Clinical use of plerixafor in combination with granulocyte-colony stimulating factor in hematopoietic stem cell transplantation

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Abstract: Plerixafor is a CXC4:CXCL12 antagonist that has an expanding role in the stem cell mobilization phase of the hematopoietic stem cell transplant procedure. The drug is currently licensed by the FDA to be used in combination with granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells into the peripheral blood for collection and subsequent autologous transplantations in patients with non-Hodgkin’s lymphoma and multiple myeloma. Plerixafor is particularly useful in patients who have been heavily pretreated or as effective therapy for frontline salvage of poor peripheral blood stem cells mobilizers. In conjunction with G-CSF, plerixafor can be successful in decreasing the number of apheresis days and therefore the associated additional risks and cost of more apheresis procedures. Patients taking plerixafor, when compared to the side effect profile of G-CSF alone, do not report significantly more side effects.

Keywords: plerixafor, AMD3100, autologous stem cell mobilization, non-Hodgkin’s lymphoma, multiple myeloma, CXCR4, CXCL12

The role of plerixafor in mobilization of patients with multiple myeloma or non-Hodgkin’s lymphomas

The goal of a hematopoietic stem cell transplant is to improve the progression free and/or overall survival in patients with hematologic malignancies. A critical first step is to mobilize and collect sufficient number of stem cells capable of prompt and durable hematopoietic reconstitution. Mobilized peripheral blood stem cells (PBSCs) have progressively replaced bone marrow, used since the 1960s, as the preferred source of stem cells used for the reconstitution of hematopoiesis.\(^1,2\) This shift to PBSC is based on the demonstration of improved clinical outcomes; including faster engraftment, less invasive collection, and reduced morbidity.\(^3,4\) A current target goal for discharge after hospitalization include standard engraftment parameters of: 1) absolute neutrophil count greater than 0.5 × 10^9/L in 10 to 12 days and 2) platelet count greater than 20 × 10^9/L in 15 to 30 days. To achieve these targets, most transplant centers use a minimal mobilization requirement for a successful engraftment at approximately 2.0 × 10^6 CD34^+ cells/kg based on actual body weight. Optimal cell dose needed to enhance the likelihood for a successful transplant with long-term complete sustained hematopoietic engraftment has been proposed as greater than 5 × 10^6 CD34^+ cells/kg.\(^5,6\) Failure to transplant sufficient number of hematopoietic stem cells can lead to delayed engraftment, ongoing transfusion dependence, graft failure, and possibly death.

According to the Center for International Blood and Marrow Transplant Research (CIBMTR), more than 18,000 allogeneic and autologous transplant procedures were
performed in the US in 2006 with continued annual increases in that number projected.\textsuperscript{7} Autologous hematopoietic stem cell transplant (ASCT) is the preferential therapy for many of these hematologic malignancies, particularly for multiple myeloma (MM) and non-Hodgkin’s lymphoma (NHL). MM and NHL accounted for 72\% of the more than 10,000 ASCT performed in North America in 2005.\textsuperscript{8} During that year, MM accounted for 42\% and currently is the most common indication for high-dose chemotherapy and ASCT.\textsuperscript{9} The combination of high-dose chemotherapy with ASCT continues to be recommended for patients with newly diagnosed MM, within the first year of diagnosis, and is preferred as an early treatment rather than as a salvage treatment for relapsed, refractory disease.\textsuperscript{10} This ongoing recognition of the importance of ASCT for myeloma is highlighted by the novel Blood and Marrow Transplant (BMT) Clinical Trials Network (CTN) (BMT CTN) and intergroup clinical trial that opened for accrual in the winter of 2009 in which all patients under age 70 with responding myeloma within the first year of treatment will proceed to transplantation and are then randomized to one of three consolidation and maintenance arms.\textsuperscript{11}

