Plerixafor for autologous CD34⁺ cell mobilization

Huda Salman
Hillard M Lazarus
Division of Hematology-Oncology, Blood and Marrow Transplant Program, University Hospitals Case Medical Center, Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Abstract: High-dose chemotherapy and autologous transplantation of hematopoietic cells is a crucial treatment option for hematologic malignancy patients. Current mobilization regimes often do not provide adequate numbers of CD34⁺ cells. The chemokine receptor CXCR4 and ligand SDF-1 are integrally involved in homing and mobilization of hematopoietic progenitor cells. Disruption of the CXCR4/SDF-1 axis by the CXCR4 antagonist, plerixafor, has been demonstrated in Phase II and Phase III trials to improve mobilization when used in conjunction with granulocyte colony-stimulating factor (G-CSF). This approach is safe with few adverse events and produces significantly greater numbers of CD34⁺ cells when compared to G-CSF alone. New plerixafor initiatives include use in volunteer donors for allogeneic hematopoietic cell transplant and in other disease targets.

Keywords: plerixafor, autologous hematopoietic cell transplant, CD34, lymphoma, myeloma, granulocyte colony-stimulating factor (G-CSF)

Core Evidence clinical impact summary for plerixafor/autologous progenitor cell mobilization

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<th>Evidence</th>
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<td>Safe and efficient HPC mobilization for autologous bone marrow transplant</td>
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<td>Non-Hodgkin’s lymphoma</td>
<td>Randomized clinical trial (26)</td>
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<td>Clinical trials indicating safety and efficacy</td>
<td>Higher percentage of patients are mobilized to facilitate autologous transplants</td>
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<td>Safe approach</td>
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<td>Economic evidence</td>
<td>More expensive than using G-CSF alone</td>
<td>Successful HPC mobilization with fewer attempts may account for part of the cost difference.</td>
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<td></td>
<td></td>
<td>Possibility of autologous transplants to save further therapy or prolong disease-free intervals may also account for part of the cost difference as mobilization rate is higher using plerixafor.</td>
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Abbreviations: G-CSF, granulocyte colony-stimulating factor; HPC, hematopoietic progenitor cell.
Introduction
Hematopoietic stem cell (HSC) transplantation is a crucial treatment option for hematological malignancies. Current mobilization regimes frequently result in inadequate numbers of hematopoietic progenitor cell (HPC). The chemokine receptor CXCR4 and ligand SDF-1 are integrally involved in homing and mobilization of HPCs. Disruption of the SDF-1/CXCR4 axis by the CXCR4 antagonist, plerixafor, was demonstrated in clinical trials to improve mobilization when it was included in the mobilization regimen. Plerixafor exerts its effect by reversibly blocking the ability of HPCs to bind to the bone marrow matrix. When used with granulocyte colony-stimulating factor (G-CSF), plerixafor helps increase the number of these progenitor cells in the peripheral blood.

In this review, we analyze the literature pertinent to plerixafor development, its safety, and the evidence for its clinical efficacy as a HPC-mobilizing agent in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) requiring autologous cell transplantation.

History and drug development
Plerixafor was originally developed as a potential anti-HIV agent because it antagonizes the chemokine receptor 4 (CXCR4), which serves as a coreceptor for the entry of T-lymphotropic HIV strains into host T-lymphocyte cells. During pharmacokinetic studies of the drug, leukocytosis was observed. Hendrix et al reported that the plasma concentration of plerixafor declined gradually after a single intravenous dose, while the white blood cell count gradually increased, reaching a maximum count of ~3 times its baseline at 6 h. This leukocytosis appeared to result from CD34+ cell mobilization.

Further work demonstrated that the administration of plerixafor resulted in a consistent increase in the number of CD34+ cells in the peripheral blood, suggesting that it could be used as a potential CD34+ -cell-mobilizing agent in the setting of autologous transplantation.

