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REVIEW

The Role of Plerixafor in the Management of Non-Hodgkin's Lymphoma and Hematopoietic Stem Cell Transplantation

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Abstract: Autologous hematopoietic stem cell transplantation (HSCT) is an established treatment for relapsed chemotherapy sensitive non-Hodgkin's lymphoma (NHL) and an important component of anti-myeloma therapy. Recovery of bone marrow function after autologous HSCT is dependant on the dose of infused hematopoietic stem cells (HSCs) after bone marrow ablation. Despite the use of chemotherapy and granulocyte colony-stimulating factor (G-CSF) based mobilization regimens, some patients are unable to mobilize adequate numbers of $CD34^+$ HSCs and cannot undergo potentially lifesaving autologous HSCT. Plerixafor (AMD3100 or Mozobil) is a newly licensed drug which is used with G-CSF to mobilize $CD34^+$ HSCs for autologous HSCT, reducing apheresis requirements, and the rate of primary mobilization failure. Plerixafor and G-CSF "rescue" protocols allow the successful mobilization of HSCs in patients that have failed standard G-CSF based mobilization protocols. Hematopoietic stem cell biology and the use of Plerixafor in the management of NHL are reviewed.

Keywords: Plerixafor, AMD3100, mozobil, stem cell, mobilization, lymphoma

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Introduction

Non-Hodgkin's lymphoma (NHL) is diagnosed in around 65,000 people, and causes around 20,000 deaths in the United States each year. NHL is classified into indolent subtypes of NHL, such as follicular lymphoma which is incurable but has a median survival of around 10 years, and aggressive subtypes of NHL such as Diffuse large B cell lymphoma (DLBCL) or Burkitt's lymphoma (BL) which can be cured in approximately 60% of patients, but have a 40%–50% 5 year mortality rate.

The standard first line treatment for the most common subtype of aggressive NHL, DLBCL is CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy in combination with Rituximab (R) for CD20 positive tumours,[1,2] and consolidation radiotherapy for residual post chemotherapy masses.[3] BL is treated with intensive chemotherapy regimens such as CODOXM/IVAC.[4] The International Non-Hodgkin's Lymphoma Prognostic Factors Project stratifies patients with DLBCL by age ≤60 years old versus >60 years old, serum lactate dehydrogenase, performance status, tumour stage, and extra-nodal site involvement to predict relapse free-survival and overall survival. Four risk groups are identified which predict five-year survival rates of 73%, 51%, 43%, and 26%.[3]

The standard treatment for recurrent aggressive NHL is myeloablative chemo-radiotherapy followed by HSCT.[5] The 5 year event-free survival of patients that undergo high dose chemotherapy and transplantation is around 46%.[6] As survival rates between autologous and allogeneic HSCT for NHL are similar,[7,8] the majority of patients with relapsed NHL undergo autologous HSCT which requires the successful mobilization of HSCs from the bone marrow (BM).

HSCT is also an accepted treatment for patients with chemotherapy resistant indolent NHL, and is commonly used for other haematological malignancies such as multiple myeloma (MM), and Hodgkin's Lymphoma (HL).[6,9,10]

Stem Cell Mobilization in Patients with NHL

The use of peripheral blood stem cells (PBSC) to reconstitute multilineage haematopoiesis after myeloablative conditioning and autologous transplantation was developed in the 1980s, and requires the mobilization and storage of HSCs for infusion after myeloablative chemo-radiotherapy. Stem cell mobilization is usually performed with granulocyte colony-stimulating factor (G-CSF) either alone or in combination with chemotherapy. A nucleated stem cell dose of around 2×10^8/kg is considered sufficient to support HSCT,[11] although doses of 1×10^8/kg have been successfully used.[12] Many centres combine HSCs mobilization with second line chemotherapy for DLBCL such as DHAP, (R)-ESHAP, and (R)-ICE[13] to assess chemotherapy sensitivity during mobilization, and to limit exposure to additional chemotherapy.

