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EDITORIAL

The role of plerixafor in optimizing peripheral blood stem cell mobilization for autologous stem cell transplantation

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High-dose chemotherapy with or without radiation therapy is an effective treatment strategy for patients with non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and Hodgkin's lymphoma. The myelosuppressive or myeloablative effects of high-dose chemotherapy, however, require subsequent hematopoietic stem cell (HSC) transplantation to help restore bone marrow function. The preferred HSC source is from the patient's peripheral blood.[1] This requires stem cell mobilization from the bone marrow into the bloodstream for collection. The classical HSC mobilization approach relies on granulocyte colony-stimulating factor (G-CSF) either as a single agent or in conjunction with chemotherapy (chemomobilization). This is considered the standard of care for HSC mobilization despite evidence that mobilization fails in 5–40% of cases.[2,3] Plerixafor is a novel CXCR4 chemokine-receptor antagonist for autologous HSC mobilization, which gained Food and Drug Administration (FDA) approval in 2008 and European Medicines Agency (EMEA) approval in 2009. This editorial will consider the benefits and limitations of G-CSF HSC mobilization and examine the potential role of plerixafor in daily clinical practice.

Irrespective of the mobilization regimen used, the success or failure of HSC mobilization is, in part, dictated by the target number of cells to be harvested. The generally accepted minimum $CD34^+$ cell yield for transplant is $\geqslant 2 \times 10^6$ $CD34^+$ cells/kg,[4] although higher cell doses of $4–5 \times 10^6$ $CD34^+$ cell/kg or greater are associated with faster neutrophil and platelet recovery, reduced hospitalizations, reduced blood transfusions and antibiotic treatment.[5] Many transplant centers, therefore, define their target cell dose as an 'optimal' dose (usually $4–6 \times 10^6$ $CD34^+$ cells per kg of recipient body weight). Higher cell doses may be collected from patients with MM when tandem transplantation is considered. There are also acknowledged risk factors for suboptimal HSC mobilization. These include older age (>60 years); progressive disease and heavy bone marrow involvement; previous chemotherapy and/or radiotherapy; type of antineoplastic drug used (for example, fludarabine, melphalan, lenalidomide and so on); previously failed mobilization attempts; platelet counts of $\leqslant 100 \times 10^9$/l before apheresis; and neutropenic fever during mobilization.[2,4–9] Risk factors, practical constraints, as well as the need to reduce tumor burden by disease-specific chemotherapy, affect the choice of mobilization method for each patient.

G-CSF (filgrastim and lenograstim)-mediated HSC mobilization is believed to involve the disruption of adhesion molecules such as vascular cell adhesion molecule-1, c-kit, CXCR4 and SDF-1 to release stem cells from bone marrow niches.[10] The definitive mechanism is unclear; however, there is evidence that the sympathetic nervous system is also involved in regulating HSC attraction to bone marrow niches.[11] As a single agent, G-CSF is used mostly at a dose of 10 μg/kg subcutaneously daily, initiated 4 days before the first apheresis session and continued until the last day of apheresis. Circulating $CD34^+$ cells usually peak on days 5–6 after G-CSF initiation. Stem cells are usually collected in a median of 2–5 apheresis sessions.[3] G-CSF has a relatively mild toxicity profile, although rarely have severe adverse events such as splenic rupture, lung injury and vascular events been reported.[12] A significant number of patients are unable to mobilize sufficient cells for auto-HSC transplantation with G-CSF alone. In a retrospective study of 1834 NHL, Hodgkin's lymphoma and MM patients, 26.8, 26.4 and 6.6%, respectively, were unable to collect the required $\geqslant 2 \times 10^6$ $CD34^+$ cells/kg.[4]