Mechanism of action
CXCR4 is a chemokine receptor expressed on several cell types including CD34+ cells. Stromal-derived factor-1α (SDF-1α), also known as CXCL12, is a member of the chemokine superfamily of chemotactic cytokines produced predominantly by mesenchymal stromal cells of tissues such as bone marrow. Chemotaxis of CXCR4 toward SDF-1α plays an important role in the trafficking and homing of HPCs to the bone marrow compartment. CXCR4 helps anchor cells to the marrow matrix, either directly via SDF-1α or through the induction of other adhesion molecules. Plerixafor is a receptor antagonist that reversibly blocks the binding of CXCR4 to SDF-1α. Disruption of the binding of CXCR4 and SDF-1α results in the rapid egress of CD34+ cells from the bone marrow matrix into the circulation.

Further, plerixafor synergistically augments the mobilization effect of G-CSF on CD34+ cells. Hematopoietic differentiation of transplanted CD34+ cells was similar after plerixafor or G-CSF mobilization methods.

Cells mobilized by a combination of plerixafor and G-CSF are not simply a mixture of cells mobilized by each agent separately, but represent a unique biological profile as gene expression of the cells was different. Some of the genes were upregulated in the cells mobilized by the combination of plerixafor and G-CSF, whereas they were not upregulated in the cells mobilized by either agent alone. Studies on patients with NHL or MM indicated that mobilization of CD34+/CD38− cells, a more primitive subset of CD34+ cells, was eightfold higher with the addition of plerixafor to a G-CSF regimen when compared to G-CSF alone.

Pharmacokinetics
Plerixafor is not absorbed after oral administration but it rapidly penetrates tissues after subcutaneous injection. Its distribution is confined mostly to the extravascular space and the distribution half-life is about 0.3–0.4 h. This agent is bound to human plasma proteins up to about 60%. It is neither metabolized by human liver microsomes nor does it inhibit or induce cytochrome P450 enzymes.

The major route of elimination is through the kidney. Approximately 70% of the dose was excreted unchanged in the urine during the first 24 h after a single subcutaneous injection of 240 µg/kg in healthy volunteers.

In NHL or MM patients, the mean t1/2 was 5.1 h, similar to that in healthy subjects. A statistically significant correlation was noted between renal function (as determined by creatinine clearance (CrCl)) and plerixafor clearance, as reported in phase I clinical trials. The t1/2 was delayed and the AUC increased in subjects with moderate or severe renal impairment.

Safety and therapeutic efficacy
Phase I clinical trials
Phase I pharmacokinetic (PK) and pharmacodynamic (PD) studies in healthy volunteers demonstrated that plerixafor
administered either alone or in combination with G-CSF resulted in dose-dependent mobilization of CD34+ cells in the peripheral blood.1

PK parameters for NHL and MM patients were comparable to normal volunteers. Plerixafor was rapidly absorbed after subcutaneous administration with no observable lag time; peak plasma concentrations occurred 0.5 h after administration in most patients. Plerixafor was cleared rapidly, with a median terminal half-life of 4.6 h. The median maximum increase in the number of CD34 circulating cells from baseline was 4.2 (range, 3.0–5.5), with the maximum increase noted approximately 10 h after plerixafor injection. Plerixafor was safe and effective in mobilizing CD34+ cells for transplantation.21,23,24 Toxicities greater than NCI-CTC grade 1 were rarely observed; the predominantly reported adverse events were diarrhea and vomiting.

Phase II trials
In a Phase II trial conducted in NHL patients, plerixafor subcutaneous injection after four consecutive days of G-CSF resulted in significant increment of the blood CD34+ cells followed by normalization of the cell count within 24 h after cessation of plerixafor.15

In another study, the combination of G-CSF with plerixafor25 significantly increased the CD34+ cell count in patients with NHL and MM. The median number of CD34+ cells collected by five consecutive apheresis was 5.7 × 10⁶ cells/kg in NHL patients and 12.0 × 10⁶ cells/kg in MM patients.

