD34⁺ cells in multiple myeloma [88] and non-Hodgkin's lymphoma [89] patients in fewer days and allowed more patients to proceed to successful hematopoietic transplantation. In a third trial, AMD3100 (plerixafor) and G-CSF successfully mobilized

sufficient cells for transplant in a large proportion of patients who previously failed G-CSF mobilization with G-CSF [90].

The success of AMD3100 and G-CSF significantly addresses a number of areas of improvement in PBSCM; however, it still requires multiple dosing. It will be interesting to determine if AMD3100 can be successfully used in combination with single dosing with Pegfilgrastim or in combination with other chemokines or used as a stand-alone mobilizer, taking advantage of the rapid mobilization that is the hallmark of chemokine axis mobilization.

Not all mobilized hematopoietic stem cells are created equal

Stem cell number, cell cycle status [91,92], facilitating or accessory cell content [93,94] or intrinsic differences in homing or proliferative properties [67,95,96] affect the ultimate function of the HSC graft. The superiority of G-CSF-mobilized PBSCs raises questions concerning stem cell quantity versus quality. Although total clonogenic cells in the PBSC graft often exceed that of marrow grafts [97,98], earlier engraftment has also been seen when equivalent numbers of stem/progenitor cells were transplanted, suggesting that stem cell quality may impact efficacy [99]. Differences in gene and protein expression patterns and function have been described, at least *in vitro*, but have not led to an understanding of the enhanced engraftment properties of G-CSF-mobilized PBSCs. Recently, however, differential homing of G-CSF-mobilized stem cells resulting from enhanced motility and low CD26 expression relative to bone marrow stem cells have been suggested as contributing factors for enhanced engraftment [100]. In addition, detailed analysis of PBSCs mobilized by alternative regimens has begun to shed significant light on the importance of the HSC populations mobilized.

In contrast to G-CSF, chemokine mobilization occurs rapidly. In mice, PBSC mobilization by MIP1 α , CTCE0021 and AMD3100 is maximal within 60 min, while mobilization by GRO β is maximal at 15 min. Synergistic PBSCM is seen when MIP1 α , CTCE0021, AMD3100 or GRO β are combined with G-CSF (Table 2) and combinations of chemokines alone without G-CSF are synergistic [71]. Even more dramatic synergy is seen using chemokine combinations and G-CSF [71]. In competitive transplant studies G-CSF, AMD3100 and GRO β -mobilized cells contribute significantly to donor repopulation, with GRO β -mobilized cells producing significantly higher chimerism than G-CSF or AMD3100-mobilized cells (Table 2) [71, 101]. Significantly higher chimerism is observed using GRO β and G-CSF or AMD3100 and G-CSF-mobilized cells. In general, the GRO β and GRO β plus G-CSF-mobilized grafts contain twice the number of Sca-1⁺, c-kit⁺, lineage^{neg} (SKL) cells and three times the number of CD34^{neg} SKL cells, compared with G-CSF mobilized grafts [101], suggesting that increased HSC frequency contributes to superior performance. In secondary transplant studies that test for HSC self-renewal, one expects chimerism in the second host to be identical to that in the primary host, and is in fact what is observed for G-CSF-mobilized cells (Table 2). The marrow cells from mice receiving grafts mobilized by GRO β or AMD3100 alone, or GRO β or AMD3100 plus G-CSF, however, show significantly higher contribution to chimerism than observed in the primary transplant (Table 2), suggesting chemokine-mobilized HSCs are inherently more competitive than bone marrow or G-CSF-mobilized HSCs [71,78,101]. The enhanced engraftment properties of GRO β -mobilized PBSCs are also apparent in that recipients recover white blood cell counts faster than G-CSF-mobilized PBSCs [72,73,101].

Extensive characterization of PBSCs mobilized by GRO β and G-CSF indicates that GRO β -mobilized HSCs show significantly lower levels of apoptosis, significantly enhanced marrow homing that is less dependent on the SDF-1/CXCR4 axis and express more activated adhesion receptors, lower expression of CD26 and twice the number of CD26⁺ SKL cells compared with

G-CSF-mobilized cells [101^{**}], which are likely responsible for their superior engraftment capacity.

