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IMPROVED PATIENT OUTCOMES USING PLERIXAFOR WITH G-CSF TO IMPROVE STEM CELL MOBILIZATION

Ghazala Nathu*, Noor Hammam MS, Adila Nathu MD MD PhD, Muhammad Ashir MBBS MS

USA.

***Corresponding Author: Ghazala Nathu**

USA.

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ABSTRACT

Autologous hematopoietic stem cell (HSC) transplantation is a crucial treatment for patients undergoing high-dose chemotherapy for conditions such as Hodgkin's disease, non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), leukemias, and certain solid tumors. Successful transplantation depends on the ability to collect an adequate number of CD34+ HSCs from the peripheral blood, a process that can be challenging for some patients using standard mobilization methods like chemotherapy and granulocyte colony-stimulating factor (G-CSF Plerixafor, an FDA-approved agent used in combination with G-CSF, has significantly improved stem cell mobilization, particularly in patients with lymphoma and myeloma who struggle to mobilize sufficient cells. Its introduction has expanded the number of patients eligible for transplantation, reducing the need for multiple apheresis sessions and improving collection efficiency. However, due to its high cost, plerixafor is typically reserved for patients who fail standard mobilization strategies. Ongoing research continues to explore its broader applications, including its potential use in allogeneic transplantation and other hematologic conditions. As the role of plerixafor in stem cell therapy evolves, its impact on transplantation success and patient outcomes remains an important area of study.

INTRODUCTION

Plerixafor has emerged as a crucial agent in the mobilization of hematopoietic stem cells (HSCs) for autologous transplantation, particularly in patients with multiple myeloma and lymphoma. Mobilization failure remains a significant challenge in these patients, as standard approaches using granulocyte colony-stimulating factor (G-CSF) alone do not always yield sufficient CD34+ cells for successful transplantation. Preapheresis peripheral blood (PB) CD34+ cell count is a strong predictor of mobilization success and is commonly used to guide clinical decisions. However, a universally accepted threshold for predicting mobilization failure has not been established, leading to institution-specific strategies regarding the use of plerixafor.

Clinical studies have demonstrated that adding plerixafor to G-CSF significantly enhances stem cell mobilization across all preapheresis PB CD34+ cell count groups. Patients treated with plerixafor consistently achieved higher total CD34+ cell yields than those receiving G-CSF alone, regardless of their initial CD34+ levels. Importantly, a greater proportion of plerixafor-treated patients were able to collect both the minimum ($\geq 2 \times 10^6$ cells/kg) and optimum ($\geq 6 \times 10^6$ cells/kg) stem cell doses on each day of apheresis. As a result, plerixafor use reduced the number of apheresis sessions needed to reach the target stem cell dose, thereby improving efficiency and patient experience.

Despite its proven benefits, the high cost of plerixafor limits its widespread use. Many centers restrict plerixafor administration to patients predicted to fail mobilization with G-CSF alone, ensuring cost-effectiveness while maximizing the likelihood of successful transplantation. However, research suggests that even patients with higher preapheresis PB CD34+ counts ($\geq$20 cells/μL) benefit from plerixafor, as it increases the probability of collecting optimal stem cell doses in a shorter timeframe. This efficiency advantage has prompted discussions about expanding plerixafor use beyond traditionally defined "poor mobilizers."

Beyond its role in autologous transplantation, plerixafor is being investigated for broader applications. These include its potential use in allogeneic stem cell transplantation for healthy donors and as an adjunct therapy to enhance the efficacy of chemotherapy in acute leukemias. As research continues, the optimal patient selection criteria and cost-effectiveness of plerixafor will remain important considerations. Its ability to improve stem cell collection efficiency, particularly in patients at risk of mobilization failure, underscores its value in modern transplant protocols.

1. Mobilization of Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) are responsible for producing all types of blood cells, including red blood cells, platelets, and immune cells, through a process called hematopoiesis. HSCs have the unique ability to both renew themselves and differentiate into various blood cells. The first step in this process is when HSCs turn into hematopoietic progenitor cells (HPCs), which are then further specialized into specific blood cell types. HPCs can be easily measured in laboratory tests, making them a common marker to evaluate HSC function.

