# The Use of Plerixafor for Peripheral Blood Stem Cell Mobilisation Reduces the Frequency of Mobilisation Failure in Patients Planned to Undergo Autologous Transplantation

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## Abstract

High-dose chemotherapy with or without radiation followed by autologous haematopoietic stem cell transplantation (auto-HSCT) is now the standard of care for patients with chemosensitive relapsed aggressive non-Hodgkin's lymphoma (NHL), chemosensitive relapsed Hodgkin's disease (HD) and multiple myeloma (MM). Autologous haematopoietic stem cells also provide haematopoietic support after the administration of high-dose chemotherapy in relapsed NHL and MM. However, certain patients fail to mobilise a sufficient number of haematopoietic stem cells using standard cytokine-assisted mobilisation strategies. Recently, plerixafor, a novel bicyclam capable of specifically and reversibly binding to the CXCR4 receptor on haematopoietic stem cells, has been granted European approval, in combination with granulocyte colony-stimulating factor, for the enhancement of haematopoietic stem cell mobilisation to the peripheral blood for collection and subsequent autotransplantation in poorly mobilising lymphoma and MM patients. In this article the authors present their initial experience with plerixafor in a case series at their own institutions in Scandinavia.

## Keywords

Autologous, stem cell, mobilisation, granulocyte colony-stimulating factor (G-CSF), autologous stem cell transplantation (auto-SCT), peripheral blood stem cells (PBSCs), chemotherapy, plerixafor

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Autologous haematopoietic stem cell transplantation (auto-HSCT) has been used successfully in certain forms of haematological cancer and is now the standard of care for relapsed non-Hodgkin's lymphoma (NHL) and for subgroups of patients with multiple myeloma (MM).[1–3] Auto-HSCT also provides haematopoietic support after the administration of high-dose chemotherapy in relapsed NHL and MM. Several clinical trials comparing conventional chemotherapy with high-dose chemotherapy and auto-HSCT have shown improved outcomes in patients who received auto-HSCT.[4–6] While bone-marrow-derived cells were originally the main source of stem cells in autologous transplants, they have largely been replaced by peripheral blood stem cells (PBSCs). Clinical trials have demonstrated that PBSCs offer several advantages over bone-marrow-derived cells, such as more rapid engraftment, faster recovery times and reduced need for transfusion support.[7–10] However, circulating levels of haematopoietic stem cells, as measured by the surrogate marker CD34+, which is expressed on haematopoietic stem and progenitor cells, are relativity low. Early investigations showed that stem cells could be harvested from the peripheral blood during the recovery phase after myelosuppressive chemotherapy[11] and that cytokines, such as granulocyte colony-stimulating factor (G-CSF; filgrastim) and granulocyte macrophage colony-stimulating factor (GM-CSF; sargramostim) could improve stem cell mobilisation.[12] G-CSF promotes the proliferation and differentiation of HSC[13] while promoting the release of enzymes that prevent these cells from attaching to the bone marrow stroma.[14] These discoveries led to the use of recombinant cytokines in mobilisation regimens, either alone or following chemotherapy, to enhance PBSC collection by apheresis. This review will discuss current approaches, issues and developments in reducing failure to collect sufficient PBSCs in auto-HSCT in NHL and MM. The authors also present their initial experience in a case series of patients treated at their own institutions in Scandinavia with plerixafor, a new agent for stem cell mobilisation.

## Current Haematopoietic Stem Cell Mobilisation Strategies

The number of harvested PBSCs is determined by several factors, including disease status, prior treatment, patient age, gender and previous mobilisation attempts.[15–17] The efficiency of stem cell mobilisation and collection is of primary importance since it has a major influence on the success of the auto-HSCT.[18,19] Studies suggest that for successful haematopoietic recovery and sustained engraftment a minimum infusion of ≥2.0x10$^6$ CD34+ cells/kg bodyweight is required.[14,20,21] Furthermore, mobilisation and infusions ≥5x10$^6$ CD34+ cells/kg bodyweight are associated with more rapid platelet recovery and overall survival.[22–25]

