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Current Clinical Indications for Plerixafor

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Summary
Autologous and allogeneic hematopoietic stem cell (HSC) transplantation are considered the standard of care for many malignancies including lymphoma, multiple myeloma, and some leukemias. In many cases, mobilized peripheral blood has become the preferred source for HSCs. Plerixafor, an inhibitor of the interaction between CX chemokine receptor 4 (CXCR4) and stromal derived factor-1 alpha (SDF-1), has been evaluated in clinical trials and approved by the FDA and EMA. This agent has very modest toxicity and appears to be quite potent at HSC mobilization. Current clinical indications for the use of plerixafor are the subject of this review.

Introduction

Hematopoietic stem cell transplantation (HSCT) as a treatment modality for disease dates back to studies performed in the late 1930s and early 1940s [1–5]. An important breakthrough occurred in the 1970s with the detection of the human leukocyte antigen (HLA) system, which allowed allogeneic transplants without potentially fatal complications such as rejection and severe graft-versus-host disease (GVHD) [6, 7]. A second important breakthrough occurred in the mid-1980s, when several groups showed that it was possible to collect hematopoietic stem cells (HSCs) from the peripheral blood by apheresis after administration of chemotherapy [8–11] or growth factors such as granulocyte colony-stimulating factor (G-CSF) (filgrastim; Neupogen®, Amgen, Thousand Oaks, CA, USA) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (sargramostim; Leukine®, Genzyme Corporation, Cambridge, MA, USA) [12, 13]. To date, peripheral blood remains the most common source of HSCs, and several agents are available or under investigation for HSC mobilization. Chemotherapeutic agents such as cyclophosphamide and other cytostatic drugs have been used in conjunction with growth factors to mobilize stem cells into the peripheral blood in patients with multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) [14–16]. Additionally, disease-specific regimens, including ICE (ifosfamide, carboplatin, etoposide), RICE (rituximab + ICE), IVE (ifosfamide, vincristine, etoposide), DHAP (cisplatin, cytarabine, dexamethasone), and D-PACE (dexamethasone, cisplatin, adriamycin, cyclophosphamide, etoposide), have been used in combination with cytokines for HSC mobilization into the peripheral blood [17–20]. Cytokines alone (e.g., G-CSF, GM-CSF, and stem cell factor (SCF; Stemgen®, Biovitrum, Stockholm, Sweden) have been extensively studied and are known to effectively mobilize HSCs, but typically result in lower CD34+ cell numbers [21]. Plerixafor (Mozobil®, Genzyme, Cambridge, MA, USA), a new small molecule, has been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in HSC mobilization for autologous transplant for patients with lymphoma and MM. This review summarizes available clinical literature focusing on the current use of plerixafor.

Plerixafor + G-CSF

In December 2008, the FDA approved the use of plerixafor, in combination with G-CSF (filgrastim), to mobilize HSCs from peripheral blood of patients with NHL and MM, who will subsequently undergo an autologous stem cell transplant. This decision was based on evidence from phase I, II and III clinical trials. Clinical data suggest that plerixafor has similar activity in Hodgkin's lymphoma and solid tumors.

Two phase III, multicenter, randomized (1:1), double-blind, placebo-controlled studies were performed to compare the