Chemotherapy used in intensive myelosuppressive treatments mobilizes HSCs to the peripheral blood as a result of compensatory neutrophil production following chemotherapy-induced aplasia. Chemotherapy used in conjunction with G-CSF is more effective in mobilizing HSCs than either chemotherapy or G-CSF alone.[13] However, one study reports that the percentage of patients achieving a minimum 2×10^6 $CD34^+$ cells/kg is similar to those using G-CSF alone; failure rates are similar, and remobilization attempts with G-CSF with or without chemotherapy are equally likely to fail.[4] Nevertheless, G-CSF with chemotherapy may achieve more successful mobilizations in patients heavily pretreated with chemotherapy,[14] and cyclophosphamide, or etoposide, in combination with G-CSF has been used to rescue MM patients treated upfront with lenalidomide who demonstrated reduced HSC mobilization with G-CSF alone.[8,15–18] A steep dose–response curve exists for cyclophosphamide, with myelosuppression being the dose-limiting factor.[19]

Chemomobilization in combination with G-CSF is often disease specific and may eliminate the need for separate mobilization therapy following induction or salvage treatment. In lymphoma, salvage chemotherapy regimens such as IVE (ifosfamide, vincristine, etoposide), IEV (ifosfamide, epirubicin, etoposide), ICE (ifosfamide, carboplatin, etoposide) or DHAP (cytarabine, cisplatin, dexamethasone) are frequently used to both reduce tumor burden and enhance stem cell mobilization.

Patient responses to chemomobilization are variable. Unpredictable times to peak peripheral blood $CD34^+$ cells may result in delays to apheresis and inefficient use of health-care resources.[20] Chemomobilization is also associated with dose-dependent patient morbidity, greater risk of infection and febrile neutropenia, more hospital admissions and drug-specific toxicities, compared with G-CSF alone.[21] In addition, chemotherapy may damage the bone marrow microenvironment and impair engraftment with possible long-term adverse effects and compromised future mobilization attempts.[3,13] Thus, unless the antitumor activity is proven, chemotherapy to mobilize HSCs may not be cost-effective and may result in some risks for patients.

Plerixafor was developed in response to the unmet need for more effective mobilization agents. Plerixafor is a small bicyclam molecule that reversibly and selectively antagonizes the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1-α (SDF-1-α or CXCL12), resulting in mobilization of $CD34^+$ cells to the

peripheral blood. Plerixafor is rapidly absorbed following subcutaneous injection reaching peak concentrations in 30–60 min, and alone results in rapid increases in peripheral blood $CD34^+$ cells following a single injection in healthy donors. It exhibits linear kinetics over studied doses of 40–240 μg/kg, is eliminated unchanged in urine and has a half-life of 3–5 h in patients with normal renal function.[22,23] Plerixafor as a single agent has also been investigated in patients with MM, all of whom achieved enough cells for at least one transplant and demonstrated prompt recovery of hematopoietic function.[24] When plerixafor is combined with G-CSF, HSC mobilization is enhanced compared with either plerixafor or G-CSF alone with peak $CD34^+$ cell counts 10–14 h following administration.[25] Plerixafor is generally safe and well tolerated both in healthy volunteers and in patients with NHL and MM.[23–27] Most adverse effects are described as mild and transient (Table 2). Severe adverse events are rare and include hypotension and dizziness after drug administration and thrombocytopenia after apheresis.[28] In common with other HSC mobilization regimens, there is a potential risk of tumor cell mobilization and increased risk of metastases. The clinical significance of tumor cell mobilization is unclear, however, and may not affect long-term outcomes.[29,30] Data indicate that tumor cell contamination is not evident, or not significantly increased, following plerixafor treatment, compared with G-CSF alone, in MM and NHL patients.[31,32] However, increased circulating tumor cells have been reported in acute myelogenous leukemia and plasma cell leukemia patients. Therefore, plerixafor is not recommended for HSC mobilization in leukemia patients.