Unfortunately, for some patients, the current mobilisation regimens are associated with mobilisation failure rates of up to 30%.[26–30] Unsuccessful initial stem cell mobilisation can increase costs due to

further mobilisation attempts and, more importantly, may adversely affect outcome.[17,31–33] A general hindrance is the current lack of a defined optimal strategy to mobilise stem cells for peripheral collection, which can result in inadequate and variable yields. Moreover, there is still insufficient evidence with regard to which of the two most commonly used mobilisation strategies – cytokines plus chemotherapy or cytokines alone – is the most effective, although the former schedule has been shown to improve collection rates.[15] Defining and identifying poor mobilisers and non-mobilisers will also help to optimise patient care. Currently, many studies define poor mobilisers as patients with collection <2.0x10$^6$ CD34$^+$ cells/kg bodyweight following three to five days of leukapheresis, while the definition of non-mobilisers is less well defined.[31,34,35]

Current mobilisation strategies present significant challenges and unmet clinical needs. While the use of recombinant cytokines in the form of G-CSF or GM-CSF alone or in combination with chemotherapy substantially increases PBSC count, many patients still fail to mobilise sufficient yields of PSBCs to ensure successful engraftment. Moreover, the different chemotherapy-based schedules have resulted in variable yields[15,26,36–38] and are associated with significant toxicity.

Many transplant centres in Scandinavia use a combination of chemotherapy and G-CSF for peripheral blood progenitor stem cell (PBPC) mobilisation of myeloma and lymphoma patients. The advantage of this approach is that PBPCs are collected as part of the induction chemotherapy treatment before high-dose therapy; the disadvantage is the unpredictability of the expected day of PBPC collection, which needs to be planned in close collaboration between clinical departments. As listed in *Table 1*, the different chemotherapy/G-CSF regimens have different time-points with regard to both when to start the mobilisation and on which day to collect PBPCs.

More recently, the role of new mobilising agents has been evaluated. Plerixafor (Mozobil®, Genzyme), an antagonist of CXCR4, was approved for use in combination with G-CSF to enhance mobilisation of HSCs to the peripheral circulation for collection and subsequent auto-HSCT in patients with lymphoma and MM whose cells mobilise poorly.

## The Burden of Haematopoietic Stem Cell Mobilisation Failure

To obtain rapid and sustained tri-lineage engraftment after high-dose therapy, a minimal level of 2x10$^6$ CD34$^+$ cells/kg is desirable; infusion of more than 5x10$^6$ CD34$^+$ cells/kg further accelerates platelet engraftment.[15,39] We have previously demonstrated the mobilisation of sufficient numbers of CD34$^+$ cells to allow high-dose therapy in more than 80% of patients with malignant lymphoma.[40,41] However, in approximately 20% of patients insufficient numbers of CD34$^+$ cells are harvested in spite of three to five consecutive days of leukapheresis. These patients, considered poor mobilisers, will either receive further remobilisation attempts or will be excluded from high-dose therapy, even though it can be curative.

Most investigators have remobilised patients with G-CSF. Patients who fail initial mobilisation require a treatment-free interval of four to six weeks until a second attempt can be performed. In lymphoma patients such a chemotherapy-treatment-free period could increase the risk of relapse or progression of the disease, and thus exclude the patient from further high-dose therapy with autologous stem cell support. This could, in the worst case, imply that the disease is no longer curable. Thus, avoiding a treatment-free period could be of great benefit for these patients.