Hematopoietic stem cell transplantation (HSCT) is an important treatment for blood cancers. In allogeneic HSCT, stem cells from a donor are used, typically for leukemia, offering a potential cure. Autologous HSCT, which uses the patient's own stem cells, is used for treating cancers like multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) after high-dose chemotherapy. While HSCs can be taken directly from the bone marrow, the procedure is painful and requires anesthesia. To avoid this, doctors often use peripheral blood stem cells, which are easier to collect, especially for autologous transplants.

Although HSCs naturally circulate in and out of the bone marrow, their numbers in peripheral blood are very low, making them difficult to collect without special treatment. To increase the number of HSCs in the blood, patients are given mobilization agents, like granulocyte-colony stimulating factor (G-CSF) or chemotherapy drugs such as cyclophosphamide. Unfortunately, 5–40% of patients don't mobilize enough HSCs for a successful transplant. To address this, the FDA approved plerixafor in 2008, which, when combined with G-CSF, helps move more HSCs into the blood for easier collection, especially in patients with NHL and MM. This combination is particularly useful for patients who do not respond well to G-CSF alone.[4]

2. Granulocyte Colony Stimulating Factor

G-CSF is a glycoprotein, growth factor, and cytokine that promotes the mobilization of hematopoietic progenitor cells (HPCs) by reducing the chemokine stromal cell-derived factor 1 (SDF-1, CXCL12), primarily through its degradation by neutrophil elastase. It also stimulates the release of various proteases into the bone marrow (BM), which cleave adhesion molecules believed to be critical for HPC trafficking and mobilization.

G-CSF causes a peak in CD34+ cells in the peripheral blood within 4 to 6 days. Its advantages as a mobilization agent include outpatient administration, low toxicity, and predictable timing for apheresis. However, some drawbacks include lower CD34+ stem cell yields compared to combination regimens, the need for more apheresis sessions, and a reduced likelihood of obtaining stem cell products with high CD34+ cell content, as shown in Table 1.

Chemotherapy mobilizes stem cells by inducing marrow aplasia, followed by stimulation of hematopoietic recovery. This typically results in a 2.5-fold increase in HPC yields. The rise in peripheral blood stem cells (PBSCs) usually coincides with neutrophil recovery after chemotherapy-induced nadir. Combining chemotherapy with G-CSF results in higher CD34+ cell yields compared to G-CSF alone, though the timing of peak CD34+ cell counts may vary depending on the regimen used, making it harder to predict when to initiate apheresis. The most commonly used chemotherapy regimens include cyclophosphamide at various doses, especially for patients with multiple myeloma (MM). Patients with lymphoma may be mobilized with regimens such as ifosfamide, carboplatin, and etoposide (ICE); dexamethasone, doxorubicin, cytarabine, and cisplatin (DHAP); or etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP). Studies show that cyclophosphamide at 1.5 to 4 g/m² combined with G-CSF results in predictable CD34+ cell count peaks.

The advantages of using chemotherapy plus G-CSF for stem cell mobilization include higher stem cell yields, fewer apheresis sessions, and anti-tumor activity for certain diseases. The disadvantages include a greater need for hospitalization due to neutropenic fever, lower predictability for timing collections with some regimens, and toxicity and complications associated with the chemotherapy, as detailed in Table 1.

TABLE 1. PBSC mobilization agents

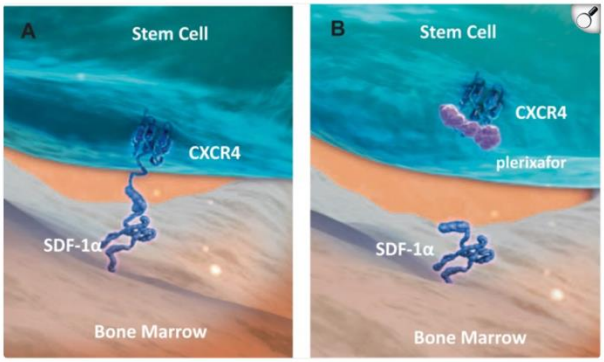
Mobilization agent	Mechanism of action	Advantages	Disadvantages
G-CSF	1. Induces a reduction in SDF-1 via degradation by neutrophil elastase 2. Increase in CXCR4 in the BM 3. Induces release of proteases into the BM	1. Outpatient administration 2. Low toxicity 3. Predictable time to peak CD34+ cells 4. Predictable timing of apheresis	1. Lower CD34+ cell yields compared to combination regimens 2. More apheresis sessions 3. Lower probability of stem cell products with high CD34+ cell content
Chemotherapy	Marrow aplasia with subsequent stimulation of hematopoietic recovery	1. Higher number of CD34+ cells compared to G-CSF 2. Fewer apheresis sessions 3. Antitumor activity	1. Need for hospitalization 2. Unpredictable time to peak CD34+ cells 3. Unpredictable timing of apheresis 4. Greater toxicity and complications
Plerixafor	Reversible antagonist of CXCR4 (blocks CXCR4–SDF-1 interactions)	1. Higher number of CD34+ cells (when used with G-CSF) compared to G-CSF 2. Fewer apheresis sessions 3. Stem cell grafts with more CD34+ cells 4. Higher likelihood of successful mobilization and collection 5. Predictable time to peak CD34+ cells	High cost