The mobilization efficacy of plerixafor was demonstrated in two phase III, multicenter, randomized, double-blind, placebo-controlled studies, which investigated primary HSC mobilization in patients with NHL and MM.[28,33] The primary end point for the NHL trial was the collection of $\geqslant 5 \times 10^6$ $CD34^+$ cells/kg in $\leqslant 4$ days of apheresis; and $\geqslant 6 \times 10^6$ $CD34^+$ cells/kg collected in $\leqslant 2$ days of apheresis for the MM trial. The treatment protocol for both patient groups was G-CSF (10 μg/kg/day) + plerixafor (240 μg/kg) or G-CSF (10 μg/kg/day) + placebo. Placebo or plerixafor was administered on the evening of day 4 within a standard G-CSF mobilization regimen and apheresis was initiated on day 5 irrespective of peripheral blood $CD34^+$ cell count. Treatment was continued for up to four apheresis sessions or until the target number of $CD34^+$ cells was collected (Figure 1).[28,33]

In the NHL group, 89 (59%) of 150 patients in the plerixafor group and 29 (20%) of 148 patients in the placebo group achieved the primary end point ($P<0.001$). Of the plerixafor group, 135 (90%) underwent transplantation after initial mobilization compared with 82 patients (55%) in the placebo group ($P<0.001$). Median time to platelet and neutrophil engraftment was similar in both groups. In the MM group, 106 of 148 (71.6%) patients in the plerixafor group and 53 of 154 (34.4%) patients in the placebo group met the primary end point ($P<0.001$). A total of 54% of plerixafor-treated patients reached the $CD34^+$ cell target after one apheresis, whereas 56% of the placebo-treated patients required four apheresis sessions.

Patients with NHL in either arm of the above phase III clinical trial who failed mobilization ($<0.8 \times 10^6$ $CD34^+$ cells/kg in two apheresis sessions or $<2 \times 10^6$ $CD34^+$ cells/kg in four sessions) were eligible for a 'rescue' protocol. After a minimum 7-day rest period, these patients received G-CSF (10 μg/kg/day) for 4 days, followed by daily plerixafor (240 μg/kg) plus G-CSF and apheresis for up to 4 days. Of the 68 patients failing initial mobilization (plerixafor, $n=11$; placebo, $n=57$), 62 patients (91%) entered the rescue procedure ($n=10$ for plerixafor arm, $n=52$ for placebo arm). Four of 10 patients (40%) from the plerixafor group and 33 of 52 (63%) from the placebo group mobilized $\geqslant 2 \times 10^6$ cells/kg from the rescue mobilization alone.[34]

Plerixafor has also been made available to poor mobilizers through a compassionate use program. Results from a recent European compassionate use program study in 56 patients (32 with MM and 24 with lymphoma), who had collectively failed 73 previous mobilization attempts, showed a 75% successful collection rate ($\geqslant 2 \times 10^6$ $CD34^+$ cells/kg) in a median of two apheresis procedures when treated with plerixafor and G-CSF. A total of 71% of plerixafor-treated patients reached $\geqslant 10$ $CD34^+$ cells/μl on day 5 (median 17.9, range 2.8–192.2) after a 7.6-fold expansion from day 4. Of note, 84% of MM patients mobilized successfully, including those who had a previous auto-HSC transplantation or who had been treated with lenalidomide.[35]

Compassionate use program outcomes in patients who had previously failed to mobilize sufficient cells for transplant (that is, at least 2×10^6 $CD34^+$ cells/kg) achieved success rates of 60% for NHL ($n=63$), 71% for MM ($n=35$) and 76% for Hodgkin's lymphoma ($n=17$) when treated with plerixafor and G-CSF.[35] Other authors have reported similar success rates (70–85%) in patients who had failed previous mobilization attempts.[32,36,37]

Patients who have been heavily pretreated with chemotherapy are at particular risk of mobilization failure.[6,38] The effect of plerixafor on HSC mobilization in these patients was investigated in 28 patients with NHL or MM treated with more than nine cycles of chemotherapy, platinum-based therapy and/or radiotherapy to bone marrow sites. The median increase in circulating $CD34^+$ cells/μl was 2.6-fold after plerixafor and G-CSF therapy, enabling auto-HSC transplantation in all 28 patients.[39]

