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REVIEW

Plerixafor for autologous CD34+ cell mobilization

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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

Outcome measure	Evidence	Implications
Disease-oriented evidence		
Multiple myeloma	Randomized clinical trial (31)	Safe and efficient HPC mobilization for autologous bone marrow transplant
Non-Hodgkin's lymphoma	Randomized clinical trial (26).	Safe and efficient HPC mobilization for autologous bone marrow transplant
Patient-oriented evidence	Clinical trials indicating safety and efficacy	Higher percentage of patients are mobilized to facilitate autologous transplants Safe approach May be beneficial in patients who are heavily treated and particularly those treated with lenalidomide
Economic evidence	More expensive than using G-CSF alone	Successful HPC mobilization with fewer attempts may account for part of the cost difference. 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 plarixafor.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HPC, hematopoietic progenitor cell.

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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.[1,2] Hendrix et al[1] 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.[2–10]

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.[11–16]

Further, plerixafor synergistically augments the mobilization effect of G-CSF on $CD34^+$cells.[5] Hematopoietic differentiation of transplanted $CD34^+$cells was similar after plerixafor or G-CSF mobilization methods.[17]

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.[18,19] 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.[18] 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.[19]

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%.[20] 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.[1,21]

In NHL or MM patients, the mean $t_{½}$ was 5.1 h, similar to that in healthy subjects.[22] A statistically significant correlation was noted between renal function (as determined by creatinine clearance (CrCl)) and plerixafor clearance,[23,24] as reported in phase I clinical trials. The $t_{½}$ 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 plerixafor[22] significantly increased the $CD34^+$ cell count in patients with NHL and MM. The median number of $CD34^+$ cells collected by five consecutive apheresis was 5.7×10^6 cells/kg in NHL patients and 12.0×10^6 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 1 Summary of the results of the non-Hodgkin lymphoma phase III clinical trial

Results	Plerixafor + G-CSF N = 150	Placebo + G-CSF N = 148
Met primary end point (%)	59.3	19.6
Achieved minimum collection (%)	86.7	47.3
Mean no. of $CD34^+$ ($\times 10^6$ cells/kg)	6.06	4.09
Median time to platelet engraftment (days)	20	20
Median time to WBCs engraftment (days)	10	10
Follow-up period (months)	12	12
One-year mortality (%)	12	12.8

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 0.8×10^6 $CD34^+$ cells/kg after two apheresis days or 2×10^6 $CD34^+$ 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.[29–31] Randomization was based on baseline platelet count ($<200 \times 10^3/\mu L$ versus $\geq 200 \times 10^3/\mu L$) 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 6×10^6 $CD34^+$ cells/kg in two or fewer apheresis days, rather than 5×10^6 $CD34^+$ cells/kg in four or fewer apheresis procedures. Additional

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

Results	Plerixafor + G-CSF N = 148	Placebo + G-CSF N = 154
Met primary end point (%)	71.6	34.4
Achieved minimum collection (%)	95.9	92.9
Mean no. of $CD34^+$ ((10^6 cells/kg)	5.84	4.41
Median no. of apheresis to collect the target $CD34^+$ cell no.	1	4
Rescue procedures (%)	0	4.6
One-year mortality (%)	4.7	3.9
Follow-up period (months)	12	12

provisions for the use of open-label plerixafor plus G-CSF included failure to collect at least 0.8×10^6 $CD34^+$ cells/kg after two apheresis days or 2×10^6 $CD34^+$ cells/kg in four apheresis days, or patients who were scheduled for tandem transplantation in whom $<4 \times 10^6$ $CD34^+$ 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.[30]

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]

Dosing and administration

On the basis of the above clinical evidence, the Food and Drug Administation approved plerixafor as a mobilization agent at a dose of 240 μg/kg actual body weight of the patient. The prescription uses subcutaneous injection beginning on the fourth day of G-CSF pretreatment.[20] In most published studies, plerixafor was administered 10 h prior to apheresis for up to a total of four consecutive days, or until the target was met. This approach had been logistically difficult to execute, as it meant the patient typically would have to come into the treatment center approximately at 10:00 p.m. in the evening before apheresis; the procedure had to begin at 8:00 a.m. the next morning. More recently, several abstracts at the American Society of Hematology Annual Meeting in 2009 reported that there were no significant differences in apheresis yield between patients who received plerixafor 5–15 h prior to apheresis.[33,34] With this updated information, many centers have altered their practice. At our institution, patients come to our treatment area at 5:00 p.m. on the appropriate day, then receive the plerixafor injection, and return to begin apheresis the following morning at 8:00 a.m. The dose should not exceed 40 mg/day.