**Table 1: Chemotherapy Regimens, Start of Granulocyte Colony-stimulating Factor and Optimal Day for Start of Apheresis Used at the Authors' Treatment Centres**

| Chemotherapy Type | Weekday Chemotherapy Started (Day 1) | Day G-CSF Started | Day Apheresis Started |
|---|---|---|---|
| Cyclophosphamide | Saturday | Day 5 | Day 11 |
| (M)IME | Friday | Day 7 | Day 12 |
| CHOEP | Friday | Day 7 | Day 12 |
| IGEV | Friday | Day 6/7 | Day 12 |
| VIP | Thursday | Day 6 | Day 13/14 |
| IKE | Thursday | Day 5 | Day 13 |
| Ara-C | Wednesday | Day 5 | Day 14 |
| DHAP | Wednesday | Day 4 | Day 14 |
| Cyclo/Eto | Wednesday | Day 6 | Day 15 |
| RAT regimen | Tuesday | Day 7 | Day 15 |
| Block C | Tuesday | Day 7 | Day 15 |

*Ara-C = 1-α-arabinofuranosylcytosine; Block C = cytarabine, etoposide, eldisine; CHOEP = cyclophosphamide/adriamycin/vincristin/etoposide/prednisolon; Cyclo/Eto = cyclophosphamide/etoposide; DHAP = high-dose Ara-C and dexamethasone; IGEV = ifosfamide, gemcitabine, vinorelbine; IKE = iphosphamide, metyl-gag, etoposide; (M)IME = methyl-gag, Ifosfamide, methotrexate and etoposide; RAT = daunorubicin, cytarabin, tioguanin; VIP = vinblastine/ifosfamide/cisplatin.*

## Clinical Data for the Safety and Efficacy of Plerixafor, a Novel Haematopoietic Stem Cell Mobiliser

The chemokine ligand stromal-cell-derived factor (SDF-1) found on osteoblasts and bone marrow endothelium is capable of binding to the CXCR4 chemokine receptor on haematopoietic progenitor cells, and this interaction retains HSCs such that they are no longer available for apheresis.[14,42] Plerixafor is a symmetrical bicyclam capable of specifically and reversibly binding to the CXCR4 receptor on HSCs.[43–45] As a result, plerixafor is a competitive inhibitor of SDF-1 and impedes the CXCR4/SDF-1 interaction, thus enhancing HSC mobilisation. Pre-clinical studies found that plerixafor is poorly absorbed when administered orally;[46] thus, it is currently given subcutaneously at a dose of 0.24mg/kg bodyweight/day. Plerixafor is primarily excreted unchanged through the renal route;[46] as a result, the clearance rate of this drug depends on renal function and thus decreases in patients with renal impairment, in whom dose reductions may be required.

### Clinical Evidence for Plerixafor

Plerixafor has been evaluated both alone and in combination with G-CSF in patients with NHL and MM. The pre-clinical and clinical development programme for plerixafor is summarised in *Table 2*.

NHL and MM patients had a seven-fold increase in circulating CD34$^+$ cells six hours after a single dose of plerixafor at a concentration of 0.24mg/kg.[47] Another trial illustrated that plerixafor (0.16–0.24µg/kg) added to G-CSF on day four, six to 12 hours before apheresis, mobilised more CD34$^+$ cells per leukapheresis than G-CSF alone.[48]

The study by Stiff et al.[25] recruited a set of heavily pre-treated patients who constituted a population that historically have a high

