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Optimizing stem cell collection through CXCR4 antagonists

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1. ABSTRACT

Currently, nearly all the autologous stem cell transplantation and majority of allogeneic stem cell transplantation are performed using circulating peripheral blood stem cells. At steady conditions, less than 0.05% of the peripheral white cells are believed to be CD34+, a surrogate marker for stem cells. The content of hematopoietic CD34+ cells in the blood can be increased dramatically following recovery from myelosuppressive chemotherapy and/or the administration of hematopoietic growth factors (GM-CS or G-CSF), and an engrafting dose of stem cells can be collected by large volume apheresis following hematopoietic cytokine treatment. However these strategies fail to result in an adequate number of hematopoietic cells in 5-30% of the cases, limiting the ability of patients to receive high dose chemotherapy and stem cell transplantation in the treatment of their cancer. Plerixafor, a CXCR4 antagonist has been found to be a potent stem cell mobilizer and it's superiority used in combination with G-CSF over G-CSF alone has been seen in non-Hodgkin's lymphoma and multiple myeloma in double blind randomized phase III clinical trials, leading to FDA (Food and Drug Administration) approval. This review article describes the development of plerixafor to mobilize stem cells and optimal strategies for stem cell collection from peripheral blood.

2. INTRODUCTION

In 2010, there will be an estimated 20,180 new cases of multiple myeloma (MM), with an estimated 10,650 deaths, and 65,540 estimated new cases of non-Hodgkin's lymphoma (NHL), with an estimated 20,210 deaths. Similarly, there will be estimated 17,660 new cases of acute leukemia (myeloid and lymphoid), with an estimated 10,370 deaths (1). Autologous hematopoietic stem cell transplantation (auto-HSCT) is the standard of care for patients with MM or chemosensitive relapsed high- or intermediate-grade NHL, providing necessary hematopoietic support after the administration of high dose chemotherapy (HDT) (2-6). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the standard of care in patients with intermediate- or high-risk acute myelogenous leukemia (7) and with high risk acute lymphocytic leukemia (8). Increasing number of auto- and allo-HSCT is performed worldwide. Center for International Blood and Marrow Transplant Research (CIBMTR) estimated that approximately 30,000 auto- and 25,000 allo-HSCT were performed worldwide in 2009 (9).

Historically bone marrow has been used as the source of hematopoietic stem cells (the pluripotent progenitor cells that are capable of self-renewal as well as differentiating to a defined set of differentiated

progenitors). In 1980s, studies in animals and human (10-13) revealed that peripheral blood stem cells (PBSC) can potentially be used as a source of stem cells to reconstitute the bone marrow after HDT. Currently almost all the auto-HSCT and a majority of allo-HSCT are performed using circulating PBSC (9). PBSC can be harvested without the need of general anesthesia and discomfort of multiple of bone marrow aspirations. Patients with metastasis to bone marrow can be transplanted with auto-HSCT as there is a potential for harvesting a product that is free of malignant cells (14). Compared to bone marrow derived stem cells, transplantation with PBSC leads to faster reconstitution of bone marrow with hematopoietic cells resulting in shorter time to neutrophil and platelet recovery in both, auto-HSCT (15, 16) and allo-HSCT (17-19) settings. PBSC reduces time to transfusion independence and the period of intravenous antibiotic administration (20). It also improves the immune reconstitution over bone marrow grafts after allotransplantation (21).