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safety and efficacy of plerixafor and G-CSF with placebo and G-CSF in the mobilization of CD34+ cells. The studies were very similar in design with few exceptions. The first trial [22] was open to patients with NHL, who required (and were eligible for) an autologous HSC transplant in first or second complete or partial remission. All patients were given G-CSF 10 μg/kg subcutaneously daily in the morning for up to 8 days. Beginning on the evening of day 4, patients received either 240 μg/kg plerixafor as a subcutaneous injection or placebo daily for up to 4 days. Apheresis was started on the morning of day 5 and continued for up to 4 days or until ≥5 × 10^6 CD34+ cells/kg were successfully collected. A total of 298 patients were randomized. The proportion of patients in the plerixafor arm achieving the primary end point was significantly higher than that in the placebo arm (59.3 vs. 19.6%; $p < 0.001$). The median number of cells mobilized in the plerixafor arm was 5.69 × 10^6 CD34+ cells/kg versus 1.98 × 10^6 CD34+ cells/kg in the placebo arm, and the increase in CD34+ cells before and after intervention was 5-fold with plerixafor and 1.4-fold for placebo ($p < 0.001$). Treatment with plerixafor plus G-CSF did not have a deleterious effect on days to engraftment, durability of engraftment, or mortality in the 12 months after transplant. The second phase III trial [23] was similar in design to the first study but assessed patients with MM rather than NHL. The study group consisted of transplant-eligible MM patients in first or second complete or partial remission. 302 patients were randomized. The median number of cells mobilized (median 109 cells/μl vs. 33 cells/μl; $p < 0.001$) and the increase in collection on days 4 and 5 (pre and post intervention) were again significantly higher in the plerixafor arm compared to the placebo arm (4.8-fold vs. 1.7-fold; $p < 0.001$). Both groups had equivalent engraftment rates (99.3% with plerixafor and 100% with placebo) as well as time to neutrophil engraftment (11 days) and platelet engraftment (18 days). Overall survival at 12 months was the same.

In current clinical practice, the use of plerixafor is limited to difficult to mobilize patients. Data on the success of mobilization in these patient groups can be obtained from the compassionate use program (CUP) trials. In a paper by Duarte et al. [24], 56 patients from Spain and the UK, who were previous mobilization failures i.e. who mobilized less than 2 × 10^6 CD34+ cells/kg, were enrolled in a CUP. 75% of previous failures were successfully rescued using G-CSF plus plerixafor, and ultimately 35 patients (63%) underwent transplant with an average of 3.1 ± 1.2 (1.9–7.7) × 10^6 CD34+ cells/kg. Remarkably, 71% of patients met the secondary end point of collecting ≥10 × 10^6 CD34+ cells/kg.

In Germany, Hübel et al. [25] reported on 60 patients (a mix of previously failed mobilizations and predicted poor mobilizers) from 23 centers. In patients receiving 4 days of G-CSF prior to initiating plerixafor, NHL patients mobilized a median of 2.79 × 10^6 CD34+ cells/kg, MM patients a median of 4.47 × 10^6 CD34+ cells/kg, and Hodgkin's disease patients a median of 2.41 × 10^6 CD34+ cells/kg. All patients, irrespective of the underlying disease, needed a median of two apheresis treatments. Other compassionate reports have been similar: Calandra et al. [26] for example, reported that 66% of patients with NHL, MM, and Hodgkin's disease, who had previously failed to mobilize sufficient numbers of CD34+ cells with chemotherapy or cytokine therapy for transplant, could be successfully remobilized with plerixafor and G-CSF.

Additional to failed mobilizers and predicted poor mobilizers, the pre-emptive use of plerixafor may include slow mobilizers of difficult to mobilize patient groups such as myeloma patients pretreated the lenalidomide [27]. Current developments include intravenous mobilization with plerixafor combined with G-CSF in lymphoma patients [28] or combination of plerixafor, G-CSF, and rituximab for B-cell-reductive, chemotherapy-free mobilization in lymphoma [29].

Plerixafor is very well tolerated, and severe adverse effects are rare in the order of less than 2% and include hypotension/dizziness, and thrombocytopenia. The most common adverse effects in the phase III studies were gastrointestinal (especially diarrhea and nausea) and injection site erythema.

The effect of plerixafor plus G-CSF on tumor cell contamination has been investigated in NHL [22, 23] and MM patients [30]. Although the total number of patients examined overall was limited, there did not appear to be an increase in tumor cells in the apheresis product following plerixafor above that observed or expected with G-CSF. Thus, contamination of an apheresis product would be expected to be similar to that obtained by standard G-CSF mobilization.