NHL accounted for 30\% of the ASCT in North America in 2005,\textsuperscript{5} but more importantly, this malignancy has had constant increase in numbers over the past 3 decades and has now become the number five killer of Americans from cancerous causes. Thus, the expectation is that the need for hematopoietic stem cell transplantation (HSCT) will continually increase based on the increase in this disease. HSCT is recommended in the setting of first chemotherapy-sensitive relapse for diffuse large B cell lymphoma, first complete remission (CR) in high-intermediate to high-risk patients, based on international prognostic index (IPI), and for many other clinical scenarios in NHL. In addition, peripheral ASCT is preferentially preferred over BMT or allogeneic transplant.\textsuperscript{12,13}

While the Food and Drug Administration (FDA) has approved both granulocyte colony stimulating factor (G-CSF; filgrastim) and granulocyte-macrophage colony stimulating factor (GM-CSF; sargramostim) for the mobilization of autologous stem cells, the predominant method of mobilizing CD34\(^+\) stem cells into the peripheral blood in either the autologous or allogeneic setting uses G-CSF. GM-CSF mobilizes fewer CD34\(^+\) cells than G-CSF and has been incorporated into combined mobilization strategies, although whether this is true synergy or whether the same augmented collection could be achieved by dose escalation of G-CSF alone, remains unclear.\textsuperscript{14} G-CSF based PBSC mobilization can be performed in combination with chemotherapy or with 4 to 6 days of daily treatment of G-CSF, with previous studies demonstrating a dose response of G-CSF alone up to levels of 32 \(\mu g/kg\). The different types of mobilization agents have their own kinetics with respect to CD34\(^+\) stem cells mobilization from the bone marrow and have unique dosing regimens. G-CSF and chemotherapy was the main option and requires 1 to 3 weeks for mobilization, as a consequence of awaiting hematological recovery of the bone marrow from the insult. Studies combining G-CSF with chemotherapy agents did not show a constant difference in overall survival or progression-free survival when compared to G-CSF alone.\textsuperscript{15} At the other end of the spectrum are the more recent discoveries of receptor/signaling pathway antagonists where enhanced and effective mobilization of CD34\(^+\) stem cells can occur in a matter of hours.

Finally, it is important to note that despite efforts to standardize approaches to maximize cell collection in all patients, approximately 25\% of individual patients undergoing mobilization have been proven to be ‘poor mobilizers’, collecting less than 2.0 \(\times\) 10\(^6\) CD34\(^+\) stem cells/kg.\textsuperscript{16,17} The factors that can lead to insufficient PBSC mobilization are multifactorial and include: individual variation in responsiveness to G-CSF,\textsuperscript{18,19} degree and type of pre-treatment with primary and salvage regimens,\textsuperscript{20,21} specific type of hematopoietic malignancy,\textsuperscript{20,22,23} and presence or absence of underlying marrow fibrosis. Patients who fail initial mobilization regimens are also more likely to fail remobilization.\textsuperscript{24} To create transplant opportunities, alternative mobilization approaches for primary and salvage efforts have been explored, recognizing that a failed mobilization for an HSCT patient would either require no longer pursuing transplant or utilizing an allogeneic donor, with its increased risks of non-relapse mortality.\textsuperscript{7} Such options included recombinant human stem-cell factor which failed to gain FDA approval for US use, but has been developed as a clinical product in other countries, including Canada and Australia,\textsuperscript{25} development of novel mobilization molecules such as pixy 321 (G-CSF/IL3 ), and combining G-CSF and GM-CSF. Another very exciting development has been the evaluation of plerixafor as a stem cell mobilization agent that led to its recent FDA approval in December 2008 for patients with MM and NHL. In this review, the clinical application of plerixafor primarily in MM and NHL patients will be discussed in the overall context of the transplant setting.

**CXCR: CXCL 12 axis and initial studies of plerixafor**

Plerixafor (Mozobil\textsuperscript{®}; Genzyme Corp; previously known as AMD3100, JM 3100, SDZ SID 791) was initially tested in the mid 1990s by Anored, Inc. as a potent inhibitor of particular
Plerixafor is a white to off white hygroscopic crystalline solid with a molecular weight of 502.79 g/mol (for the free base). Plerixafor is considered a bicyclam, consisting of two cyclam rings coupled through a 1,4-phenylenebis(methylene) moiety (proper chemical name: 1,1’-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetracane). It is water soluble and exists at a 4 protonated state at physiological pH (Figure 1).