Putting these findings in perspective, the aim of HSC mobilization is always to collect sufficient $CD34^+$ cells for transplantation, preferably in the first mobilization attempt and ideally with a minimum of apheresis sessions. Each failure or delay to collect HSCs extends the time to high-dose chemotherapy and increases the risk of disease progression. The benefits and limitations of G-CSF alone and G-CSF in combination with chemotherapy as stem cell mobilizing agents are summarized in Table 1. On the basis of outcomes from clinical trials and US and European Union compassionate use program outcomes, plerixafor in combination with G-CSF provides a compelling alternative strategy (Table 2). Plerixafor alone may also have a role in circumstances in which G-CSF or

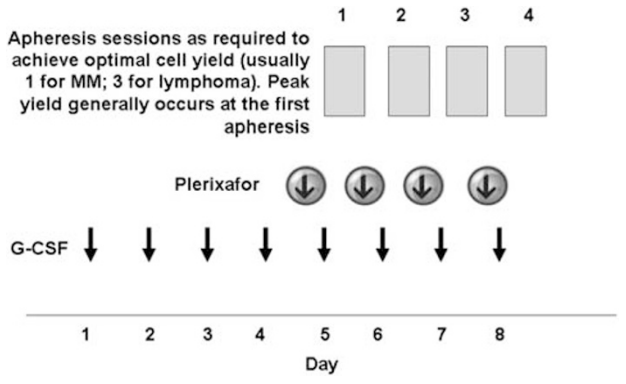

Figure 1 HSC mobilization and apheresis schedule for plerixafor in conjunction with G-CSF as described in phase III trials.[46,47]

Table 1 Summary of benefits and limitations of most widely used traditional HSC mobilization methods

Method	*Benefits*	*Limitations*
Standard G-CSF therapy alone	Relatively low toxicity, common adverse events include bone pain, headache, anemia and decreased platelet counts	Lower $CD34^+$ cell yields compared with G-CSF+chemotherapy
	Predictable peak $CD34^+$ level (4–5 days); reliable apheresis scheduling	Variable failure rates
	Outpatient administration	
	Generally, high efficacy	
	Reduced costs compared with G-CSF+chemotherapy	
G-CSF+chemotherapy	Higher HSC yields compared with G-CSF alone	Less predictable peak $CD34^+$ (10–18 days); less efficient use of apheresis facilities
	Anticancer activity	Greater toxicity compared with G-CSF alone
	Fewer apheresis procedures	No improvement in failure rates compared with G-CSF
		May incur damage to bone marrow microenvironment, impair engraftment and impair future mobilizations
		Need to hospitalize patients for 1–3 days for administration of chemotherapy
		Need for daily blood tests to monitor $CD34^+$ mobilization
		Higher costs compared with G-CSF alone
		No benefit compared with G-CSF alone in the second mobilization attempt

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HSC, hematopoietic stem cell.

Table 2 Summary of benefits and limitations of plerixafor

Method	*Benefits*	*Limitations*
Plerixafor+G-CSF	Predictable time to peak $CD34^+$ cells ($\sim$11 h): reliable apheresis planning; more efficient use of healthcare resources	Currently indicated for failed or poor mobilizers in Europe and not in general first-line treatment
		Limited data on outcomes in association with chemomobilization
	Fewer mobilization failures compared with G-CSF alone, reduced need for remobilization	Likely to be more expensive than current mobilization options
	More patients able to proceed to high-dose chemotherapy	
	Faster time to high-dose chemotherapy	
	Reduced risk of disease progression	
	More cells per apheresis: higher cell doses for auto-HSCT; possible option of collecting cells for tandem/salvage transplant	
	Fewer apheresis sessions, fewer procedural side effects	
	Fewer days of G-CSF	
	Adverse events: mild and transient (most commonly diarrhea, nausea and injection site reactions)	