Despite the use of G-CSF, approximately 25%–30% of patients with haematological malignancies will fail to mobilize adequate PBSCs and therefore cannot receive potentially curative high-dose chemotherapy that requires PBSC support.[14,15] Failure to mobilize adequate PBSCs can double the costs of BM transplantation-related care.[16] Clinical factors such as patient age, mobilization technique, time to stem cell mobilization, number of prior therapies, prior lenalidomide, melphalan, fludarabine or radiation exposure, low grade indolent NHL, and BM involvement adversely affect the success of stem cell mobilization.[17,18] Plerixafor (AMD3100 or Mozobil®; Genzyme) is a newly licensed drug which is used with G-CSF to mobilize PBSC for autologous HSCT in patients with MM and NHL. The use of Plerixafor increases the chance of successful primary stem cell mobilization, and allows the 'rescue' of patients that fail standard mobilization protocols.

Hematopoietic Stem Cell Biology

The majority of $CD34^+$ HSCs are located within the BM and only make up 0.05% of peripherally circulating blood cells. Clinical observations of increased numbers of peripherally circulating HSCs during hematopoietic recovery after chemotherapy allowed the development of chemotherapy based mobilization protocols. The subsequent discovery of human G-CSF[19] and granulocyte-macrophage colony-stimulating factor (GM-CSF)[20] led to use of recombinant forms of these proteins in standardized protocols for mobilizing human $CD34^+$ stem cells for autologous HSCT.

Although the majority of the HSC compartment is located within the specialized niches of the endosteal and endothelial BM, normal host defense

and repair mechanisms require a constitutive steady state release of HSCs into the peripheral blood circulation. Physiological stresses such as tissue injury, inflammation, or artificial clinical treatments such as G-CSF and chemotherapy, induce massive proliferation of hematopoietic stem and progenitor cells in the BM. This increases the rate of progenitor cell egress into the circulation, a process termed mobilization. For autologous transplantation, PBSC are preferred over BM derived stem cells as their collection is less invasive, associated with reduced morbidity, faster engraftment, and better immune reconstitution.[21–23]

The mechanism of HSC mobilization from the BM to the peripheral circulation is poorly understood, but appears to be initiated following stress signals such as injury or inflammation, which activates neutrophils and osteoclasts. Administration of chemotherapy or G-CSF mimics these stress signals, primarily activating granulocytes that release proteolytic enzymes including elastase and various matrix metalloproteinases (MMPs). Cytokine and chemokine stimulation then disrupts the anchorage of hematopoietic progenitors to the BM stromal cells.

The release of HSCs into the peripheral circulation is tightly regulated by the stromal cell derived factor-1 (SDF-1)-CXCR4 axis which is highly conserved across species, and essential for normal stem cell trafficking within the BM microenvironment. SDF-1 was first discovered as a pre-B cell growth factor, secreted by the mouse MS5 BM stromal cell line. The major SDF-1 chemokine receptor is CXCR4, which is expressed by many cell types including neuronal, endothelial, epithelial, muscle, liver, hematopoietic, lymphoid, and myeloid cells.

Modulations in the interactions between the G-protein coupled chemokine receptor CXCR4 and SDF-1, also designated CXCL12[24] regulate homing and mobilization. CXCR4 is inactivated during $\alpha_4\beta_1$ integrin (VLA-4) and P/E selectin adhesion molecule degradation. Disruption of HSC stromal niche interactions then leads to detachment and entry of HSCs into the peripheral circulation. Other dynamic processes involved in HSC mobilization include ligand/integrin and cytokine receptor interactions such as VLA-4/VCAM-1, CD62L/PSGL, CD44/HA, and Kit/Kit ligand.