Plerixafor + Chemotherapy

Even though the majority of the clinical trials of plerixafor mobilization focused on patients receiving G-CSF alone, it is clinically well recognized that the administration of chemotherapy, most often high-dose cyclophosphamide with or without other agents prior to growth factor, enhances CD34+ mobilization. The particular type of regimen used varies according to the primary diagnosis, but this strategy has often been utilized for patients who have already failed mobilization with G-CSF alone or who, due to a large tumor burden, may benefit from additional cytoreduction before transplant. The drawbacks of chemotherapy utilization are mainly related to the toxicities and complications derived from the use of chemotherapy itself as well as the increase in the duration and cost of the mobilization regimen. However, chemotherapy-based mobilization is widely used and for some transplant programs represents the standard of care. An important question is whether the addition of plerixafor to a chemotherapy + G-CSF regimen will further improve efficacy.

One feasibility study combining plerixafor and chemomobilization has been previously published [31]. In this study, 26 MM patients and 14 NHL patients received plerixafor, which resulted in an about 2-fold increase in collection yield after

plerixafor injection when compared to the collection on the previous day. However, based on blood CD34+ counts and yields, most of the patients in that trial were standard mobilizers or even good mobilizers. Recently, a small series of patients who mobilized poorly with chemomobilization and received plerixafor [32] suggested efficacy of this strategy. Also, a German study including chemomobilized patients receiving plerixafor and with a previous mobilization failure was published recently [25]. Reports suggest that this combination is effective. Using plerixafor along with chemomobilization is probably the most effective way to obtain maximal CD34+ cell doses. Secondly, use of chemomobilization helps to avoid excessive cryopreservation volumes for the apheresis product. If 3 blood volumes are processed per apheresis, the benefit of plerixafor to reduce the apheresis number can be maximized. An algorithm used by Douglas et al. [33] for the administration of plerixafor includes: whether the patient reached the anticipated mobilization day specific for each mobilization regimen, whether the total white blood cell (WBC) count is between 4 and 20 on the first plerixafor day, and whether the peripheral CD34+ count is below 15/μl in an afebrile patient. Jantunen et al. [34] found an algorithm of WBC > 10/nl and peripheral blood CD34+ counts ≤ 10/μl had a sensitivity of 0.97 and specificity of 1.00 to identify patients for plerixafor use, provided that all patients with a maximum peripheral blood CD34+ count of ≤10/μl would have needed plerixafor. An increasing number of studies is evaluating plerixafor administration in conjunction with chemomobilization, showing the acceptance of this approach [35, 36].

'Up-front' use of plerixafor is currently recommended in only one specific patient group, namely adult patients with dialysis-dependent renal failure. For this group of patients, international experience has shown plerixafor along with G-CSF to be highly effective with relatively low toxicity, and also to be simple to schedule around hemodialysis sessions [37]; whereas the alternative approaches of G-CSF alone or of chemomobilization both have the disadvantage of lower efficacy (especially G-CSF alone), and for chemomobilization also the higher toxicity and poorer predictability.

Plerixafor as a Single Mobilization Agent and in Combination with Novel Drugs

Due to lower numbers of CD34+ cells mobilized by plerixafor alone than G-CSF alone, the use of plerixafor alone for mobilization would appear limited to patients who are intolerant of G-CSF. In splenectomized subjects, plerixafor appears the mobilization agent of choice when compared to G-CSF as shown in a collective of thalassemia patients [38]. Recent experimental studies suggest that addition of a sphingosine 1 agonist to plerixafor can significantly increase HSC mobilization in an experimental setting [39]. Similarly, addition of a small molecule VLA-4 inhibitor to plerixafor can substantially increase mobilization [40]. Clinical data are eagerly awaited for these agents.

Resource Utilization and Patient Tolerance

Administration of plerixafor represents an incremental expense to the mobilization process which is relatively easy to measure. Potential associated cost reductions are more complex and, in some cases, more challenging to measure. Reduction in the number of apheresis sessions and associated charges to third party payers is easily measured, but the cost savings to collection and cryopreservation centers (with fixed salaries, space, and other costs as well as variable costs for supplies and disposables) is more difficult to pinpoint. Similarly, while it is clear that fewer patients will require remobilization and more will proceed to transplant, the impact of these outcomes on the overall costs of caring for these patients is more difficult to quantify when assessing the overall medicoeconomic impact of utilizing plerixafor. Higher cell doses may lead to more rapid platelet recovery leading to reduction in transfusion expenses, but these potential savings have yet to be formally demonstrated. Measurement of how addition of plerixafor thus impacts patient morbidity, treatment tolerance, time missed from work (and its associated cost to society), and patient satisfaction/sense of well-being is even more difficult. A number of investigators have attempted to address these challenging issues. Patient selection seems to be the most critical factor in rendering application of plerixafor cost-effective [41–45].