**Table 2: Pre-clinical and Clinical Development of Plerixafor**

| Reference/Clinical Trial Number | Study Topic | Trial Phase/ Status |
|---|---|---|
| Burroughs et al.[58] | Plerixafor mobilisation of PBSCs in a canine model | Pre-clinical |
| Larochelle et al.[59] | Plerixafor mobilisation of HSCs and long-term repopulating capacity in non-human primates | Pre-clinical |
| Broxmeyer et al.[60] | Evaluation in murine and human systems for mobilising capacity, alone and in combination with G-CSF | Pre-clinical |
| Liles et al.[61] | Plerixafor mobilisation of HPCs from marrow to peripheral blood in healthy human volunteers | Initial clinical |
| Liles et al.[52] | Administration of plerixafor alone and in combination with a standard 5-day G-CSF regimen in healthy volunteers | Phase I |
| Devine et al.[47] | Assessment of safety and clinical effects of plerixafor in MM and NHL | Phase I |
| Flomenberg et al.[48] | Evaluation of plerixafor plus G-CSF compared with G-CSF alone in mobilising HPCs and engraftment | Stem cell collection trial |
| Stiff et al.[25] | Efficacy and toxicity of combining G-CSF with plerixafor to mobilise stem cells in NHL and MM | |
| Fowler et al.[49] | Combined use of plerixafor and G-CSF in patients previously failing to mobilise sufficient PBSCs | |
| Cashen et al.[62] | Efficacy and safety of HSC mobilisation with plerixafor in Hodgkin's lymphoma | Phase II |
| Calandra et al.[35] | Plerixafor plus G-CSF mobilisation of CD34+ cells in NHL, Hodgkin's disease and MM patients previously failing mobilisation | Compassionate use protocol |
| DiPersio et al.[50] | Safety and efficacy of plerixafor in mobilising HSCs for ASCT in NHL patients. | Phase III |
| DiPersio et al.[51] | Safety and efficacy of plerixafor with G-CSF in mobilising HSCs in patients with MM | Phase III |
| NCT00103662[63,51] | Mobilisation of stem cells with plerixafor in MM patients | Completed |
| NCT00241358[64,65] | Plerixafor for transplantation of sibling donor stem cells | Active, not recruiting |
| NCT00665314[66] | Addition of plerixafor to a G-CSF mobilisation regimen in NHL and MM | Completed |
| NCT00901225[67] | Rescue of poor mobilisers in auto-HSCT | Recruiting |
| NCT00903968[68] | Combination plerixafor and bortezomib in MM | Recruiting |
| NCT00822770[69] | Plerixafor and G-CSF with busulfan, fluarabine and thymoglobin | Recruiting |
| NCT00838357[70] | Plerixafor as a front-line mobilisation agent in combination with G-CSF in NHL or MM | Recruiting |
| NCT00733824[71] | Intravenous plerixafor for collection of autologous peripheral blood stem cells in NHL patients | Recruiting |
| NCT00741325[72] | Long-term follow-up for NHL patients from 3101 trial | Enrolling by invitation |
| NCT00741780[73] | Long-term follow-up for NHL patients from 3102 trial | Enrolling by invitation |

*ASCT = autologous stem cell transplant; G-CSF = granulocyte colony-stimulating factor; HPCs = haematopoietic progenitor cells; HSCs = haematopoietic stem cells; NHL = non-Hodgkin's lymphoma; PBSCs = peripheral blood stem cell; MM = multiple myeloma.*

risk of mobilisation failure with standard cytokine regimens. The results showed that all 49 NHL and MM patients mobilised with G-CSF plus plerixafor completed mobilisation and 47 of these patients (96%) proceeded with transplantation; CD34+ cells in the circulation increased by 2.5-fold after just one dose of plerixafor. A further study[49] found that 17 of 20 patients who had previously failed to reach sufficient mobilisation of HSCs achieved successful CD34+ cell mobilisation after one apheresis procedure when treated with the combination of plerixafor and G-CSF. Two pivotal phase III trials of plerixafor were conducted in NHL[50] and MM[51] patients. The first study evaluated the safety and efficacy of plerixafor in mobilising HSCs for auto-HSCT of NHL patients and the second study evaluated the safety and efficacy of G-CSF plus plerixafor in mobilising HSCs in MM patients compared with G-CSF plus placebo. Finally, the compassionate use protocol designed to assess the effects of plerixafor in patients who had failed prior mobilisation attempts showed consistent results in rates of successful CD34+ cell remobilisation.[35]

## Plerixafor in Non-Hodgkin's Lymphoma

In a phase III multicentre, randomised, double-blind, placebo-controlled study, 298 NHL patients needing auto-HSCT received 10µg/kg G-CSF subcutaneously daily for up to eight days. On the evening of day four and for up to four days thereafter, patients were given daily injections of 0.24mg/kg of plerixafor (n=150) or placebo (n=148) subcutaneously. Beginning on day five, patients started daily apheresis for up to four days or until ≥5x10$^6$ CD34+ cells/kg were collected. The primary end-point was the percentage of patients from whom ≥5x10$^6$ CD34+ cells/kg could be collected in four or fewer days.[50]