G-CSF administration decreases the expression of SDF-1 receptors on the BM stroma and induces significant down-regulation of SDF-1 mRNA in BM stromal cells.[25–28] The mechanisms that decrease SDF-1 receptor expression and disrupt the SDF-1/CXCR4 axis are unclear, although there is evidence that G-CSF treatment leads to proteolytical inactivation of CXCR4 by neutrophil elastase, MMP-9 and catepsin-G. However MMP-9 and catepsin-G deficient mice display normal stem cell mobilization after G-CSF treatments, suggesting a role for additional mechanisms.[29,30]

The Clinical Development of Plerixafor

Plerixafor (AMD3100) is a low molecular weight bicyclam which was initially developed as a potential drug to target the human immunodeficiency virus (HIV). Plerixafor inhibits HIV replication by binding to CXCR4, which is essential for HIV entry into $CD4^+$ T cells. The discovery of Plerixafor's (AMD3100) ability to mobilize HSCs has similarities to the discovery of phosphodiesterase 5 inhibitors for the treatment erectile dysfunction,[31] in that it's elevating effects on white blood cell counts were serendipitously observed during its evaluation as an HIV treatment.[32] In the BM, Plerixafor reversibly antagonizes the CXCR4 receptor, disrupting the interaction between CXCR4 on $CD34^+$ HSCs and SDF-1 on BM stromal cells. This blocks the chemotactic function of SDF-1,[33] displacing previously anchored $CD34^+$ HSCs, causing their release from the BM microenvironment into the peripheral blood (see Fig. 1).[23,34]

Plerixafor is also a potent and rapid mobilizer of endothelial progenitor and angiogenic cells.[35] In an animal model, Plerixafor mobilized multiple subtypes of $CD34^+$ cells including B cell, T cell, and mast cell precursors, whilst G-CSF-mobilized more neutrophil and mononuclear phagocyte $CD34^+$ precursors.[35,36] As G-CSF and Plerixafor have differing mechanisms of action, it was recognized early during the drug development process that combinations of both agents could act synergistically.[37]

During the first phase I study evaluation of Plerixafor (AMD-3100) as a potential HIV treatment, healthy human volunteers were given single intravenous infusions of Plerixafor at 10, 20, 40, or 80 µg/kg. Plerixafor was well tolerated without any Grade II or above side effects. During the study, unexpected reversible dose dependant increases in white blood cells counts were observed in the study participants.[32]

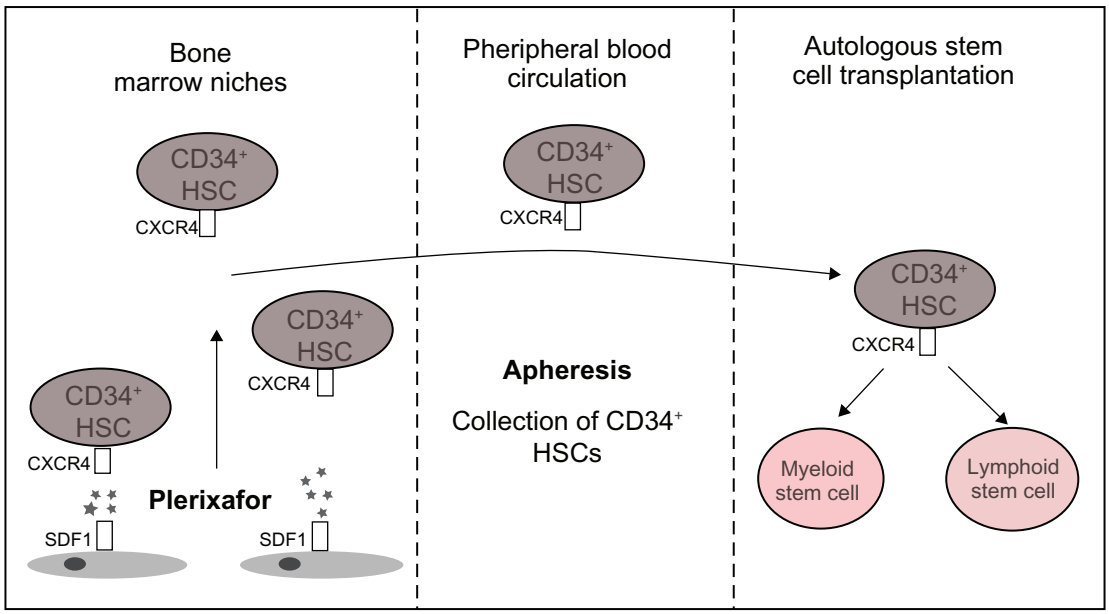

Figure 1. The use of Plerixafor in HSCT mobilization.