In preclinical studies, the frequency of severe combined immunodeficient (SCID) reconstituting cells (SRCs) was higher in AMD3100-mobilized PBSCs compared with G-CSF [78]. In rhesus macaques, AMD3100-mobilized CD34⁺ cells showed long-term reconstituting capacity, with AMD3100-mobilized PBSCs containing more G₁ cells and higher CXCR4 and very late antigen-4 (VLA-4) expression, which likely contribute to enhanced engraftment [82]. Higher expression of genes associated with antiapoptosis, cell motility and cell cycle were found in CD34⁺ cells mobilized by AMD3100 and G-CSF compared with G-CSF alone, which may support their superior repopulating ability [102]; however, further functional studies are needed. In a clinical study [103^{**}], AMD3100-mobilized PBSCs demonstrated a three-fold higher repopulating frequency in NOD/SCID mice despite two-fold lower CD34⁺ cell counts compared with G-CSF mobilized PBSCs, although only marginally better repopulating frequency was observed when purified CD34⁺ cells were used. In matched sibling donors, AMD3100-mobilized sufficient CD34⁺ cells for transplant in one leukapheresis in 10/11 patients, and although containing fewer CD34⁺ cells and more T cells than with mobilization by G-CSF, engraftment kinetics were similar to G-CSF with no appreciable increase in GVHD [104], suggesting that the AMD3100-mobilized HSCs have enhanced intrinsic HSC function.

Mobilization beyond hematopoietic stem cell

The emerging role of marrow as a site of adult stem cells that contribute to tissue repair raises the question of whether mobilizing agents can mobilize stem cells other than HSCs or whether new agents can be developed that differentially mobilize adult stem cells. Reestablishment of circulation to limit tissue damage is critical following myocardial infarction (MI) or limb ischemia. Cytokines including vascular endothelial growth factor (VEGF), angiopoietin, G-CSF and GM-CSF mobilize EPCs with high proliferative capacity [1,105–108] and circulating angiogenic cells (CACs) that contribute to neovascularization through paracrine mechanisms [109–111]. In animal models, autologous mobilization showed improved neovascularization and ventricular function; however, in randomized double-blind trials, no significant improvement in cardiac function was observed in acute MI patients mobilized by G-CSF [112,113]. Likely, the kinetics of EPC mobilization by G-CSF may not be optimal for this application since peak APC mobilization is not achieved until days 4–5 [114]. However, in two recent studies, intracoronary cell infusion with G-CSF-mobilized PBSCs showed a trend towards efficacy over systemic G-CSF administration in patients with MI [115^{*}], and intracardiac injection of autologous G-CSF-mobilized CD34⁺ cells in patients with intractable angina provided evidence for feasibility, safety and efficacy [116^{*}]. A recent study [117^{*}] shows that transplantation of autologous G-CSF-mobilized CD34⁺ cells into the muscle of ischemic limbs demonstrated therapeutic angiogenesis, and in a report [118^{*}] of a single patient, injection of autologous G-CSF-mobilized CD133⁺ EPCs produced long-term limb salvage, symptomatic relief and functional improvement. Recently, single administration of AMD3100 was shown to rapidly and significantly mobilize EPCs and CACs and that these cells could be harvested by leukapheresis after 4 h [119^{**}]. This exciting finding offers potential strategies to rapidly mobilize cells to sites of vascular injury in an acute setting and to collect cells that can be directly transplanted into ischemic tissue.

MSCs can be isolated from umbilical blood [120–122]; however, isolation from peripheral blood and the ability to mobilize MSCs are not clear. The presence [123–126] and absence [127,128] of MSCs in peripheral blood have been reported. In general, this controversy stems from variation in the volume of blood used as a source of cells, differences in the methods used to identify MSCs and the stringency used to establish the criteria of stem cell activity. However, in two studies [126,129] using mobilized blood and adherence to fibrin microbeads, MSCs

were isolated from normal donors and cancer patients. In primates, circulating fibroblastoid colony-forming units (CFU-F) that demonstrated both adipogenic and osteogenic differentiation were detected in animals treated with G-CSF and SCF [130]. Although the controversy concerning detection of circulating MSCs needs resolution, it is becoming apparent that with appropriate stimuli they can be mobilized. From a therapeutic standpoint, however, it needs to be determined what role mobilized MSCs may play versus recruitment locally at sites of injury.