Additionally, Stiff et al reported that in patients with NHL and MM, the combination of plerixafor and G-CSF was well tolerated and resulted in a superior yield of CD34+ cells mobilization.25

Table I Summary of the results of the non-Hodgkin lymphoma phase III clinical trial

<table>
<thead>
<tr>
<th>Results</th>
<th>Plerixafor + G-CSF</th>
<th>Placebo + G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met primary end point (%)</td>
<td>59.3</td>
<td>19.6</td>
</tr>
<tr>
<td>Achieved minimum collection (%)</td>
<td>86.7</td>
<td>47.3</td>
</tr>
<tr>
<td>Mean no. of CD34+ cells (×10⁶ cells/kg)</td>
<td>6.06</td>
<td>4.09</td>
</tr>
<tr>
<td>Median time to platelet engraftment (days)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Median time to WBCs engraftment (days)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>One-year mortality (%)</td>
<td>12</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Phase III trials
Two randomized, double-blind, placebo-controlled, HPC mobilization Phase III studies were conducted in patients undergoing autologous HPC transplantation for NHL (n = 298) and MM (n = 302).26–31 The studies were of identical duration (12 months), shared general design characteristics, and assessed the effects of the addition of plerixafor to G-CSF in terms of mobilization efficiency and graft durability in patients undergoing four or less apheresis procedures.

Primary and secondary end points in the NHL study are listed in Table 1. Patients who failed to collect either 0.8 × 10⁶ CD34+ cells/kg after two apheresis days or 2 × 10⁶ CD34+ cells/kg or more in four apheresis days could enter an open-label rescue procedure with plerixafor plus G-CSF.

The addition of plerixafor to G-CSF for HPC mobilization resulted in a significantly higher CD34+ cell collection in fewer days of apheresis and a higher proportion of patients (90% versus 55.4%) proceeding to transplant than with G-CSF alone.27–29 A statistically significant greater number of patients achieved the primary end point of the study in the plerixafor plus G-CSF arm (59.3% versus 19.6%; P < 0.001). This group also attained the minimum collection after 1 day (56.5 versus 20.4; P < 0.001) and by the end of the treatment period (86.7 versus 47.3), these patients also obtained a significantly higher number of CD34 cells (Table 1).26–28 About 7% of patients initially treated with the combination of plerixafor and G-CSF therapy required the rescue procedure compared to 52.7% in the placebo plus G-CSF arm. Most subjects were salvaged with the crossover to the plerixafor-containing arm and attained an adequate HPC dose for transplantation.

Considering its significant mobilization efficiency, similar median time to engraftment, and mortality rate during 12 months of follow-up, these data demonstrated that plerixafor in combination with G-CSF may be recommended for patients who have difficulty mobilizing CD34+ cells for autologous transplantation.

The second Phase III mobilization trials enrolled MM patients in first or second complete or partial remission.28–31 Randomization was based on baseline platelet count (<200 × 10⁹/µL versus ≥200 × 10⁹/µL) and planned single versus tandem autograft. The primary and secondary endpoints were the same as in the NHL study except that the target for CD34+ cell dose was increased to 6 × 10⁶ CD34+ cells/kg in two or fewer apheresis days, rather than 5 × 10⁶ CD34+ cells/kg in four or fewer apheresis procedures. Additional
provisions for the use of open-label plerixafor plus G-CSF included failure to collect at least 0.8 × 10⁶ CD34⁺ cells/kg after two apheresis days or 2 × 10⁶ CD34⁺ cells/kg in four apheresis days, or patients who were scheduled for tandem transplantation in whom <4 × 10⁶ CD34⁺ cells/kg were collected.