A subsequent phase I study was initiated to evaluate the safety and efficacy of Plerixafor in the mobilization of hematopoietic progenitor cells. Twenty-six healthy human volunteers aged between 24 and 33 years old received either a single 80 µg/kg subcutaneous (SC) injection of Plerixafor, or increasing doses of SC Plerixafor (range 40 to 240 µg/kg), or 3 consecutive days of 80 µg/kg of SC Plerixafor. Single and increasing doses of Plerixafor (80 to 240 µg/kg) resulted in a dose dependant increase in neutrophils, lymphocytes, monocytes, eosinophils, basophils, circulating $CD34^+$ stem cells, and a 6 to 10 fold increase in circulating myeloid and erythroid colony forming units. The effects were maximal at 6 hours after Plerixafor administration. Importantly serial administration of 80 µg/kg of Plerixafor produced similarly sustained daily increases in circulating $CD34^+$ stem cells, suggesting that Plerixafor could be used to boost circulating HSC numbers during apheresis.

A phase I study assessed the safety and clinical efficacy of Plerixafor in patients with multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). The patients with NHL (6) and MM (7) were potential candidates for autologous HSCT and had not received chemotherapy for at least 4 weeks. The patients received single doses of Plerixafor at 160 µg/kg (6 patients) or 240 µg/kg (7 patients) and were monitored for changes in white blood cell count (WBC) and drug side effects. Plerixafor administration resulted in a statistically significant increase in total WBC and total numbers of circulating $CD34^+$ stem cells. The effects were maximal at the 240 µg/kg dose and similar between the groups with MM and NHL. The reported side effects were mild (grade I) and unrelated to drug dose.[22]

The efficacy of Plerixafor in combination with G-CSF for the clinical mobilization of stem cells for use in HSCT was initially evaluated in a phase II study of 25 patients with NHL (10/25) and MM (15/25).[37] The primary study endpoint was to determine if the addition of Plerixafor to G-CSF mobilized more $CD34^+$ cells than G-CSF alone. The secondary endpoint was to determine if the addition of Plerixafor to G-CSF reduced the number of apheresis sessions for the collection of 5×10^6 $CD34^+$ cells/kg. The patients were treated with either daily G-CSF 10 µg/kg/day SC for 8 days or with G-CSF 10 µg/kg/day SC for 4 days, and Plerixafor 160 µ/kg/day SC for up to 8 days until the collection of at least 5×10^6 $CD34^+$ cells/kg HSCs.

The trial protocol was amended to include a higher dose of Plerixafor after an interim study in healthy volunteers found that the maximum increase in circulating $CD34^+$ cells was 9 hours after 240 µg/kg of SC Plerixafor.[38] Around 90% of the trial patients underwent successful autologous transplantation after treatment with Plerixafor and G-CSF, and the trial provided the first evidence that the combination of the Plerixafor

with G-CSF was superior to G-CSF alone for HSC mobilization for autologous transplantation.[37]

The role of Plerixafor in the treatment of NHL was established by a landmark phase 3 multicenter, randomized, double-blinded, placebo-controlled trial (Study 3101) in which 298 patients with NHL were randomized (1:1) between mobilization with G-CSF (10 μg/kg/day) with or without Plerixafor 240 μg/kg.[39] The trial patients were candidates for autologous HSCT, with either a complete or partial response to first or second line chemotherapy, had minimal co-morbidities, and an eastern Cooperative Oncology Group performance status of 0 or 1. Patients with a high risk of treatment related complications were ineligible for the trial. Apheresis was started on day 5 and continued until the collection of $\geq 5 \times 10^6$ $CD34^+$ cells/kg. Patients underwent autologous HSCT within 5 weeks of the last HSCT collection and were treated according to local guidelines.