After 12 months of follow-up, results in the plerixafor group were significantly more favourable than those in the placebo group. The primary end-point was met by 59.3% of patients in the plerixafor group and by only 19.6% of the placebo group (p<0.001).[50] In addition, significantly more patients underwent HSC transplantation after initial mobilisation when treated with plerixafor than with placebo (90 and 55%, respectively; p<0.001). Median time to engraftment was similar in both groups, and the most common adverse events associated with plerixafor were gastrointestinal disorders and injection-site reactions. Therefore, relative to G-CSF alone, addition of plerixafor to G-CSF led to a significantly higher proportion of NHL patients achieving ample CD34+ cell numbers for transplantation in fewer apheresis days.[50]

## Plerixafor in Multiple Myeloma

A second phase III multicentre, randomised, double-blind, placebo-controlled trial focused on the safety and efficacy of plerixafor plus G-CSF (n=148) in mobilising HSCs in MM patients compared with G-CSF plus placebo (n=154).[51] Using the same protocol as the previous phase III trial, the primary end-point was the percentage of patients who collected ≥6x10$^6$ CD34+ cells/kg within two apheresis sessions. Again, significantly more patients receiving plerixafor met the primary end-point than those receiving placebo (71.6 versus 34.4%; p<0.001). Furthermore, 54% of the plerixafor-treated group reached the target CD34+ cell level after just one apheresis collection. Both plerixafor and G-CSF were well tolerated among patients, and the combination proved more effective at mobilising CD34+ cells than G-CSF alone.[51]

## Safety of Plerixafor

The safety profile of plerixafor has been examined in healthy volunteers as well as in patients with haematological diseases. In

healthy volunteers, single doses of subcutaneous plerixafor were well tolerated, with negative effects being mild and short-lived. The most common adverse events reported were gastrointestinal issues such as increased stool frequency, abdominal distension or bloating, nausea and diarrhoea. Other events included injection-site erythema, facial/perioral paraesthesias, headache and dry mouth.[46,52,53] Patients with NHL and MM reported similar drug-related adverse effects.[50,51]

## The Nordic Experience with Plerixafor in Poorly Mobilising Patients

In our recent experience of treatment of children and adults with neuroblastoma, malignant lymphoma and MM at three different Scandinavian institutions, six patients were remobilised using G-CSF and plerixafor (see *Table 3*) and another five patients were mobilised using G-CSF + chemotherapy + plerixafor (see *Table 4*).

### Mobilisation Using Plerixafor in Addition to Granulocyte Colony-stimulating Factor

All of these six patients had once to twice previously failed to mobilise sufficient CD34+ cells in a chemotherapy and G-CSF mobilisation regimen. Four of the six patients were admitted to apheresis and all four patients reached a sufficient peripheral stem cell collection based on CD34+ cell count.

In this pilot study the administration of plerixafor was highly variable at each transplant centre, thus it is not possible to determine an optimal time for the initiation and end-point of plerixafor treatment when combined with G-CSF. In patients 1 and 3 the CD34+ cell concentration in peripheral blood was not detectable at day four following G-CSF, and only a low level was detected at day five. Administration of plerixafor in the evening of day five had no effect on mobilisation of both CD34 cells and leukocytes at day six. The possibility that the patients had mobilised more efficiently as a result of additional days receiving plerixafor cannot be excluded. Patients 2 and 5 confirm that the peak CD34+ cell mobilisation with a combination of G-CSF and plerixafor occurs consistently on days five and six.

In this pilot study of G-CSF + plerixafor we were able to successfully and predictably remobilise 60% of heavily pre-treated patients. No conclusions can be drawn with regard to plerixafor in combination with G-CSF in patients with absolutely minimal CD34+ cells. Our experience in patients 1 and 3 might suggest that at very low CD34+ counts not all patients benefit from plerixafor treatment. The minimal threshold of CD34+ cells in peripheral blood prior to the use of plerixafor needs to be determined.