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]

In a murine leukemia model, plerixafor mobilized labeled APL^{luc} 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.

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/kg[36] 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.[20]

Plerixafor plus G-CSF should be used with caution in patients with splenic enlargement,[20] although splenic rupture has not been reported in clinical trials.[37]

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.[20,35] 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.[20] In pregnant animals, plerixafor resulted in numerous embryo–fetal toxicities such as anophthalmia, cardiac defects, dilatation of olfactory ventricles, 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.[1,4]

Lenalidomide therapy may impair mobilization of $CD34^+$ cells.[38–41] Mark et al[42] 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.[42] 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[43] 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 5.6×10^6 $CD34^+$ 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.[43]

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.[44]

Plerixafor also may have a role in leukemia chemosensitization via its possible mobilization of leukemia cells.[35] This strategy of rendering the acute myeloid leukemia cells more amenable to be targeted by chemotherapy is being tested in clinical trials.[45]

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.[13,46,47] 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

1. Hendrix CW, Flexner C, MacFarland RT, et al. Pharmacokinetics and safety of AMD-3100, a novel antagonist of the CXCR-4 chemokine receptor, in human volunteers. *Antimicrob Agents Chemother*. 2000; 44(6):1667–1673.
2. de Clercq E. The bicyclam AMD3100story. *Nat Rev Drug Discov*. 2003; 2(7):581–587.
3. diPersio JF, Uy GL, Yasothan U, Kirkpatrick P. Plerixafor. *Nat Rev Drug Discov*. 2009;8(2):105–106.
4. Liles WC, Broxmeyer HE, Rodger E, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist. *Blood*. 2003;102(8):2728–2730.
5. Broxmeyer HE, Orschell CM, Clapp DW, et al. Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist. *J Exp Med*. 2005;201(8):1307–1318.
6. Fruehauf S, Seeger T, Maier P, et al. The CXCR4 antagonist AMD3100 releases a subset of G-CSF-primed peripheral blood progenitor cells with specific gene expression characteristics. *Exp Hematol*. 2006; 34(8):1052–1059.
7. Reddy GK, Crawford J, Jain VK. The role of plerixafor (AMD3100) in mobilizing hematopoietic progenitor cells in patients with hematologic malignancies. *Support Cancer Ther*. 2006;3(2):73–76.
8. Flomenberg N, Devine SM, Dipersio JF, et al. The use of AMD3100 plus G-CSF for autologous hematopoietic progenitor cell mobilization is superior to G-CSF alone. *Blood*. 2005;106(5):1867–1874.
9. Liles WC, Rodger E, Broxmeyer HE, et al. Augmented mobilization and collection of CD34+ hematopoietic cells from normal human volunteers stimulated with granulocyte-colony-stimulating factor by single-dose administration of AMD3100, a CXCR4 antagonist. *Transfusion*. 2005;45(3):295–300.
10. Hatse S, Princen K, Bridger G, de Clercq E, Schols D. Chemokine receptor inhibition by AMD3100 is strictly confined to CXCR4. *FEBS Lett*. 2002;527(1–3):255–262.
11. Burger JA, Peled A. CXCR4 antagonists: targeting the microenvironment in leukemia and other cancers. *Leukemia*. 2009;23(1):43–52.
12. de Clercq E. The AMD3100story: the path to the discovery of a stem cell mobilizer (Mozobil). *Biochem Pharmacol*. 2009;77(11):1655–1664.
13. Fricker SP, Anastassov V, Cox J, et al. Characterization of the molecular pharmacology of AMD3100: a specific antagonist of the G-protein coupled chemokine receptor, CXCR4. *Biochem Pharmacol*. 2006; 72(5):588–596.
14. Tan Y, Li Y, Xiao J, et al. A novel CXCR4 antagonist derived from human SDF-1beta enhances angiogenesis in ischaemic mice. *Cardiovasc Res*. 2009;82(3):513–521.