Results of this trial demonstrated a statistically superior outcome with the combination of plerixafor and G-CSF in terms of meeting the primary and secondary end points (Table 2). Graft durability rate in both arms after 100 days, mean platelet and neutrophil count, as well as the mean hemoglobin concentration 100 days after transplantation and 12 months after were the same in both arms.³²

In this study, tandem transplantation was planned for 48% of patients in the plerixafor arm and for 43.5% of patients in the placebo arm. The actual percentage of patients who underwent tandem transplantation was less than planned (21.6% and 15.6%, respectively) due to the failure to collect sufficient CD34⁺ cells.²⁹–³¹ In a post hoc analysis of these two Phase III clinical studies, infused CD34⁺ cell dose was not associated with hematopoietic recovery for neutrophil, lymphocyte, and red blood cell in either NHL or MM patients.³²

### Table 2 Summary of the results of the multiple myeloma phase III clinical trial

<table>
<thead>
<tr>
<th>Results</th>
<th>Plerixafor + G-CSF</th>
<th>Placebo + G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 148</td>
<td></td>
<td>N = 154</td>
</tr>
<tr>
<td>Met primary end point (%)</td>
<td>71.6</td>
<td>34.4</td>
</tr>
<tr>
<td>Achieved minimum collection (%)</td>
<td>95.9</td>
<td>92.9</td>
</tr>
<tr>
<td>Mean no. of CD34⁺ (10⁶ cells/kg)</td>
<td>5.84</td>
<td>4.41</td>
</tr>
<tr>
<td>Median no. of apheresis to collect the target CD34⁺ cell no.</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Rescue procedures (%)</td>
<td>0</td>
<td>4.6</td>
</tr>
<tr>
<td>One-year mortality (%)</td>
<td>4.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

In a murine leukemia model, plerixafor mobilized labeled APL³⁶ cells from marrow to the spleen and the peripheral blood.³⁵ These preclinical data suggest a potential risk for the use of plerixafor to mobilize CD34⁺ cells in patients with acute leukemia.

### Adverse events

In the two Phase III clinical studies,²⁸,³¹ the most common adverse reactions associated with plerixafor in combination with G-CSF were gastrointestinal toxicities and injection site erythema. Nearly, all adverse events noted were mild to moderate in intensity and of short duration. Up to 37% and 34% of patients treated with the combination of plerixafor and G-CSF have reported diarrhea and nausea, when compared with 17% and 22% in the G-CSF and placebo arm, respectively. Other reported GI side effects were flatulence and vomiting. Two patients in the plerixafor arm experienced serious adverse events,²⁸ including one patient with hypotension and dizziness after plerixafor administration and one patient with thrombocytopenia after apheresis. Plerixafor was discontinued in three NHL patients due to a generalized seizure, systemic reactions not specified, and a central venous catheter-associated infection. All patients, however, remained in the study. No MM patients experienced serious adverse events attributed to plerixafor.³¹ Other investigators have reported potentially serious adverse events with mobilization procedures including leukocytosis, thrombocytopenia, tumor cell mobilization, splenic enlargement, and very rarely, splenic rupture.²⁰

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### Special considerations

Plerixafor dose should be reduced in patients with an estimated creatinine clearance <50 mL/min. The recommended daily dose of the drug in this patient population is 160 µg/kg³⁶ and should not exceed 27 mg/day.²⁰ The safety of administering plerixafor in patients undergoing hemodialysis has not been...
determined as these patients were excluded in the above-discussed studies.

Dosing in overweight patients has to be adjusted using up to 175% of ideal body weight.

Plerixafor plus G-CSF should be used with caution in patients with splenic enlargement, although splenic rupture has not been reported in clinical trials.

**Potential contraindications**

Plerixafor should not be used in leukemia patients because the drug may potentially cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Thrombocytopenia has also been observed in patients receiving plerixafor, so close platelet count monitoring in this group is recommended.

Plerixafor has teratogenic potential and is labeled as pregnancy category D. In pregnant animals, plerixafor resulted in numerous embryo-fetal toxicities such as anophthalmia, cardiac defects, dilatation of olfactory vesicles, retarded skeletal development, and fetal death. It is unknown whether plerixafor is excreted in human milk.