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation.

chemotherapy-based mobilization is not suitable, although HSC mobilization is modest compared with plerixafor and G-CSF in combination G-CSF.[24]

The current indication in Europe for plerixafor is 'in combination with G-CSF to enhance mobilization of HSCs to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and MM, whose cells mobilize poorly'. This indication allows physicians to use plerixafor in the broad group of patients who are at risk of poor mobilization, as well as those who have previously failed conventional mobilization. The effectiveness of plerixafor in increasing HSC mobilization suggests an additional potential role in primary mobilization to reduce the risk of mobilization failure. This is especially appropriate in patients who, on monitoring of peripheral blood $CD34^+$ cell counts, do not mobilize HSCs at a rate consistent with achieving target yields or do not achieve sufficient numbers of circulating $CD34^+$ cells to proceed to apheresis. Preemptive administration of plerixafor in these cases may 'rescue' the mobilization process and enable the patient to proceed promptly to high-dose chemotherapy without having to undergo an expensive and time-consuming repeat mobilization. Similarly, patients who are predicted to be poor mobilizers on the basis of age, treatment history and disease profile may also benefit potentially from plerixafor in first-line treatment to help avoid further mobilization attempts.[32,39]

In cases in which chemotherapy with G-CSF is used only for mobilization purposes, plerixafor could be used to replace

chemomobilization and avoid unnecessary exposure to the side effects of chemotherapy. Plerixafor with G-CSF, compared with cyclophosphamide with G-CSF, has demonstrated similar numbers of cells collected, similar costs of mobilization and similar clinical outcomes,[40,41] although mobilization with plerixafor provides greater predictability for apheresis.[41] Plerixafor in combination with chemomobilization has not been extensively studied, although a preliminary study in NHL and MM patients indicates that plerixafor may be added safely to chemotherapy with G-CSF-based mobilization regimens and may accelerate the rate of increase in $CD34^+$ cells.[42]

Following the introduction of plerixafor, the International Myeloma Working Group reviewed stem cell mobilization issues for transplantation in MM patients. It recommends studies to look at optimizing collection strategies after exposure to novel therapies (particularly lenalidomide-based combinations) with plerixafor and G-CSF or plerixafor plus chemotherapy.[16,17] The ability to mobilize greater numbers of $CD34^+$ cells may provide more opportunities to deliver optimal cell doses at transplant with faster engraftment and, potentially, better long-term outcomes.[30,43,44] Increased $CD34^+$ cell yield, in addition, may allow cells to be stored for tandem or salvage transplantation, avoiding the need to attempt mobilization at a time when mobilization could be challenging for the patient.

Although investigators usually focus on $CD34^+$ yield as a major factor predicting transplant success, other factors such as the quality of the cell product composition, rate of engraftment and immune reconstitution may also contribute to long-term outcomes. A faster time to engraftment lowers the risk of potentially fatal infections and bleeding. This may be influenced not only by the total $CD34^+$ cell dose but also by levels of $CD34^+$ cell subsets, which influence neutrophil or platelet engraftment.[45,46] It has been suggested that the more primitive HSCs mobilized by plerixafor in combination with G-CSF may have a greater capacity for reconstituting bone marrow compared with those mobilized by G-CSF alone.[47]

In conclusion, the availability of plerixafor is a significant advance, increasing the number of patients for whom auto-HSC transplantation is a potentially effective treatment option and increasing the number of patients able to proceed, in as short a time as possible, to high-dose chemotherapy. On the basis of currently available mobilization regimens, we expect plerixafor to become increasingly the mobilization method of choice for MM, NHL and Hodgkin's lymphoma patients likely to benefit from high-dose chemotherapy.

Conflict of interest

Dr Mohty has acted as a consultant to Genzyme and Amgen, the products of which are discussed in this manuscript. Drs Duarte, Russell and Hübel have also acted as consultants to Genzyme.

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