3. Plerixafor Mechanism of Action

Chemokine receptors, including CXCR4, play a crucial role in regulating the movement and retention of cells, particularly hematopoietic stem cells (HSCs), which are essential for blood cell formation. CXCR4, found on various cell types such as immune cells and stem cells, helps guide HSCs to the bone marrow where they are maintained and protected. This receptor binds to its ligand, CXCL12, which is produced by stromal cells in the bone marrow. The interaction between CXCR4 and CXCL12 ensures the proper homing, retention, and function of HSCs, making it vital for HSC transplantation, where the successful engraftment of transplanted stem cells in the bone marrow is essential for recovery.

During HSC transplantation, one of the challenges is ensuring that the transplanted HSCs home to the bone marrow and survive long enough to engraft and produce new blood cells. The CXCR4/CXCL12 interaction plays a central role in this process by guiding the transplanted HSCs to the bone marrow niche. By inhibiting this interaction with drugs like plerixafor, which blocks CXCR4, researchers can mobilize HSCs from the bone marrow into the bloodstream, allowing them to be collected more easily for transplantation. Plerixafor's ability to disrupt the CXCR4/CXCL12 binding is particularly useful in situations where it's difficult to obtain enough stem cells for transplantation.[7]

Plerixafor has proven beneficial in enhancing HSC transplantation outcomes by improving the collection of HSCs for patients in need of stem cell transplants, such as those with leukemia or lymphoma. The drug works by inhibiting CXCR4, preventing the retention of HSCs in the bone marrow and facilitating their release into the bloodstream. This allows for more efficient collection of HSCs for transplant. Additionally, studies have shown that plerixafor is a selective inhibitor of CXCR4, and by understanding its binding mechanism, researchers can optimize its use to improve stem cell mobilization. This approach has had a significant impact on stem cell transplantation, enhancing patient outcomes by ensuring a greater number of viable stem cells are available for transplantation and engraftment.



Mechanism of HSC mobilization by plerixafor. A **HSCs are retained in the bone marrow niche by the CXCR4/CXCL12 interaction.** B **Binding of plerixafor to CXCR4 inhibits CXCL12 ligand binding and releases HSC from the bone marrow niche.**

4. Previous Studies

Efficacy of Plerixafor in Hematopoietic Stem Cell Mobilization in Multiple Myeloma

A study was conducted to evaluate the mobilization efficacy of plerixafor in combination with granulocyte colony-stimulating factor (G-CSF) versus a placebo plus G-CSF in patients with multiple myeloma. The study stratified patients by their preapheresis peripheral blood (PB) CD34(+) cell count into groups of <10, <15, <20, and ≥20 cells/μL. Preapheresis PB CD34(+) cell count is an important predictor of hematopoietic stem cell (HSC) mobilization and is commonly used to optimize the timing, cost, and success of HSC collection, particularly in multiple myeloma patients. However, a uniform threshold for predicting mobilization failure based on this count has not been established, leading to the development of institution-specific mobilization protocols.

The results of the study showed that, regardless of the preapheresis PB CD34(+) cell count, the total yield of CD34(+) cells collected via apheresis was significantly higher in the plerixafor group than in the placebo group. Moreover, a greater proportion of patients in the plerixafor group achieved the minimum (≥2 × 10^6 cells/kg) and optimal (≥6 × 10^6 cells/kg) stem cell yields on each day of apheresis. As a result, patients in the plerixafor-treated group required significantly fewer apheresis days to reach these target cell doses across all cell count groups.