15. Gazitt Y, Freytes CO, Akay C, Badel K, Calandra G. Improved mobilization of peripheral blood CD34+ cells and dendritic cells by AMD3100 plus granulocyte-colony-stimulating factor in non-Hodgkin's lymphoma patients. *Stem Cells Dev*. 2007;16(4):657–666.
16. Devine SM, Vij R, Rettig M, et al. Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction. *Blood*. 2008;112(4):990–998.
17. Hess DA, Bonde J, Craft TP, et al. Human progenitor cells rapidly mobilized by AMD3100 repopulate NOD/SCID mice with increased frequency in comparison to cells from the same donor mobilized by granulocyte colony stimulating factor. *Biol Blood Marrow Transplant*. 2007;13(4):398–411.
18. Donahue RE, Jin P, Bonifacino AC, Metzger ME, Stroncek D. AMD3100 and granulocyte colony stimulating factor (G-CSF) mobilize different CD34+ cell populations based on global gene and micro RNA expression [50th ASH Annual Meeting Abstract]. *Blood*. 2008;112(11):1385.
19. Fruehauf S, Seeger T, Dillmann F, et al. The CXCR4 antagonist AMD3100 mobilizes a more primitive subset of CD34+ cells than G-CSF. *Onkologie*. 2005;28 Suppl 3:145.
20. Prescribing Information. Mozobil (Plerixafor Injection). Cambridge, MA: Genzyme Inc. Available from: www.mozobil.com. Accessed Sep 17 2009.
21. Hubel K, Liles WC, Broxmeyer HE, et al. Leukocytosis and mobilization of CD34+ hematopoietic progenitor cells by AMD3100, a CXCR4 antagonist. *Support Cancer Ther*. 2004;1(3):165–172.
22. Stewart DA, Smith C, MacFarland R, Calandra G. Pharmacokinetics and pharmacodynamics of plerixafor in patients with non-Hodgkin lymphoma and multiple myeloma. *Biol Blood Marrow Transplant*. 2009;15(1):39–46.
23. MacFarland R, Ewesuedo RB, Badel K, Calandra G. Pharmacokinetics of plerixafor (AMD3100) in volunteers with renal impairment [49th ASH Annual Meeting Abstract]. *Blood*. 2007;110(11):2878.
24. MacFarland R, Scarborough R, Becker S, et al. Pharmacokinetics of AMD3100 in volunteers with renal impairment. *Bone Marrow Transplant*. 2007;39 Suppl 1:S155.
25. Stiff PJ, Micallef I, McCarthy P, et al. Treatment with plerixafor in non-Hodgkin's lymphoma and multiple myeloma patients to increase the number of peripheral blood stem cells when given a mobilizing regimen of G-CSF: implications for the heavily pretreated patient. *Biol Blood Marrow Transplant*. 2009;15(2):249–256.
26. diPersio JF, Micallef I, Stiff PJ, et al. A Phase III, multicenter, randomized, double-blind, placebo controlled, comparative trial of AMD3100 (plerixafor)+G-CSF vs placebo+G-CSF in non-Hodgkin's lymphoma (NHL) patients for autologous hematopoietic stem cell (aHSC) transplantation [49th ASH Annual Meeting Abstract]. *Blood*. 2007;110(11):601.
27. diPersio JF, Micallef I, Stiff PJ, et al. Months report from the Phase 3 study of plerixafor+G-CSF vs placebo+G-CSF for mobilization of hematopoietic stem cell for autologous transplant in patients with NHL [50th ASH Annual Meeting Abstract]. *Blood*. 2008;112(11):1136.
28. diPersio JF, Micallef IN, Stiff PJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:4767–4773.
29. diPersio JF, Stadtmauer EA, Nademanee AP, et al. A Phase III, multicenter, randomized, double-blind, placebo-controlled, comparative trial of AMD3100 (plerixafor)+G-CSF vs G-CSF+placebo for mobilization in multiple myeloma (MM) patients for autologous hematopoietic stem cell (aHSC) transplantation [49th ASH Annual Meeting Abstract]. *Blood*. 2007;110(11):445.
30. diPersio JF, Stadtmauer EA, Nademanee AP, et al. 12 Months report from a Phase 3 study of plerixafor + G-CSF vs placebo + G-CSF for mobilization of hematopoietic stem cell for autologous transplant in patients with multiple myeloma [50th ASH Annual Meeting Abstract]. *Blood*. 2008;112(11):3312.
31. diPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood*. 2009;113(23):5720–5726.