A total 150 patients received Plerixafor and 148 received placebo in combination with G-CSF. The addition of Plerixafor to G-CSF mobilized $\geq 5 \times 10^6$ $CD34^+$ HSCs/kg in ≤ 4 apheresis days in 59% of patients whereas only 19.6% of the placebo treated patients mobilized $\geq 5 \times 10^6$ $CD34^+$ HSCs/kg. Apheresis requirements were significantly reduced in the Plerixafor treated group where 87% of patients collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg in ≤ 4 apheresis days, when compared to only 47% of patients in the placebo group.

The differences between the efficacy of the Plerixafor and placebo mobilization schedules was reflected in the rate of successful transplantation and engraftment. Ninety percent of the Plerixafor treated patients underwent HSCT after initial mobilization, and received a median of 5.41×10^6 cells/kg (range, 1.95 to 17.6×10^6 cells/kg) of $CD34^+$ HSCs. Whereas only 54% of placebo treated patients underwent HSCT after initial mobilization, receiving a median of 3.85×10^6 cells/kg of $CD34^+$ HSCs (range, 1.98 to 8.74×10^6 cells/kg; $P < .001$). There were no significant differences in platelet or neutrophil engraftment, or in overall survival at 12 months between the Plerixafor and placebo treated groups (88 vs. 87%) that underwent HSCT.

Importantly for routine clinical practice, the trial allowed patients on both study arms that failed to collect $\geq 0.8 \times 10^6$ $CD34^+$ cells/kg after 2 apheresis days or $\geq 2 \times 10^6$ $CD34^+$ cells/kg in ≤ 4 apheresis days, to cross over onto an open-label rescue protocol. The rescue protocol consisted of a 7 day rest period, followed by 4 days of G-CSF (10 μg/kg/day), then 4 days of G-CSF with Plerixafor 240 μg/kg, and up to 4 days of apheresis. The rescue protocol was highly successful and 62 of the 68 (91%) patients successful mobilized $\geq 2 \times 10^6$ $CD34^+$ cells/kg. Overall, 61% of the patients that failed standard G-CSF mobilization and 40% of Plerixafor treated patients were able to successfully mobilize with this protocol. Plerixafor was well tolerated across all patient groups and side effects were mild.[39]

The Use of Plerixafor in Routine Clinical Practice

The recommended dose of Plerixafor in adults is 240 μg/kg SC daily at 6 to 11 hours before the initiation of apheresis for a maximum of 7 days. The dose of Plerixafor should be reduced to 160 μg/kg daily if the patient has a reduced creatinine clearance (20–50 mL/minute). There is no guideline for dosing patients with a creatinine clearance of less than 20 mL/minute. The use of Plerixafor should be avoided in pregnancy as it has been shown to be teratogenic in animal studies. The side effects of Plerixafor administration are transient and mild and include erythema and stinging at injection sites (29% of patients), perioral paresthesias (10% of patients), nausea (17% of patients), and mild gastrointestinal disturbance such as diarrhoea (38% of patients).[39]

Plerixafor based mobilization in patients with leukemia should be avoided as it may mobilize leukemic

Table 1. The side effects of Plerixafor administration.