Bioavailability is 87% after subcutaneous injection. Two phase I trials examined pharmacokinetics in 29 healthy volunteers. The volunteers received subcutaneous injections of 40, 80, 160, 240 or 320 µg/kg. The data demonstrate a two compartment model with first-order absorption characteristics and an indirect effect model for the release of bone marrow CD34+ cells to the peripheral blood. Clearance of plerixafor is 5.17 ± 0.49 L/h and volume of distribution is 16.9 ± 3.79 L/h. The maximal effect occurs at 12.6 ± 4.89 hours and 50% of maximum response occurs at 5.37 ± 1.31 hours. 38

Intravenous (IV) infusion route examined in 12 volunteers at a dose of 10, 20, 40, 80 µg/kg demonstrated similar white blood cell (WBC) count peaking as subcutaneous dosing. WBC peaked at 6 hours post IV administration with a similar WBC increase when compared to higher doses used during subcutaneous administration. The Cmax for IV dosing was 515 (range, 470–521) ng/mL and the AUC was 1044 (range, 980–1403) ng·h/mL. Oral dosing demonstrated no appreciated plasma levels up to 160 µg/kg.49

Plerixafor is not a substrate, inhibitor, or inducer of P450 isozymes. As a selective antagonist of CXCR4, plerixafor also demonstrates no cross reactivity with other chemokine receptors, CCR1-3 or CCR1-9. While plerixafor is capable of binding CXCR4 receptor, it does not interact with other chemokine receptors, CXCR1-3 or CCR1-9. While plerixafor is capable of binding CXCR4 receptor, it does not interact with other chemokine receptors.

**Review of pharmacology, mode of action, pharmacokinetics of plerixafor**

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**Figure 1 Chemical structure of plerixafor.**
not elicit intracellular calcium fluxes, induce chemotaxis, or trigger CXCR4 internalization. The natural ligand of CXCR4, CXCL 12, is also cross reactive with CXCR7; however plerixafor is not. The current model describing the interaction between CXCL 12 and CXCR4 proposes that CXCL 12 associates with cellular glycosaminoglycans via its carboxy terminus leaving the N-terminus of CXCL 12 free to bind the CXCR4 receptor expressed by hematopoietic cells and or non-hematopoietic cells (during remodeling events). Plerixafor is capable of inhibiting CXCL 12 binding to CXCR4 with a $K_d$ of 651 ± 37 nM. The data show that plerixafor is a tight binding, slowly reversible inhibitor of CXCR4.

The current 2008 FDA approval of plerixafor is in combination with G-CSF at a dose of 10 µg/kg used to mobilize hematopoietic stem cells into the peripheral blood for collection and subsequent autologous transplantations in patients with NHL and MM. Administration of plerixafor should begin after 4 days of daily treatment with G-CSF and 11 hours prior to apheresis. It is supplied as a single use vial containing 1.2 mL of 20 mg/mL solution. Plerixafor administration can continue for 4 consecutive days. Dosing of plerixafor is 0.24 mg/kg of actual body weight and has been verified for patients up to 175% of ideal body weight. The total daily dosage should not exceed 40 mg/day. Patients with moderate to severe renal impairment ($C_{L,F} \leq 50$ mL/min) should receive a dose reduction of one-third and a maximum daily dosage of 27 mg/day. Approximately 70% of a daily dose is excreted unchanged via kidneys in healthy volunteers in the first 24 hours. The plasma half-life is 3 to 5 hours. In 543 patients reported for drug approval, the median exposure to plerixafor is 2 days (range 1 to 7 days). Used as a single agent, peak mobilization of CD34+ cells is between 6 and 9 hours post administration. When G-CSF is added, a sustained elevation in the peripheral blood CD34+ count occurs from 4 to 18 hours, with the peak CD34+ count between 10 and 14 hours.