Hematopoietic stem cells reside in the bone marrow and circulate in a very low number in blood, comprising therefore approximately 0.01-0.05% of cells. Therefore, harvesting stem cells from the blood under steady state is challenging. A major factor in the success of auto-HSCT is the kinetics of hematopoietic recovery following high-dose chemotherapy which is, in turn, influenced by the dose of reinfused stem and progenitor cells (22, 23). Although no absolute thresholds exist, the usual minimum number of CD34+ cells (a surrogate marker for hematopoietic stem cells) required for proceeding with autologous stem cell transplant and sufficient to ensure prompt hematopoietic reconstitution are thought to be 2.0 to $2.5x10^6$ CD34+ cells/kg body weight. The optimum number to ensure rapid hematopoietic reconstitution is at least $5.0x10^6$ CD34+ cells/kg (24). Higher number of reinfused CD34+ cells are associated with faster neutrophil engraftment (defined as first of 3 consecutive days where the absolute neutrophil count is $>0.5x10^9$ cells/L), platelet engraftment (defined as first day where the platelet count is $>20x10^9$ /L in absence of transfusion for previous 7 days) (24, 25) and with decreased need for transfusions of red cells and platelets or administration of prophylactic antibiotics (25). In murine models, number of transplanted hematopoietic stem cells correlates with speed of immune reconstitution with more rapid recovery of T and B lymphocytes (26). Some studies even report improved survival in patients receiving higher dose of cells (27, 28). However, benefits of re-infusing $>5.0x10^6$ CD34+ cells/kg are not well defined. Since harvesting the minimum required PBSC from patients with apheresis under steady state conditions is not practical, mobilization of stem cells to peripheral blood from their niche in the marrow is pivotal to the success of transplantation. The number of previous chemotherapy cycles, peripheral blood white cell counts and prior irradiation are commonly reported prognostic factors for poor PBSC mobilization (29, 30). Since the donors for allo-HSCT are usually healthy volunteers, failure to mobilize sufficient PBSC is rare in this setting. However, a major pitfall in auto-HSCT is that a significant number of patients fail to mobilize a sufficient number of CD34+ cells required for successful hematopoietic reconstitution of bone marrow. This article will focus on mobilization of stem cells for auto-HSCT and review a number of developments which have improved our understanding of the biology and mechanisms of stem cell mobilization.

3. BIOLOGY AND MECHANISMS OF STEM CELLS MOBILIZATION

Hematopoietic stem cells (HPSCs) reside in bone marrow in a highly organized three dimensional microenvironment comprised of stromal cells, osteoblasts, osteoclasts, endothelial cells and extracellular matrix, which is rich in collagens, fibronectins and proteoglycans. HPSCs are anchored to the marrow microenvironment by interactions between wide range of adhesion molecules expressed on cell-surface of HPSCs and their ligands expressed on the marrow stroma. The adhesion molecules expressed on HSPCs cell surface include CXC receptor 4 (CXCR4), CXCR2, leukocyte function-associated antigen-1 (LFA-1), very late antigen-4 (VLA4), tyrosine kinase receptor c-kit, Mac-1, the cell surface glycoproteins CD44 and CD62L. The cognate ligands for these adhesion molecules expressed on the bone marrow stroma include stromal cell-derived factor-1 (SDF-1, also known as CXCL12), Gro β, vascular cell adhesion molecule-1 (VCAM-1), kit ligand (KL), CD62, hyaluronic acid, P-selctin and glycoprotein ligand-1 (31-33).

Inhibition of the adhesion molecule-ligand interaction between HPSCs and stromal cells result in improved stem cell mobilization. Substantial evidence exists as proof of this concept. Soluble c-kit receptor mobilizes CD34+ cells by disrupting the interaction of ligand with c-kit on HPSCs cell surface (34). Treatment with anti-VLA4 antibodies in combination with G-CSF (Granulocyte Colony Stimulating Factor) results in 5-8 fold enhancement in stem cell mobilization in mice and primates (35). The interaction between SDF-1 and its receptor CXCR4 regulates hematopoietic stem cell trafficking and survival in the bone marrow microenvironment. During stem cell mobilization with G-CSF, expression of SDF-1 protein and mRNA in the marrow is down regulated following G-CSF binding to receptors on monocytic lineage cells (macrophages and osteoclasts) in the bone marrow microenvironment (36-39). Plerixafor, the subject of this review, mobilizes stem cells by its inhibitory effect on SDF-1/CXCR4 interaction. Disruption of the interactions between adhesion molecules and their ligands is the basis for clinical stem cell mobilization. Better understanding of the interactions between stem cells and bone marrow microenvironment may result into new targets for mobilization.