Safety and efficacy of plerixafor in pediatric patients have not been established in a controlled clinical study. In the two Phase III clinical studies, safety and effectiveness did not appear to differ between elderly and young subjects. Caution should be exercised for geriatric patients, especially those with renal impairment.

**New initiatives**

As plerixafor has been proven to be safe and effective in mobilizing CD34+ cells from normal donors, its utilization in the setting of allogeneic transplantation is a potentially novel and intriguing approach.

Lenalidomide therapy may impair mobilization of CD34+ cells. Mark et al evaluated the efficacy of cyclophosphamide in overcoming the suppressive effect of lenalidomide on HPC collection in myeloma patients. Twenty-eight patients were included in the study and had received induction therapy with clarithromycin, lenalidomide, and dexamethasone (BiRD). Following induction, patients underwent HPC collection either with G-CSF alone, or G-CSF and cyclophosphamide (Cy) for mobilization. Approximately 33% of patients who received G-CSF alone were not able to collect adequate HPC; however, all of the patients who received Cy had successful collection ($P < 0.0001$). The authors concluded that Cy was effective in HPC mobilization of patients previously receiving lenalidomide. The use of Cy as a HPC-mobilizing agent, however, delays ASCT time to autograft and increases the risk of neutropenic fever and hospitalization.

Micallef et al reported retrospectively the use of plerixafor in MM patients previously treated with lenalidomide; 40 patients had previous mobilization attempts and 20 patients were undergoing initial mobilization. The overall median number of CD34+ cells collected was $5.6 \times 10^6$ CD34+ cells/kg. Eighty percent of those who had previous mobilization attempts were able to achieve a minimum goal of $\geq 2 \times 10^6$ CD34+ cells/kg. In those patients receiving plerixafor and G-CSF as initial mobilization attempt, all achieved the minimal goal of $\geq 2 \times 10^6$ CD34+ cells/kg.

Recently, the International Myeloma Working Group (IMWG) published guidelines for HPC collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. The IMWG recommends that patients undergo early mobilization of HPC (preferably within the first four cycles of initial therapy). They also recommended that those patients aged more than 65 years and those who have received newer agents, including lenalidomide, undergo mobilization with either reduced-dose Cy and G-CSF, or G-CSF alone, with addition of plerixafor and G-CSF if the first leukapheresis attempt results in $> 2 \times 10^6$ CD34+ cells/kg collected. They could not recommend up front use of plerixafor in this setting until further clinical trials were completed.

Plerixafor also may have a role in leukemia chemosensitization via its possible mobilization of leukemia cells. This strategy of rendering the acute myeloid leukemia cells more amenable to be targeted by chemotherapy is being tested in clinical trials.

Finally, in other preclinical studies, plerixafor may exert beneficial effects in the treatment of inflammatory diseases such as rheumatoid arthritis and asthma. Ostensibly, the salutary effects may result from inhibition of the reaction between CXCR4 and SDF-1α involved in the pathogenesis of inflammation. The value of this therapeutic strategy has not yet been tested in the clinical arena.

**Summary**

Plerixafor is approved for use in combination with G-CSF for CD34+ cells mobilization for subsequent autologous transplantation in NHL or MM patients. The combination of plerixafor and G-CSF is superior to G-CSF alone in the number of CD34+ cells collected and the number of required apheresis procedures.
Other potential beneficial therapeutic uses of plerixafor remain to be investigated. These include its use in mobilization failures in more heavily treated patients or in patients given agents known to impair mobilization such as lenalidomide. Other potential uses are the mobilization of leukemic blasts in order to render them more susceptible to chemotherapy effect, use in mobilization of volunteer donors in the allograft setting, and possibly its use in chronic inflammatory disorders.

Disclosure
The authors report no conflicts of interest in this work.

References