There is some evidence implying plerixafor may mobilize leukemic cells during mobilization and therefore should not be used in patients with leukemia. Other contraindications include leukocytosis and thrombocytopenia, although these are considerations, as these are standard sequelae of G-CSF mobilization with or without chemotherapy. The current recommendation is to examine any patient who reports upper left quadrant pain, shoulder pain, or scapular pain for splenic integrity. This precaution is based on murine studies that demonstrated splenic enlargement. The murine studies did involve continual plerixafor administration lasting 2 to 4 weeks at 4 × higher dosage than that given during clinical trials. The concern about the spleen and its potential for rupture with prolonged dosing arises from reports of splenic rupture in patients undergoing stem cell mobilization with G-CSF alone.

The most common adverse events, reported in >10% of people taking plerixafor with G-CSF, regardless of relatedness, are diarrhea, nausen, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting. The adverse events throughout the clinical trials have been similar to those seen in the early trials, consisting of mild complaints involving gastrointestinal complaints, headaches, dry mouth, and injection site reaction.

**Preclinical efficacy studies of plerixafor**

Plerixafor is capable of inducing HSPC mobilization in multiple species due to the conserved function of the CXCR4: CXCL 12 axis. Murine studies demonstrated that plerixafor can rapidly, and in synergy with G-CSF, mobilize human and murine HSPCs. Murine HSPCs mobilized with plerixafor were capable of long term engraftment in severe combined immunodeficiency (SCID) mice. The study also showed that the addition of plerixafor to G-CSF leads to enhanced numbers of HSPCs. The mobilized cells express a phenotype characteristic of highly engrafting murine HSPCs.

Canine studies demonstrated that plerixafor treatment alone could lead to durable grafts. Dogs were treated with 920 cGY total body irradiation and transplanted with either autologous plerixafor mobilized PBSCs or plerixafor mobilized PBSCs from antigen identical littermate. Autologous and allogeneic transplanted canines had normal marrow function at 1 year and chimerism levels were 97% to 100%. Plerixafor has also been studied as single agent for mobilization of stem cells in a rhesus macaque model. The study demonstrated that plerixafor was capable of mobilizing a long-term repopulating population of cells that had intrinsic differences from the population mobilized with G-CSF. There appeared to be increase in expression of cell-surface markers implicated in retention and homing in the plerixafor mobilized CD34+ cells.

Plerixafor with or without G-CSF gene expression data has also been examined in the rhesus macaque. The data confirm previous studies that suggest that the composition of the stem cells depends on the mobilization protocol. The study demonstrated that plerixafor based CD34+ cells include more B, T, and mast cell precursors while G-CSF based protocols have more neutrophil and mononuclear phagocytes.
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Plerixafor clinical trials and analysis

There are 32 registered clinical trials currently listed in clinicaltrials.gov (3 withdrawn or terminated prior to enrollment) involving plerixafor and hematological malignancies at the time of preparation of this manuscript, confirming the interest in this novel compound.64 The trials discussed in this review are listed in Table 1.

Phase I

Following the phase I HIV trials, further phase I trials demonstrated consistent leukocytosis and mobilization of CD34+ stem cells following infusion of plerixafor in 12 healthy volunteers51 and 32 healthy volunteers.59 The effect was confirmed linear over a large range of doses and schedules.45,64 The leukocytosis is enriched for CD34+ cells and enrichment peaks approximately 6 to 9 hours after a single injection of plerixafor.65 The concentration of CD34+ cells correlates with increasing drug concentration from 40 µg/kg to 240 µg/kg. There is no change in other hematologic parameters such as platelet or erythrocyte count.59 These trials demonstrated that plerixafor was safe and tolerable with only mild and transient toxicities, including injection site erythema, nausea, headache, dry mouth, and abdominal distension unrelated to dose.