### Mobilisation Using Plerixafor in Addition to Granulocyte Colony-stimulating Factor + Chemotherapy

In three out of five patients (9, 10 and 11), plerixafor was introduced into a G-CSF + chemotherapy regimen after a previously unsuccessful mobilisation attempt. However, in two patients (7 and 8) plerixafor was administered during the primary stem cell mobilisation using G-CSF and chemotherapy to successfully prevent mobilisation failure. Patients 7, 8 and 9 had successful collection in a single day following one plerixafor administration. In patients 10 and 11, peripheral CD34+ count was <2 cells/µl and subsequent apheresis did not result in minimal stem cell collection. As can be seen in *Table 4*, leukocyte rebound may provide additional guidance for the timing of plerixafor treatment and subsequent apheresis. Retrospectively, the very low leukocyte count and CD34+ cell concentration in patients 10 and 11 suggest that plerixafor treatment may have been started too early or not continued for long enough.

**Table 3: Haematopoietic Stem Cell Remobilisation in Six Patients at Three Scandinavian Institutions Using Granulocyte Colony-stimulating Factor and Plerixafor**

| | | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
|---|---|---|---|---|---|---|
| Patient 1 | Leukocytes x10$^9$/l | 25.4 | 23.5 | 23.2 | | |
| | CD34 x10$^6$/l | 0.0 | 2.4 | 2.3 | | |
| | CD34 x10$^6$/kg | | | | | |
| | Plerixafor given | | | ↑ | | |
| Patient 2 | Leukocytes x10$^9$/l | 21.1 | 24.1 | 25.4 | 31.2 | 24.0 |
| | CD34 x10$^6$/l | 2.1 | 12,1 | 15.2 | 12.5 | 4.8 |
| | CD34 x10$^6$/kg | | | | **2.3** | **0.9** |
| | Plerixafor given | | ↑ | ↑ | ↑ | ↑ |
| Patient 3 | Leukocytes x10$^9$/l | 19.4 | 9.8 | 9.4 | | |
| | CD34 x10$^6$/l | 0.0 | 2.0 | 1.9 | | |
| | CD34 x10$^6$/kg | | | | | |
| | Plerixafor given | | | ↑ | | |
| Patient 4 | Leukocytes x10$^9$/l | 23.4 | 16.1 | 34.1 | | |
| | CD34 x10$^6$/l | 4.7 | 8.1 | 10.2 | | |
| | CD34 x10$^6$/kg | | 1.65 | **2.73** | | |
| | Plerixafor given | | | ↑ | | |
| Patient 5 | Leukocytes x10$^9$/l | 14.8 | 30.9 | 29.7 | 29.7 | |
| | CD34 x10$^6$/l | 6.4 | 36.5 | 29.9 | 24.9 | |
| | CD34 x10$^6$/kg | | **3.5** | **2.0** | **1.5** | |
| | Plerixafor given | | ↑ | ↑ | ↑ | |
| Patient 6 | Leukocytes x10$^9$/l | 32 | 39 | 27 | | |
| | CD34 x10$^6$/l | | 24 | 14.7 | | |
| | CD34 x10$^6$/kg | | **2.5** | **1.4** | | |
| | Plerixafor given | | ↑ | ↑ | | |

*Numbers in bold indicate the number of cells harvested after the use of plerixafor.*

## Summary and Conclusions

Among patients selected for high-dose therapy with autologous stem cell support, 15–20% are unable to mobilise and collect sufficient numbers of stem cells to proceed to high-dose therapy. The use of G-CSF alone or with chemotherapy plus G-CSF appears not to influence the percentage of mobilisation failures. From the data derived from the Scandinavian case series presented herein, the type and amount of chemotherapy prior to stem cell mobilisation can give some information on which patients can be poor mobilisers. However, it is difficult to predict which of the individual patients will fall into the poor mobiliser group before mobilisation has started.

The new mobilising agent plerixafor, which inhibits binding of SDF-1 to CXCR-4, was shown in recent studies to successfully mobilise several poorly mobilising patients when used in combination with G-CSF.[54] Data from our institutions confirm that addition of plerixafor to G-CSF in patients who have already undergone at least one unsuccessful mobilisation attempt made it possible to mobilise sufficient numbers of CD34+ cells to proceed to high-dose therapy.