4. CURRENT MOBILIZATION STRATEGIES AND THEIR OUTCOMES

Cytokine induced mobilization with or without myelosuppressive chemotherapy is currently the most common practice. The myeloid-acting hematopoietic growth factors GM-CSF (Granulocyte Macrophage Colony-Stimulating Factor, also known as sargramostim or

leukine) and G-CSF (Granulocyte Colony-Stimulating Factor, also known as filgrastim or neupogen) are approved by FDA (Food and Drug Administration) for mobilization of stem cells. A comparative study by Weaver *et al* (40) reported greater median CD34+ cell yield, requirement for fewer apheresis sessions, faster neutrophil and platelet recovery, fewer transfusions, fewer hospitalizations and episodes of fever in patients mobilized with G-CSF than GM-CSF. In addition, GM-CSF is thought to be more toxic than G-CSF (41). Consequently, the use of GM-CSF as a single agent for stem cell mobilization is comparatively rare, although it is used in combination with G-CSF (42).

G-CSF is usually administered at 10mcg/kg/day subcutaneously daily for 4 days before leukapheresis and is continued until the last day. Its efficacy as a single agent was established in a phase III trial by Schmitz *et al* (43), where G-CSF mobilized PBSCs were superior to their counterparts harvested from bone marrow. Biological mechanism through which G-CSF causes stem cell mobilization is not completely understood. As described earlier, G-CSF induces pleiotropic functional changes in bone marrow microenvironment that include decreasing SDF-1expression at the gene and protein level and increasing the numbers of myeloid precurosrs and granulocytes in the marrow microenvironment with concomitant release of neutrophil elastase and serine proteases cathepsin G. The primary role for G-CSF on CXCL12 mRNA levels in mobilization is supported by studies that show that G-CSF can mobilize stem cells in protease deficient mice (45), highlighting this mechanism. Recent studies indicate that G-CSF binds to receptors on bone marrow osteoclasts and /or macrophages leading to the release of a soluble mediator that down regulates SDF1/CXCL12 mRNA expression in osteoblasts and mesenchymal stromal cells leading to down-regulation of CXCL12 expressed by these cells (39, 44).

After transplantation with G-CSF mobilized PBSCs, the median time to neutrophil engraftment has been reported to be 11 days and to platelet engraftment around 11-14 days (46, 47). In general, mobilization with G-CSF is well tolerated, approximately 33% of treated patients report bone pain. Rare, but serious adverse events such as myocardial infarction, cerebral ischemia, splenic rupture, sickle cell crisis in sickle cell disease patients and acute respiratory distress syndrome have been reported (31). Despite the remarkable success of G-CSF, it has been limited by insufficient mobilization and collection of stem cells in patients. Micallef *et al* (48) reported unsuccessful stem cell mobilization in 35% of NHL patients. Desikan *et al* (49) reported that 23% of multiple myeloma patients who were treated with G-CSF as single agent failed to mobilize sufficient PBSCs to support tandem transplantations.

Addition of chemotherapy to G-CSF results into higher CD34+ cell yields in fewer apheresis sessions (46, 47, 49-51). Treatment with chemotherapy also helps with treatment of underlying disease. However, significant proportion of the patients fails to mobilize sufficient CD34+ cells even with combination of chemotherapy and G-CSF. A retrospective study by Pusic *et al* (50) reported suboptimal CD34+ cells yield in approximately 18% of patients treated with G-CSF alone and with G-CSF plus chemotherapy. In addition, higher yields of CD34+ cells with chemotherapy may be offset by associated unpredictable time to collect, increased risk of infection, cost, need for transfusion support and hospitalization; and other general complications of chemotherapy. Consequently, there remains a need for additional strategies to enhance stem cell mobilization for patients undergoing autologous peripheral blood stem cell transplantation.

5. CLINICAL DEVELOPMENT OF PLERIXAFOR

Plerixafor (1-1'- (1,4-phenylenebis-(methylene))-bis-1,4,8,11-tetraazacyclotetradecane), also known as AMD3100 or Mozobil is small bicyclam molecule developed by Genzyme corporation, Cambridge, MA for mobilization of stem cells. It reversibly and selectively binds CXCR4 disrupting the interaction with its ligand SDF-1, thereby releasing the hematopoietic CD34+ stem cells from bone marrow to the circulation (52-54). In addition to homing hematopoietic stem cells in the bone marrow, CXCR4 is a co-recepotor for T-cell tropic HIV strains entry into CD4+ T cells. Since plerixafor was noted to block the HIV entry into T cells (55, 56), it was originally developed as a treatment for HIV.