Additionally, for all stratified PB CD34(+) cell count groups, the proportion of patients proceeding to transplantation and the median time to platelet and neutrophil engraftment were similar in both the plerixafor and placebo groups. These findings suggest that plerixafor, when combined with G-CSF, improves the collection of the minimum and optimal stem cell

doses in patients who would otherwise be predicted to fail mobilization based on low PB CD34(+) cell counts. Furthermore, plerixafor plus G-CSF significantly enhances the likelihood of optimal HSC collection in patients with higher preapheresis PB CD34(+) cell counts (≥20 cells/μL) compared to placebo plus G-CSF.[5]

This analysis confirms the superior efficacy of plerixafor in combination with G-CSF, particularly in patients with low PB CD34(+) cell counts, and validates its use as an effective mobilization strategy in patients with multiple myeloma.

Improving Stem Cell Mobilization with G-CSF and Plerixafor

Plerixafor administration leads to the migration of hematopoietic stem cells (HSCs) from the bone marrow into peripheral blood, enabling collection via apheresis. Clinical trials have shown that combining G-CSF with plerixafor enhances HSC mobilization. In patients with multiple myeloma (MM) undergoing their first mobilization and with minimal prior treatment, this combination was found to double circulating peripheral CD34+ HSC counts, resulting in twice the number of CD34+ HSCs collected in half the number of apheresis sessions. However, there was no significant improvement in engraftment rates, graft durability, transplantation, or survival outcomes. In patients with Hodgkin's disease or non-Hodgkin lymphoma (NHL), where mobilization success is typically limited, G-CSF + plerixafor improved mobilization and apheresis yields, though clinical outcomes remained unchanged. Common adverse events (≥20%) of plerixafor with G-CSF include diarrhea (37%), nausea (34%), injection-site reactions (34%), fatigue (27%), and headache (22%). Plerixafor is administered at a dose of 0.24 mg/kg subcutaneously on the evening of the fourth day of G-CSF treatment, approximately 11 hours before the first apheresis session, and can be repeated for up to three consecutive days to ensure adequate HSC collection. The average wholesale price for a 24-mg vial of plerixafor is $7,500. Overall, plerixafor is an effective agent for mobilizing CD34+ HSCs, and long-term treatment outcomes in autologous transplantation with G-CSF and plerixafor are still being studied.[6]

Broadening the Scope of Plerixafor: Mobilization Efficacy Beyond Poor Mobilizers in Stem Cell Transplantation

In a randomized, double-blind trial, the combination of plerixafor and G-CSF significantly improved stem cell mobilization outcomes compared to G-CSF alone across all preapheresis CD34(+) cell count subgroups. Notably, patients with relatively high peripheral blood CD34(+) counts (≥20 cells/μL) also experienced enhanced efficiency in reaching optimal collection targets.

A greater proportion of patients in the plerixafor group achieved both the minimum collection goal of $\geq 2 \times 10^6$ CD34(+) cells/kg and the optimal target of $\geq 6 \times 10^6$ CD34(+) cells/kg on the first day of apheresis. This resulted in fewer required apheresis sessions and a higher likelihood of completing collection within two days.

These results indicate that plerixafor may have broader clinical utility beyond traditional "poor mobilizers," offering benefits even to patients with adequate baseline CD34(+) counts. By enhancing mobilization efficiency, plerixafor use could contribute to reduced healthcare costs associated with extended apheresis, hospitalization, and resource utilization, while also improving patient experience and readiness for transplantation.

Ongoing studies are further investigating the role of plerixafor in other hematologic malignancies, its synergy with emerging mobilization agents, and its potential application in allogeneic transplantation. As supporting evidence grows, expanding the use criteria for plerixafor may prove to be a cost-effective strategy for optimizing stem cell collection across a wider patient population.

DISCUSSION

The integration of plerixafor into standard mobilization regimens represents a significant evolution in the field of hematopoietic stem cell transplantation (HSCT), particularly for individuals diagnosed with multiple myeloma and lymphoma. These patients are often at elevated risk for mobilization failure, and plerixafor offers a reliable alternative or adjunct to traditional mobilization strategies. Historically viewed as a rescue medication for poor mobilizers, plerixafor has shown consistent efficacy across a wide spectrum of preapheresis CD34+ cell counts. Notably, patients with CD34+ levels exceeding 20 cells/μL—typically considered adequate—also benefit from the addition of plerixafor, suggesting its utility extends beyond rescue use and into the realm of preemptive or first-line strategies. This broader application challenges existing paradigms and supports the ongoing reevaluation of mobilization protocols.