Conclusion

It is becoming clear that different agents mobilize HSC populations with overlapping stem cell function, but also mobilize HSCs that have unique intrinsic characteristics that may facilitate and expand our use of hematopoietic transplantation for curative purposes. HSCs that have enhanced homing and engraftment properties will certainly have utility in patients who mobilize poorly but may also be useful for gene therapy approaches to increase overall gene expression levels. In addition, it is clear that the cell composition of the mobilized graft may also significantly impact outcomes, and increased understanding of the mobilization process may allow us to engineer graft composition in ways that will alter the likelihood of graft failure, GVHD and impaired immune reconstitution. Current mobilization agents and combinations have their advantages and disadvantages; however, preclinical mechanistic studies on the action of these agents as well as continued mechanism driven investigation of new mobilization targets will be critical to our ultimate understanding of stem cell function and their use in regenerative medicine.

Acknowledgments

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 424–425).

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Table 1

Peripheral blood stem cell mobilizing agents

Agent class	Examples	Time of maximal mobilization
Chemotherapy	Cytosan, 5-fluorouracil	1–3 Weeks
Growth factors	G-CSF, GM-CSF, stem cell factor, thrombopoietin, erythropoietin, growth hormone, IL-3, IL-17, parathyroid hormone, VEGF, angiopoietin-1	4–6 Days
Antibodies	Anti-VLA-4, anti-VCAM-1	1–2 Days
Polyanions	Fucoidan, dextran sulfate	1–2 h
Chemokines/chemokine mimetics	GRO β , KC (murine GRO), MIP1 α , Met-SDF-1 β , CTCE0021, CTCE0214	15min–2 h
Receptor antagonists/signaling pathway inhibitors	AMD3100, Rho GTPase inhibitor, β 2-agonists	1–6 h

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3; IL-17, interleukin-17; VCAM, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VLA-4, very late antigen-4.

Table 2

Quantitative versus qualitative peripheral blood stem cell mobilization

Mobilizer	Mobilization fold increase over baseline		% Donor chimerism ^a	
	CFU-GM	SKL	Primary	Secondary
G-CSF ^b	24 ± 5	12 ± 2	18 ± 2	23 ± 6
GROβ ^c	12 ± 2	18 ± 3	38 ± 3	58 ± 5
AMD3100 ^c	7 ± 2	6 ± 1	19 ± 2	51 ± 3
MIP1α ^c	3 ± 1	–	–	–
CTCE0021 ^c	14 ± 4	5 ± 2	–	–
GROβ + G-CSF ^d	141 ± 12	54 ± 6	53 ± 6	85 ± 6
AMD3100 + G-CSF ^d	51 ± 5	63 ± 2	50 ± 2	84 ± 3
MIP1α + G-CSF ^d	39 ± 6	–	–	–
CTCE0021 + G-CSF ^d	123 ± 14	–	–	–

CFU-GM, colony-forming units granulocyte-macrophage; G-CSF, granulocyte colony-stimulating factor; MIP1α, macrophage inflammatory protein-1α; SKL, Sca-1⁺, c-kit⁺, lineage neg cells.

^aCompetitive transplantation was performed comparing mobilized PBSCs to congenic bone marrow. In primary transplanted mice, donor chimerism in peripheral blood was analyzed at 6 months post-transplant. Bone marrow was obtained from primary mice at 6 months and transplanted in noncompetitive fashion into secondary lethally irradiated hosts and donor chimerism in peripheral blood was analyzed at 6 months post-transplant.

^bG-CSF was administered at a dose of 50 µg/kg; SC; bid × 4 days.

^cGROβ (2.5 mg/kg), CTCE0021 (25 mg/kg), MIP1α (50 µg/kg), AMD3100 (5 mg/kg), were administered as single bolus SC injections and peripheral blood cells harvested at 15 min (GROβ) or 60 min (MIP1α, CTCE0021, AMD3100) after administration.

^dGROβ, CTCE0021, MIP1α, AMD3100, were administered as single bolus injections approximately 16 h after the last dose of G-CSF (50 µg/kg; SC; bid × 4 days) and peripheral blood harvested 15 min (GROβ) or 60 min (CTCE0021, MIP1α, AMD3100) later.