In a phase I trial in healthy volunteers (57), plerixafor at single doses of up to 80 mcg/kv iv was tolerated well without any grade 2 toxicity or need for dose reduction. The adverse effects experienced by the healthy volunteers were mild gastrointestinal symptoms, such as nausea and diarrhea. It was poorly absorbed when given by mouth. When given subcutaneously, the bioavailability was 87% and elimination half life, 3.6 hours. Interestingly, all subjects experienced a dose-related elevation of the white blood cell count, from 1.5 to 3.1 times the baseline, which peaked at 6h after plerixafor administration and returned to the baseline 24 h after dosing. The same group conducted another phase I trial (58) in 40 HIV infected patients, who received continuous infusion of plerixafor from 2.5 mcg/kg/hr to 160 mcg/kg/hr. The trial was halted at 160mcg/kg/hr due to unexpected asymptomatic premature ventricular contractions. Most patients in 80- and 160 mcg/kg/hr cohorts reported paresthesias. Although treatment with plerixafor had no significant effects on HIV viral load, leukocytosis was again observed in all patients, with an estimated maximum effect of 3.4 times baseline. With minimal clinical efficacy on HIV, repeated observation of profound leukocytosis in plerixafor-treated individuals and emerging evidence for the critical role of the CXCR4-SDF-1 axis in stem cell trafficking, development of plerixafor as antiretroviral therapy was aborted and the focus was re-directed towards its potential clinical use in hematopoietic stem cell mobilization.

6. PHASE I-II STUDIES IN STEM CELL MOBILIZATION

Multiple phase I and II studies have been done to optimize feasibility and efficacy of plerixafor for

hematopoietic stem cell mobilization. Liles *et al* (59) studied single subcutaneous injection of plerixafor in healthy volunteers at doses 40-240 mcg/kg, which resulted in dose dependent increase (4-10 fold) in CD34+cells, beginning at 1 hour post dose, peaking at 9 hours and then returning to baseline by 24 hours. In another phase I study by same group (60), plerixafor at dose of 160 mcg/kg single dose subcutaneously was administered on day 5 following 4 days of treatment with G-CSF (10 mcg/kg/day). It resulted into 4 fold increase in G-CSF stimulated CD34+ cells and the authors concluded that plerixafor could be combined with G-CSF to further improve the stem cell yields. To study stem cell mobilization in patients, who received prior chemotherapy, Devine and colleagues (61) treated multiple myeloma and non-Hodgkin's lymphoma patients with single subcutaneous dose of plerixafor at 160 or 240 mcg/kg. Up to 7 fold increase in CD34+ cells was observed with 240 mcg/kg, suggesting plerixafor was an effective agent to mobilize hematopoietic stem cells in patients previously treated with chemotherapy. Plerixafor was well tolerated up to 240 mcg/kg as single subcutaneous injection in these studies, with mild and reversible adverse events, such as injection site ertythema, nausea, abdominal distension and cramps. Previously observed preventricular contractions were not seen.

Flomenberg and colleagues (62) compared the combination of plerixafor and G-CSF with G-CSF alone in a phase II study with crossover design. Twenty five patients with myeloma and non-Hodgkin's lymphoma were assigned to receive either plerixafor (160 or 240 mcg/kg) with G-CSF or G-CSF alone as their initial mobilization regimen. After two weeks washout period, they were remobilized with alternative regimen. Plerixafor plus G-CSF was superior to G-CSF alone in regards to CD34+ cells harvested per leukapheresis, number of leukaphereses required to reach the target CD34+ cell count and total CD34+ cell yield. All the patients (100%) reached the target of $2x10^6$ CD34+ cells/kg after two leukaphereses compared to 64% with G-CSF alone. Furthermore, all the nine patients, who failed to yield the minimum $2x10^6$ cells/kg were successfully remobilized with plerixafor and G-CSF. Overall the combined regimen was safe, effective and superior to G-CSF alone.