The effect of plerixafor was also explored in combination with G-CSF, using a standard G-CSF dosing schedule, in healthy volunteers. The results demonstrated a synergistic effect between the two compounds leading to a 3.8-fold increase in mobilization of CD34+ cells. The study also demonstrated that the combination of plerixafor and G-CSF is superior to either compound used in isolation and is generally safe and effective.65

Disease trials have yielded very promising results. A phase I trial in 13 patients with hematologic malignancies, 7 MM and 6 NHL, demonstrated that either 160 or 240 µg/kg plerixafor is safe and can effectively mobilize HSPC without significant adverse events.66 The combination of G-CSF plus plerixafor was superior to G-CSF alone in MM (10 patients) and NHL (15 patients).57 A preliminary report of a five-patient Spanish experience also demonstrated similar results in patients with NHL and HD.68

Phase II

The efficacy of plerixafor in heavily pre-treated patient populations was examined in 49 patients who were enrolled in a single arm, multicenter Phase II study of plerixafor (240 µg/kg) with G-CSF in MM (26) and NHL (23) patients undergoing their first mobilization. The mobilization regimen consisted of G-CSF (10 µg/kg/day) given for up to 9 days and plerixafor was started on day 4 and apheresis began on day 5. Fifty-seven percent of the patients were considered to be heavily pre-treated with 10 or more chemotherapy cycles. As a result, the heavily pre-treated patient cohort had similar mobilization characteristics as the non-heavily pretreated ones. The median CD34+ cells/kg collected was 5.9 × 10^6 in 2 days of apheresis. Ninety-six percent of the patients enrolled were able to proceed to transplant.69

Another 25-patient phase II trial compared standard G-CSF-based apheresis to apheresis with G-CSF and plerixafor in patients with MM or NHL where each patient served as their internal control. The study demonstrated superior CD34+ collection and fewer apheresis procedures with the combined G-CSF and plerixafor regimen.67 The first European trial utilizing G-CSF and plerixafor in 31 MM and

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<td>CUP</td>
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Abbreviations: A + G, plerixafor + G-CSF; AILD, angioimmunoblastic lymphoma; CUP, compassionate use protocol; G-CSF, granulocyte colony stimulating factor; IV, intravenous; SQ, subcutaneous; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; RCT, randomized controlled trial. HV, healthy volunteer; HD, Hodgkin’s lymphoma.
4 NHL patients demonstrated similar results to the other phase II trials and confirmed that there was no additional tumor mobilization in the MM patients. A second phase II European trial with 13 MM and 2 NHL patients analyzed lineage specific markers of G-CSF mobilizations and G-CSF plus plerixafor mobilization and repopulation potential in vitro and in vivo. Their data suggest that the addition of plerixafor to G-CSF mobilization may lead to the enhanced mobilization of a more primitive CD34+ cell population with high repopulation capacity.

A phase II multicenter pilot study trial consisting of 26 MM and 14 NHL patients addressed the issue of whether plerixafor can boost the PBSC mobilization associated with chemotherapy and G-CSF. The design included a first day apheresis procedure without plerixafor. Plerixafor was administered before the second apheresis procedure to allow the patients to serve as their own controls. The results suggested that the addition of plerixafor to chemotherapy and G-CSF was synergistic and resulted in a 2-fold increase in mobilized CD34+ cells. The mean rate of increase in the peripheral blood CD34 cells was 2.8 cells/µL/h pre- and 13.3 cells/µL/h post-plerixafor administration. This was a heterogeneous population in which multiple chemotherapy regimens and disease states were included in the study patients. While the design was limited by the number of patients in an individual cohort, this study succeeded as a pilot and will serve as impetus to further investigate plerixafor as an adjunct to chemotherapy and G-CSF for PBSC mobilization.

One interesting highlighted patient reported by the investigators was an individual who appeared to be in the process of failing CD 34+ mobilization with chemotherapy and G-CSF and was successfully rescued with the addition of plerixafor.