Common
Gastrointestinal disturbances
Dry mouth
Oral hypoaesthesia
Dizziness
Headache
Insomnia
Fatigue
Arthralgias
Musculoskeletal pain
Sweating
Injection-site reactions
Less common
Hypersensitivity reactions (dyspnoea and periorbital swelling)

cells which could contaminate the apheresis product.[40] A study of stem cell collections in patients with NHL and MM used quantitative DNA amplification to assess the frequency of tumor cells in the peripheral blood of patients after G-CSF, and Plerixafor with G-CSF mobilization. The study found that Plerixafor did not increase MM tumor cell mobilization and contamination within the apheresis product.[41] In order to fully address these concerns, long-term five year follow-up studies are being conducted (see Table 2)

Table 2. Current clinical trials of Plerixafor in patients with non-Hodgkin's Lymphoma (www.clinicaltrials.gov).

Clinical trials.gov identifier	Condition	Aim	Status
NCT00733824	Lymphoma	To evaluate the safety and efficacy of AMD3100 in combination with a standard G-CSF mobilization regimen in patients undergoing autologous HSCT.	Recruiting
NCT01149863	Lymphoma and myeloma	To evaluate if Plerixafor can be given at 17 hours instead of 11 hours before apheresis.	Recruiting
NCT01097057	Lymphoma	To assess the combination of rituximab, chemotherapy, G-CSF, and Plerixafor in patients with NHL undergoing mobilization of autologous PBMCs	Recruiting
NCT00901225	Multiple myeloma non-Hodgkin's lymphoma Hodgkin's disease	To evaluate the use of Plerixafor as a rescue for poor mobilizers in autologous HSCT	Recruiting
NCT01186224	Multiple myeloma plasma cell dyscrasia lymphoma lymphoproliferative disorders	To evaluate the use of Plerixafor harvesting without chemotherapy for autologous HSCT	Recruiting
NCT00741780	Patients with NHL who received Plerixafor or placebo in the AMD3100-3102 study	The long-term follow-up of patients with non-Hodgkin's lymphoma who received Plerixafor or placebo in the AMD3100-3102 study	Recruiting
NCT01158118	Leukemia, myeloid, acute myelodysplastic syndromes lymphoma, non-Hodgkin Hodgkin disease leukemia, lymphocytic, chronic, B-cell multiple myeloma	To evaluate the use of Plerixafor and sargramostim (GM-CSF) for mobilization of allogeneic sibling donors	This study is not yet open for participant recruitment
NCT01164345	Non-Hodgkin's lymphoma Hodgkin's lymphoma	To evaluate Plerixafor plus recombinant human G-CSF efficiency in mobilizing sufficient numbers of stem cells from lymphoma (NHL and HL) patients for autologous transplantation	Recruiting
NCT01076270	NHL, leukemia, HD	To evaluate Plerixafor and G-CSF for mobilization of donor PBSCs in the treatment of patients with hematological malignancies	Recruiting
NCT01164475	Non-Hodgkin's lymphoma	To evaluation weight-based dose compared to fixed dose of Plerixafor in patients with NHL weighing less than 70 kg	Not yet open for recruitment
NCT01095757	Myeloma lymphoma	To evaluation Plerixafor in combination with chemotherapy and G-CSF for stem cell collection	Recruiting

which will monitor the relapse rates, progression-free survival, and overall survival of patients treated within phase III trials.

Activity in Poor Mobilizers

Recent data from the Plerixafor European union (EU) compassionate use programme has provided additional evidence of the tolerability and effectiveness of Plerixafor in enhancing stem cell mobilization in patients that fail standard mobilization protocols. A total of 56 patients, with an average age of 60 years old (range 33 to 69), with myeloma (32/56) and lymphoma (24/56) were included in the programme. The patients had received an average of 2 previous lines of chemotherapy (range 1 to 10) and previously failed a total of 73 mobilization attempts with G-CSF (28), chemotherapy plus G-CSF (43), and G-CSF plus stem cell factor (2). The majority (75%) collected 3.0 ± 1.7 (range 0.4–10.6) $CD34^+$ cells per kg with Plerixafor plus G-CSF without any severe adverse events. In total, 63% of the patients within the open access programme were able to undergo autologous transplantation.[42]

Results from a similar open access programme in which Plerixafor was administered with G-CSF showed that Plerixafor allows the mobilization of $CD34^+$ cells in patients with NHL, MM, and Hodgkin's disease (HD) that have previously failed mobilization with chemotherapy and/or cytokine treatments.[43] Mobilization rates were similar across all groups and were 60% for patients with NHL, 71% for patients with MM, and 76% for patients with HD. No serious adverse events were reported and side effects were mild.