In a compassionate use protocol by Calandra and colleagues (63), 115 patients with MM, NHL and Hodgkin's lymphoma, who failed to yield $2x10^6$ CD34+cells/kg during initial mobilization with cytokine or chemotherapy were remobilized with plerixafor and G-CSF. This treatment resulted into successful remobilization of CD34+ cells in 60.3% NHL, 71.4% MM and 76.5% Hodgkin's lymphoma patients. The neutrophil and platelet engraftment were endurable and the combination treatment was well tolerated. This study suggested that plerixafor with G-CSF could be beneficial to patients who failed prior mobilization with chemotherapy and/or cytokines. Additional studies (64-66) also demonstrated safe and successful mobilization of CD34+ cells in heavily pretreated patients with NHL, MM and Hodgkin's lymphoma. Stewart and colleagues (67) revisited the assessment of pharmacokinetics (PK) and pharmacodynamics (PD) of plerixafor in NHL and MM patients. They were comparable to the healthy volunteers and supported the current recommended dose and timing of apheresis (G-CSF - 10 mcg/kg/day subcutaneously for 4 days in the morning and plerixafor - 240 mcg/kg s.c. on the evening before apheresis, which is usually initiated 10 to 11 hours after plerixafor dosing). This schedule was implemented in both phase III trials with MM and NHL patients.

7. PHASE III STUDIES

Based on the promising results of phase I-II studies, two phase III randomized, double-blind, placebo controlled, prospective, multicenter studies of plerixafor in patients with NHL (68) and MM (69) have been completed and published. The stem cell mobilization protocol in both of these trials was identical. Randomized patients received G-CSF (10 mcg/kg) subcutaneously daily in the morning for up to 8 days. Beginning on evening of day 4 and continuing daily for up to 4 days, patients received either plerixafor (240 mcg/kg) or placebo. Apheresis sessions were started in the morning of day 5 and continued for up to 4 days or until a target CD34+ cells of $5x10^6$ cells/kg (NHL study) or $6x10^6$ /kg (MM study) was reached.

In the NHL study (68), patients (n=298) with non-Hodgkin's lymphoma requiring an autologous hematopoietic stem cell transplantation were randomized 1:1 to receive plerixafor plus G-CSF or placebo plus G-CSF. The primary endpoint was proportion of patients reaching a target of $\geq 5x10^6$ CD34+ cells/kg in 4 or less days of apheresis. The secondary endpoints were number of patients who achieved a minimum of $2x10^6$ CD34+ cells/kg in 4 days of apheresis; number of days of apheresis required to reach the target of $\geq 5x10^6$ CD34+ cells /kg; the fold-increase in the number of circulating CD34+ cells before and after the 1st study treatment (day 4 and day 5); time to neutrophil and platelet engraftment; graft durability at 100 days, 6 months and 12 months; and adverse as well as serious adverse events. A significantly greater proportion of patients in the study arm achieved the primary endpoint (59% vs 20%, $p<0.001$). Similarly higher proportion of patients in the study arm achieved the secondary efficacy endpoint of collecting a minimum of $2x10^6$ CD34+ cells/kg in 4 days of apheresis (87% vs 47%, $p<0.001$). The time required to reach $\geq 5x10^6$ CD34+ cells/kg was significantly shorter in the study arm ($p<0.001$). The median fold-increase in the number of circulating CD34+ cells on 5th day was higher in the plerixafor arm (5 vs 1.4, $p<0.001$). Median time to neutrophil and platelet engraftment in each group was similar, 10 days for neutrophil and 20 days for platelets. There were two graft failures in plerixafor group and none in the placebo group. The authors attributed the graft failure to pre-existing myelodysplastic syndrome with chromosome 5/7 abnormalities one patient and chromosome 6 mutations (later on developed acute myeloid leukemia) in the second patient. Patients failing to collect a minimum $2x10^6$ cells/kg in less than 4 apheresis days were allowed to be rescued with plerixafor plus G-CSF. 33/52 patients in placebo group and 4/10 in plerixafor group were

successfully re-mobilized to yield targeted minimum of $2x10^6$ cells (70). A total of 7% patients in plerixafor arm compared to 35% in the placebo arm failed the mobilization process. Plerixafor was well tolerated. The most commonly observed adverse events were diarrhea, nausea and injection site erythema.