To that purpose, plerixafor can also be effectively used in the salvage setting for patients who have previously failed mobilization with chemotherapy and/or G-CSF. A 20 patient institutional experience demonstrated that G-CSF and plerixafor can be used to effectively salvage patients of multiple diagnoses who had previously failed other mobilization attempts. The patients collected a median of 3.8 × 10^6 CD34+ cells/kg in 2 days of apheresis. 16 of 20 patients were capable of proceeding to auto-SCT and platelet engraftment at approximately day 12 and platelet engraftment at approximately day 24. These results have been confirmed in a variety of other settings including a phase II trial of 20 patients with NHL and MM. That particular study also observed no evidence of tumor cell mobilization in the peripheral blood after plerixafor with G-CSF. The results were also consistent with the data obtained from the company sponsored final retrospective analysis of the safety data compiled from the 286 patients (164 NHL, 35 HD, 87 MM) who were enrolled in a compassionate use program in the United States. These results with ‘poor mobilizers’ have also been further reported in abstract form where 18/20 patients, 16/17 patients, 5/8 patients, 5/6 patients, and 2/4 patients of varying diagnoses both in Europe and the United States were then capable of proceeding to transplant. Subpopulation analysis of these patients enrolled in the compassionate use trial also identified that peripheral blood progenitors from NHL patients pretreated with fludarabine can also still be safely and predictably mobilized with plerixafor and G-CSF.

**Phase III**

There are two phase III multicenter, placebo controlled randomized trials of plerixafor + G-CSF versus placebo + G-CSF that enrolled NHL (trial # 3101), and MM, (trial # 3102) patients. A total of 298 NHL patients and 302 MM patients have been enrolled in these studies. The objective of the trials was to achieve a target number of CD34+ cells/kg within a pre-specified number of apheresis days and having successful engraftment. The NHL primary endpoints were: 1) ≥2 × 10^6 cells/kg in ≤4 apheresis days and successful engraftment and 2) ≥5 × 10^6 cells/kg in ≤4 apheresis days and successful engraftment. The MM primary endpoints were: 1) ≥6 × 10^6 cells/kg in ≤2 apheresis days and successful engraftment. Engraftment was defined absolute neutrophil count (ANC) ≥0.5 × 10^9/L for 3 days or ≥1.0 × 10^9/L for 1 day; and platelets ≥20 × 10^12/L for 7 days. Graft durability was defined as two of the following three: 1) platelets ≥50 × 10^12/L without transfusion for at least 2 weeks; 2) hemoglobin ≥10 g/dL with no erythropoietin support or transfusions for at least 1 month; 3) ANC > 1 × 10^9/L with no G-CSF for at least 1 week. The interim analysis, 100 days, showed similar results to the 1-year follow up. The NHL results demonstrated significantly increased numbers of CD34+ cells/kg recovered for autologous transplant with plerixafor and G-CSF in comparison to G-CSF and placebo. Time to achieve ≥5 × 10^6 cells/kg was also faster with plerixafor. 27.9% of NHL patients receiving plerixafor + G-CSF were able to reach this level within 1 day as compared to only 24.2% by day 4 with placebo + G-CSF. Additionally more patients proceeded directly to transplant in the plerixafor arm, 90%, than placebo, 55.4%. The MM trial showed similar significant improvement in CD34+ cells/kg yield with the plerixafor arm. Of the plerixafor group, 71.6% had achieved ≥6 × 10^6 CD34+
cells/kg in ≤2 days while 34.4% of the placebo achieved the endpoint. As noted above in the lymphoma cohort, equivalent numbers of patients in the plerixafor group achieved the primary endpoint in 1 day as the placebo did in 4 days. In both studies, the autografts were found to be durable at 1 year after the ASCT procedure.88–91

Secondary analysis

The phase III trials have also been a source of very valuable information obtained in the post-hoc analysis. In the 3101 NHL study, 124 of the 298 patients were older than 60 years. In this elderly group, 50.9% of the patients receiving G-CSF and plerixafor met the primary endpoint compared to 25.4% of the patients receiving placebo. Similarly, 145 of the 302 MM patients in 3102 were older than 60 years. Of patients receiving plerixafor 69.6% met the primary endpoint compared to 23.7% of the placebo group. The subpopulation analysis suggests that plerixafor plus G-CSF is superior than G-CSF in MM and NHL patients older than 60 years who are undergoing ASCT.92–95 Another analysis using the data set from the phase III suggested that transplanted cell dose was associated with better long-term platelet recovery.94,95 Combining the MM patients from the phase III trial and the compassionate use trial also provides support to suggest that the majority of patients pretreated with lenalidomide can be successfully mobilized with plerixafor and G-CSF.96,97