The Benefits of Prescribing Plerixafor for Healthcare Providers

In the face of increasing drug expenditure, comparative economic comparisons are increasingly being used to evaluate the use of new medications to inform healthcare resource allocation or rationing decisions. Such measures are widely used by the United Kingdom's National Heath Service, and are increasingly being adopted across Europe. In the autotransplant setting, costs associated with the mobilization include the mobilizing agents (Plerixafor, G-CSF, chemotherapy drugs, antiemetics, antimicrobials), apheresis costs, and healthcare provider costs.

So far there has only been one published cost-effectiveness analysis of autologous HSC mobilization with G-CSF and Plerixafor compared to G-CSF and cyclophosphamide.[44] In the analysis, Shaughnessy et al performed a retrospective review of patients that had participated in the Expanded Access Program and been mobilized with G-CSF plus Plerixafor. Outcomes were compared to matched historic controls that had been mobilized with G-CSF and chemotherapy.

The patients were matched for age, sex, disease, disease stage, and number of prior therapies. Mobilization costs were divided between treatment phases (preapheresis and periapheresis) and defined to be the costs of medical procedures, hospitalization, provider visits, and medications. Preapheresis costs included chemotherapy associated costs (chemotherapy, catheter insertion, catheter removal), G-CSF or Plerixafor associated costs, healthcare provider visits, hospitalization, transfusion related, and routine lab monitoring.

Periapheresis costs included apheresis and related materials, as well as flow cytometry and immunohistochemistry costs. No difference was found in the median number of apheresis days or the number of $CD34^+$ cells collected between the groups. All patients proceeded to HSCT with no difference in engraftment outcomes. Of note, the Plerixafor/G-CSF mobilization protocol resulted in more predictable collection days, and no patients required weekend apheresis. The authors conclude that the median total cost of mobilization was similar between the Plerixafor/G-CSF and control groups.[44] Although the analysis did not consider some of the additional logistical benefits of Plerixafor use, such as a more predictable start to apheresis, and reduced weekend apheresis requirements.

To help guide the clinical use of Plerixafor, Costa et al have developed a data generated decision-making algorithm for use as a potential cost-saving tool. The algorithm uses the peripheral blood $CD34^+$ count on day 4 of G-CSF administration, and the collection target $CD34^+$ count to decide between continuing with G-CSF alone or adding Plerixafor during HSC mobilization.[45] The algorithm was validated in a cohort of 34 patients undergoing HSC mobilization, and found that the use of both G-CSF and Plerixafor was most cost-effective in patients with a low peripheral blood $CD34^+$ count on the fourth day of G-CSF administration.

Another equally, if not more important issue in the HSCT setting is the quality of life of the patients

during the procedures. Although formal quality of life surveys were not done during the evaluation of the efficacy and safety of Plerixafor, patients that are mobilized with chemotherapy plus G-CSF, are much more likely to be hospitalized for safe chemotherapy administration or neutropenic fever when compared to those mobilized with Plerixafor.[44] For most patients, Plerixafor use decreases the number of apheresis procedures needed to reach the target $CD34^+$ count, reducing time spent in hospital.[46]

Regulatory Approval for the Use of Plerixafor in Patients with NHL

The US Food and Drug Administration (FDA) approved Plerixafor (Mozobil®; Genzyme) on December 15th 2008 for use in combination with G-CSF to mobilize HSCs to the peripheral blood for collection and subsequent autologous transplantation in patients with NHL and MM. The European Medicines Agency subsequently granted Plerixafor orphan drug status for the mobilization of progenitor cells prior to stem cell transplantation and marketing approval in 2009.