32. Stiff PJ, Micallef I, Nademanee AP, et al. Transplanted CD34+ cell dose is associated with long-term platelet count following autologous hematopoietic stem cell transplant in patients with non-Hodgkin's lymphoma and multiple myeloma [50th ASH Annual Meeting Abstract]. *Blood*. 2008;112(11):2175.
33. Tornatta J, Maciejewski JJ, Nathan S, et al. Efficacy of administration of plerixafor (Mozobil®) at 5:00 pm for stem cell mobilization (SCM) in patients receiving autologous stem cell transplant [51st ASH Annual Meeting Abstract]. *Blood*. 2009;114(22):3218.
34. Rosenbaum ER, Nakagawa M, Pesek G, Theus J, Barlogie B, Cottler-Fox MH. A 15-hour dosing-collection interval for plerixafor is at least as effective as the standard 10-hour interval [51st ASH Annual Meeting Abstract]. *Blood*. 2009;114(22):2152.
35. Nervi B, Ramirez P, Rettig MP, et al. Chemosensitization of acute myeloid leukemia (AML) following mobilization by the CXCR4 antagonist AMD3100. *Blood*. 2009;113(24):6206–6214.
36. MacFarland R, Hard ML, Scarborough R, Badel K, Calandra G. A pharmacokinetic study of plerixafor in subjects with varying degrees of renal impairment. *Biol Blood Marrow Transplant*. 2010;16(1): 95–101.
37. Stiff PJ, Bensinger W, Abidi MH, et al. Clinical and ultrasonic evaluation of spleen size during peripheral blood progenitor cell mobilization by filgrastim: results of an open-label trial in normal donors. *Biol Blood Marrow Transplant*. 2009;15(7):827–834.
38. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia*. 2007;21(9):2035–2042.
39. Popat U, Saliba R, Thandi R, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2009;15(6):718–723.
40. Mazumder A, Kaufman J, Niesvizky R, Lonial S, Vesole D, Jagannath S. Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients. *Leukemia*. 2008;22(6):1280–1281.
41. Paripati H, Stewart AK, Cabou S, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. *Leukemia*. 2008;22(6):1282–1284.
42. Mark T, Stern J, Furst JR, et al. Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma. *Biol Blood Marrow Transplant*. 2008;14(7):795–798.
43. Micallef IN, Ho AD, Klein LM, Marulkar S, Gandhi PJ, McSweeney PA. Plerixafor (Mozobil) for stem cell mobilization in patients with multiple myeloma previously treated with lenalidomide. *Bone Marrow Transplant*. 2010 May 17. [Epub ahead of print].
44. Kumar S, Giralt S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. *Blood*. 2009;114(9):1729–1735.
45. Clinical Trials. Chemosensitization with plerixafor plus G-CSF in acute myeloid leukemia. 2010 Sep 1. Available from: http://clinicaltrials.gov/ct2/show/NCT00906945. Accessed Oct 6 2010.
46. Matthys P, Hatse S, Vermeire K, et al. AMD3100, a potent and specific antagonist of the stromal cell-derived factor-1 chemokine receptor CXCR4, inhibits autoimmune joint inflammation in IFN-gamma receptor-deficient mice. *J Immunol*. 2001;167(8):4686–4692.
47. Lukacs NW, Berlin A, Schols D, Skerlj RT, Bridger GJ. AMD3100, a CxCR4 antagonist, attenuates allergic lung inflammation and airway hyperreactivity. *Am J Pathol*. 2002;160(4):1353–1360.