Additional observations for the clinical use of plerixafor include the following series:

1. Three female MM patients received a reduced dose of 160 µg/kg/day following 4 days of G-CSF post-dialysis, suggesting that plerixafor could also be effectively used in MM patients on dialysis.98
2. An examination of 35 patients, 31 MM and 4 NHL, suggested that plerixafor does not seem to contribute to tumor cell mobilization more than G-CSF alone.99,100
3. An analysis of 7 NHL patients who were mobilized with plerixafor plus G-CSF suggests that patients mobilized with plerixafor may actually experience improved clinical outcomes at 20 months, although it is recognized that this is a very small cohort analysis.101

Plerixafor is also undergoing assessment of efficacy in the allogeneic related donor setting as a single agent. Twenty-five HLA matched sibling donors were mobilized with 240 µg/kg plerixafor 4 hours prior to apheresis. Ninety-two percent of the donors collected ≥2 × 10⁶ CD34+ cells/kg in ≤2 apheresis. Two-thirds of the donors mobilized the target minimal number of CD34+ cells/kg, ≥2 × 10⁶ cells/kg, in 1 apheresis. The remaining donors repeated the dose of plerixafor and apheresis after 1 day of rest, on day 3. After administration of the myeloablative conditioning regimen, 20 patients proceeded to transplant with a median of 2.9 × 10⁶ CD34+ cells/kg of recipient body weight of the plerixafor mobilized stem cells. While the total CD34+ cells/kg was relatively low,102 neutrophil engraftment occurred on median day 10 and platelet engraftment on median day 12. Acute graft-versus-host disease grades 2 to 4 occurred in 35% of patients, which was similar to historical controls, with recognition that plerixafor can mobilize lymphoid populations in addition to CD34+ stem cells. After a median follow up of 277 days, 14 patients remain in remission and are transfusion independent.103

Summary of current role of plerixafor in stem cell mobilization

Plerixafor is being used in a wide variety of settings. It appears to be particularly useful in patients who have been heavily pretreated or as effective therapy for frontline salvage of poor PBSC mobilizers. In conjunction with G-CSF, plerixafor is successful in decreasing the number of apheresis days and therefore the associated additional risks and cost of more apheresis procedures. Patients taking plerixafor also report minimal side effects compared to the side effects of G-CSF.

However, the current general dosing strategy of 10 PM prior to the day of apheresis is not ideal for minimizing total costs and patient acceptability. This is due to the short stays that are required as part of the sub-cutaneous administration. Adopting a dosing strategy similar to the Devine et al103 of administration on the day of apheresis could thus lead to lower overall costs associated with the procedure. Anecdotally, some centers have chosen to exploit the prolonged duration of circulating CD 34+ progenitors seen after plerixafor administration, and are administering plerixafor at the very end of an outpatient clinic day, with apheresis beginning approximately 14 hours later with some success. Further exploration is still needed for determining the optimal use of this agent. Investigations of administration as a single agent are needed as our studies addressing ways to maximize routes of administration. Further studies are needed to clarify the role of plerixafor during chemotherapy and growth factor induced stem cell mobilization. Additionally, it may be advantageous to consider dose alterations of G-CSF in conjunction with plerixafor to maximize CD34+ stem cell recovery. Other areas of further study include determining the role of plerixafor use in the pediatric setting, and also more detailed analysis of tumor cell mobilization. As previously stated, one
study failed to demonstrate tumor cell mobilization in MM patients. However, because plerixafor has been shown to mobilize normal lymphoid cells into circulation, the possibility remains that lymphoma cells can be mobilized also. If recognized, perhaps these events can be explored, as is currently occurring with acute myeloid leukemia. Finally, it will be interesting to watch whether plerixafor will be the first in a series of agents to be used in humans which can exploit the chemokine axis.

Disclosures

RTM has received a research grant from and has participated in advisory boards and is a speaker for Genzyme Inc. CJF has no disclosures.

References