Despite its clear clinical value, the widespread implementation of plerixafor is hindered by its high cost. While its use may reduce the overall number of apheresis procedures required and shorten the time to transplantation, these benefits are weighed against the significant financial burden it places on both healthcare institutions and insurance providers. This has prompted a growing interest in optimizing the use of plerixafor through the development of predictive models. Risk stratification tools and machine learning-based algorithms are being explored as innovative solutions to help identify patients most likely to benefit from plerixafor, allowing for a more targeted and economically sustainable approach. These models use clinical and laboratory data to forecast mobilization outcomes and guide the strategic use of this costly yet powerful agent.

In addition to its applications in autologous transplantation, plerixafor is being actively investigated for broader uses in the transplantation landscape. One such area is allogeneic transplantation, where mobilizing stem cells from healthy donors without the need for chemotherapy could improve donor safety and expand the eligible donor pool. This chemo-free approach could be particularly advantageous in unrelated or older donors who may not tolerate chemo mobilization well. Furthermore, the mechanism by which plerixafor disrupts the bone marrow microenvironment—specifically the CXCR4/CXCL12 axis—has led researchers to examine its potential as an adjunctive therapy in leukemia treatment. By dislodging leukemic cells from their protective bone marrow niches, plerixafor may increase their susceptibility to chemotherapeutic agents and improve treatment responses.

However, these exciting possibilities are tempered by the need for caution. The CXCR4/CXCL12 signaling axis is not only involved in the retention and homing of hematopoietic stem cells but also plays crucial roles in immune regulation, inflammation, and organ development. Interfering with this pathway, especially over extended periods or in vulnerable populations, raises concerns about possible unintended consequences. Long-term inhibition of CXCR4 could impair immune function or contribute to adverse developmental or physiological effects that are not yet fully understood. As such, ongoing and future studies must carefully evaluate the broader biological implications of plerixafor use, including its safety profile, optimal dosing strategies, and interactions with other therapies.

Overall, plerixafor represents a significant advancement in stem cell mobilization. Its proven efficacy in both standard and high-risk populations underscores its transformative potential in transplant medicine. However, realizing its full benefit requires addressing the challenges of cost, accessibility, and long-term safety. Continued research and refinement of predictive tools will be vital in ensuring that plerixafor is used efficiently and effectively to improve patient outcomes.

CONCLUSION

The use of plerixafor in combination with granulocyte colony-stimulating factor (G-CSF) has emerged as a powerful strategy for mobilizing hematopoietic stem cells, significantly increasing CD34+ cell yields and often reducing the number of apheresis sessions required. This is particularly advantageous in patients with hematologic malignancies such as multiple myeloma and certain lymphomas, who frequently face difficulties with mobilization using traditional regimens. Clinical studies have demonstrated that the G-CSF and plerixafor combination can nearly double the number of stem cells collected in fewer procedures, thereby streamlining the transplantation process.

While these improvements are clinically meaningful from a logistical and operational standpoint, they have not yet translated into substantial gains in long-term transplant outcomes. Parameters such as time to engraftment, graft durability, and overall survival have shown little improvement compared to standard mobilization techniques. This disconnect suggests that while plerixafor enhances the technical aspects of mobilization, its influence on post-transplant biology and recovery may be more limited than initially expected.

Plerixafor is generally well tolerated, though it is associated with side effects such as nausea, diarrhea, fatigue, and localized injection site reactions. These adverse effects are usually mild but can be bothersome to some patients. Additionally, the requirement for repeated subcutaneous injections and the associated cost of therapy present practical challenges in both outpatient and inpatient settings. These considerations must be balanced against the potential benefits during treatment planning, especially when evaluating mobilization strategies for individual patients.

Ongoing clinical research continues to explore and refine the role of plerixafor in stem cell transplantation. This includes efforts to assess its long-term impact in autologous transplant recipients, identify ideal candidates for its use, and determine whether combination strategies can further enhance its effectiveness. Studies are also investigating novel approaches, including combination therapies and CXCR4-targeting agents, that may further improve the mobilization process or broaden the therapeutic impact of plerixafor.

In summary, while plerixafor does not yet appear to dramatically alter long-term clinical outcomes, it remains a critical tool in the stem cell mobilization toolkit. Its reliable efficacy, especially in hard-to-mobilize populations, makes it an asset in clinical practice. Future developments in predictive analytics, cost management, and expanded indications may further solidify its role in transplantation and hematologic care.

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