In the Multiple Myeloma study (69), patients (n=302) eligible for high dose chemotherapy and autologous stem cell transplantation were randomized 1:1 to receive plerixafor plus G-CSF or placebo plus G-CSF. The primary endpoint was proportion of patients reaching a target of $\geq 6x10^6$ CD34+ cells/kg in 2 or less days of apheresis. The secondary endpoints were percentage of patients achieving a target of $\geq 6x10^6$ CD34+ cells/kg in 4 or less days of apheresis; percentage of patients achieving a minimum of $2x10^6$ CD34+ cells/kg in 4 days of apheresis; number of days of apheresis required to reach the target of $\geq 6x10^6$ CD34+ cells /kg; time to neutrophil and platelet engraftment; graft durability at 100 days, 6 months and 12 months; and adverse as well as serious adverse events. A significantly greater proportion of patients in plerixafor group reached the primary endpoint compared to placebo group (72% vs 34%, $p<0.001$). Similarly, greater proportion of patients in plerixafor group than in placebo group achieved secondary endpoint of collecting $\geq 6x10^6$ CD34+ cells/kg (76% vs 51%, $p<0.001$) and $\geq 2x10^6$ CD34+ cells/kg (95% vs 88%, $p=0.031$) in 4 or fewer days of apheresis. The CD34+ cell count in circulation increased 4.8 fold from day 4 to day 5 in plerixafor group compared to 1.7 fold in placebo group ($p<0.001$). The transplantation outcomes were similar in both groups, with median time to neutrophil and platelet engraftment of 11 and 18 days respectively. Graft failure was not observed in any group. Seven patients in placebo group compared to none in plerixafor group failed to mobilize sufficient CD34+ cells and they were all successfully rescued with plerixafor. As in NHL study, plerixafor was well tolerated. Both studies clearly demonstrate the safety and efficacy of plerixafor. Based on results of the two studies, plerixafor in combination with G-CSF was approved by FDA for mobilization of hematopoietic stem cells in NHL and MM.

8. CHARACTERISTICS OF PLERIXAFOR MOBILIZED STEM CELLS AND ITS ROLE IN ALLOGENEIC TRANSPLANTATION

The CD34+ cells mobilized with plerixafor are intrinsically different compared to their counterparts mobilized with G-CSF. Relatively larger proportion of plerixafor-mobilized CD34+ cells are in G1 phase of cell cycles; and express CXCR4 and VLA-4 on the cell surface (71). Higher proportion of plerixafor-mobilized stem cells have more primitive phenotype, CD34+/CD38- (72). CD34+ cells mobilized by plerixafor include more T-, B- and NK cell precursors (73). Concern for GVHD in patients transplanted with allograft containing more T- and B-cell precursors is natural. However, a study in mouse model demonstrated no difference in the rate of GVHD or T-cell function with allograft mobilized by plerixafor (33). Devine and colleagues (74) demonstrated the safety and efficacy of plerixafor in mobilizing blood hematopoietic progenitors in the setting of allogeneic stem cell transplantation. 25 HLA matched sibling donors were mobilized with single dose of subcutaneous plerixafor (250 mcg/kg) without G-CSF. Apheresis in two thirds of donors collected sufficient CD34+ cells in one apheresis and all (100%) collected sufficient stem cells following 2 apheresis sessions. No adverse events greater than grade one was noted in any donor. Allografts had higher number of T, B and NK cells. Neutrophil and platelet engraftment was prompt and respectively 10 and 12 days. With a median follow up of 277 days after allo-transplantation, grade 2-4 acute GVHD was noted in 35% of patients. This pilot trial suggests that plerixafor may be a safe alternative to commonly used G-CSF for allograft mobilization, where volunteer donors do not have to go through cumbersome procedure of daily G-CSF injections for 4-6 days. Trials studying different doses, schedules and route of plerixafor administration in donors for allograft mobilization are ongoing (www.clinical trials.gov).

9. CONCLUSION

Plerixafor is an effective, safe and FDA approved regimen for mobilization of hematopoietic stem cells required for autologous transplantation. In combination with G-CSF, it yields higher number of CD34+cells in fewer apheresis sessions. Plerixafor effective in patients who fail to mobilize sufficient CD34 cells with conventional regimen of growth factor with or without chemotherapy. Its safety and efficacy in mobilization of allograft are promising; however a randomized study is needed to confirm them. Many questions remain unanswered. Should plerixafor be used in the upfront setting or only to rescue those who fail to mobilize with conventional treatment? What is the appropriate route and time of plerixafor administration? Cost and benefit analyses of using Plerixafor as mobilization agent have been recently performed and suggest that this agent is relatively cost effective compared to G-CSF alone in poorly-mobilizing patients (75).

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