The Plerixafor FDA application consisted of one efficacy and one safety database. Demonstration of clinical efficacy was based on two multi-centre, randomized, placebo-controlled trials of Plerixafor in patients with NHL and MM (Studies 3101[37] and 3102[39]) who were eligible for autologous HSCT and supportive data from two open-label studies in patients with NHL, MM and Hodgkin's disease (Studies 2101, 2106).

The FDA considered that the primary end points of the 2 randomized trials to represent a clinical benefit because the target $CD34^+$ cell doses selected ($\geq 5 \times 10^6$ $CD34^+$ cells/kg in patients with NHL and $\geq 6 \times 10^6$ $CD34^+$ cells/kg in patients with MM) are estimated to be optimal for engraftment.[47,48] Clinical safety data these studies and an additional 8 further studies in various patient populations was also included within the submission.[49]

The FDA and European Medicines Agency have recommended that Plerixafor be administered after patient has received filgrastim 10 mcg/kg once daily for 4 days. The drug should be administered subcutaneously at a dose of 240 μg/kg once daily (maximum dose: 40 mg/day), at 11 hours prior to apheresis. Plerixafor, filgrastim and apheresis should be continued daily until sufficient cells have been collected for a maximum of 4 days.

Other Roles for Plerixafor

MM is the most common indication for high dose chemotherapy with autologous stem cell rescue in North America.[50] Plerixafor has been used for stem cell collection in MM patients with encouraging results. A phase III randomized double-blind trial evaluated the addition of Plerixafor to G-CSF in patients undergoing autologous transplantation for MM. All patients were treated with G-CSF (10 mcg/kg) SC for 3 days, and received either Plerixafor (240 mcg/kg) SC or placebo daily from day 4 onwards.

Apheresis was started at day 5 and continued until the primary endpoint of the collection of 6×10^6 $CD34^+$ cells/kg or over had been met. The results were impressive with 71% (106/148) of patients within the Plerixafor group meeting the primary endpoint, when compared to only 34% (53/154) of the patients within the placebo group. Importantly 54% of the Plerixafor treated patients collected sufficient $CD34^+$ cells from a single apheresis, whereas 56% of the placebo group required four apheresis.[39]

Although Plerixafor has been approved for use in combination with G-CSF, Flomberg et al recently examined the safety and efficacy of Plerixafor as a single agent for the mobilization of HSC in patients with MM. Plerixafor (240 μg/kg) was administered subcutaneously and apheresis initiated at 6 hours after injection. The study was terminated early, as although all patients mobilized sufficient HSCs for at least one transplant, insufficient cells were mobilized for use in tandem transplantation.[51]

Although there now is an established role for autologous HSCT in NHL, the routine use of Plerixafor in MM is still uncertain, and is being explored by an expert committee at the International Myeloma Foundation. The committee have acknowledged the potential benefits of Plerixafor such as improved collection predictability, reduction of HSCT associated costs due to less apheresis procedures, and improved $CD34^+$ yields, which allow the use of HSCT as a salvage treatment in hard to mobilize patients. Although Plerixafor has been considered effective and safe, the committee have recognized the need for further

studies which incorporate pharmacoeconomic and resource utilization endpoints to clearly define the role of Plerixafor in the treatment of MM.[50]

Conclusions

The development of Plerixafor marks a highly significant milestone in the development of autologous stem cell transplantation. Plerixafor allows the salvage of mobilization resistant patients with NHL, who would otherwise have been denied potentially lifesaving medical treatment, and reduces apheresis requirements. Some important outstanding clinical questions remain, such as can Plerixafor be given at 17 hours rather than at 11 hours before apheresis and what is the the role of Plerixafor in mobilizing stem cells from allogeneic donors. Ongoing clinical trials will address these issues and further research will determine the optimal schedule and use of Plerixafor in patients that require HSCT.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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