Allogeneic Stem Cell Transplantation

Plerixafor has been used in the allogeneic stem cell transplantation setting published by Devine et al. [46]. Specific challenges are a failure rate of 8% to mobilize sufficient CD34+ cells for transplantation in healthy donors receiving single-agent plerixafor. This rate needs to be lowered. The question has been raised as to whether plerixafor-mobilized CD34+ cells may be qualitatively different than their G-CSF-mobilized counterparts and whether, based on a higher representation of less mature CD34+ cells [30], fewer cells will be required for optimal engraftment. Alternatively, use of higher doses or other routes of plerixafor administration may prove more efficacious when the drug is used as a single agent. Studies have typically added plerixafor to G-CSF after a typical (4- to 5-day) period of G-CSF administration for mobilization. Studies in HLA-identical sibling donors showed that this approach is efficacious [47].

Immunologic endpoints also need to be assessed in studies of plerixafor mobilization. There was a 2-fold higher CD3+ and CD4+ cell content in the plerixafor-mobilized allografts in this trial. However, GVHD did not appear increased, raising the question as to whether lymphocytes exposed to plerixafor may also exhibit qualitative differences from those mobilized with G-CSF [48]. G-CSF treatment induces polarization of dendritic cells toward DC2; the higher T cell content

observed in G-CSF-mobilized grafts compared with bone marrow may be tempered by increased DC2 levels. Gene expression analysis of plerixafor-mobilized donor cells has revealed no evidence of T-cell polarization. Another possible explanation for the low incidence of GVHD was that G-CSF- and plerixafor-mobilized grafts may contain more Tregs, potentially offsetting higher CD3+ cell levels. Thus, absolute levels of different cell types may not sufficiently explain transplant outcomes. Further study into the cellular characteristics of grafts is warranted. Following transplantation, CD4+ lymphocyte recovery was consistent and rapid in the plerixafor and G-CSF group. Graft rejection, GVHD, rates of relapse (as a surrogate marker of graft-versus-leukemia effects), and immunologic reconstitution will be important endpoints in future allogeneic trials.

Conclusion

Several consistent observations have been generated in the clinical studies described [49, 50]: i) Plerixafor plus G-CSF is superior to G-CSF alone for the initial mobilization of patients with MM and NHL. ii) Plerixafor plus G-CSF appears to be equally or more efficacious than other regimens used as salvage for patients with MM and NHL, who have failed another mobilization approach. iii) As a consequence of the above activities, plerixafor may allow more MM and NHL patients to proceed to transplant than would be possible without this drug. iv) Patients with Hodgkin's lymphoma and solid tumors behave similarly to their NHL counterparts. v) Plerixafor has utility in chemotherapy-based mobilization, the optimal role and schedule for this agent in this setting has to be established for each regimen and in each center. vi) A small number of trials have addressed the question of whether addition of plerixafor results in mobilization of more circulating tumor cells at the time of stem cell collection. The limited data available do not currently increase concerns about tumor mobilization (other than acute myeloid leukemia) although more studies are needed to address this issue. vii) Plerixafor is also being explored as a mobilization agent in the allogeneic setting. viii) Beyond the scope of this review, plerixafor is being evaluated for use via the intravenous route. In conclusion, plerixafor is an efficacious, non-toxic drug. If cost was not an issue, it could be recommended for routine use in autologous blood stem cell transplantation. Medicoeconomic analyses will demonstrate for which patient groups, i.e. poor mobilizers, it is cost-effective to use this agent.

Disclosure Statement

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