To our knowledge, little information exists on how plerixafor should be used in patients mobilised using chemotherapy and G-CSF. In our own experience, as shown in the case series presented, we were able to successfully mobilise three out of five patients. Moreover, two of these three patients were given plerixafor during the first mobilisation attempt, whereas the third patient was remobilised.

**Table 4: Haematopoietic Stem Cell Mobilisation in Five Patients at Three Scandinavian Institutions Using Chemotherapy, Granulocyte Colony-stimulating Factor and Plerixafor**

| | | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 |
|---|---|---|---|---|---|---|---|
| Patient 7 (a) | Leukocytes x10$^9$/l | | 0.7 | 1.3 | 3.4 | 16.0 | |
| | CD34 x10$^6$/l | | 0.6 | 1.8 | 6.5 | 22.4 | |
| | CD34 x10$^6$/kg | | | | 1.24 | **4.87** | |
| | Plerixafor given (0.24mg/kg) | | | | | ↑ | |
| Patient 8 (b) | Leukocytes x10$^9$/l | 4.9 | 5.9 | 10.1 | 26.6 | | |
| | CD34 x10$^6$/l | 6.4 | 10.0 | 11.1 | 34.6 | | |
| | CD34 x10$^6$/kg | | | 1.25 | **2.62** | | |
| | Plerixafor given (0.24mg/kg) | | | | ↑ | | |
| Patient 9 (c) | Leukocytes x10$^9$/l | | | 1.9 | 3.0 | 8.5 | 28.6 |
| | CD34 x10$^6$/l | | | 0.6 | 0.9 | 6.8 | 62.9 |
| | CD34 x10$^6$/kg | | | | | | **9.57** |
| | Plerixafor given (0.24mg/kg) | | | | | | ↑ |
| Patient 10 (d) | Leukocytes x10$^9$/l | 0 | 0.1 | 1.0 | 4.3 | 7.1 | |
| | CD34 x10$^6$/l | 0 | 0 | 0.5 | 1.9 | | |
| | CD34 x10$^6$/kg | | | | **0.1** | | |
| | Plerixafor given (0.24mg/kg) | | | ↑ | ↑ | | |
| Patient 11 (d) | Leukocytes x10$^9$/l | 0.3 | 0.9 | 4.3 | 6.1 | 7.6 | |
| | CD34 x10$^6$/l | 0 | 0 | 1.3 | 0.4 | 0.6 | |
| | CD34 x10$^6$/kg | | | **0.1** | **0** | | |
| | Plerixafor given (0.24mg/kg) | | | ↑ | ↑ | | |

*Chemotherapy given: a. Metothrexate+ ifosfamide + metyl-gag + etoposide + granulocyte colony-stimulating factor (G-CSF) (1µg/kg); b. Iphosphamide + metyl-gag + etoposide + G-CSF (10µg/kg); c. Ara-C + rituximab + G-CSF (10µg/kg); d. Cyclophosphamide + G-CSF (5µg/kg). Numbers in bold indicate the number of cells harvested after the use of plerixafor.*

There are several advantages to adding plerixafor to the primary mobilisation attempt using chemotherapy and G-CSF. Patients do not have to go through a new round of mobilisation and, most importantly, they avoid a treatment-free interval before the next round of mobilisation.

Generally, there is no firm definition of a poor mobiliser during a mobilising attempt. In a recent paper,[55] poor mobilisers, using G-CSF and chemotherapy as the mobilising regimen, were defined as patients with a peak concentration of <20/µl CD34+ cells in the blood upon stimulation. These patients were further categorised into three levels: 'borderline' poor mobilisers were patients with cell concentrations of 11–19/µl CD34+ cells, 'relative' poor mobilisers had 6–11/µl CD34 cells in the blood and 'absolute' poor mobilisers were defined as patients with <5/µl CD34 cells. Following these guidelines, all patients in the borderline poor mobilisers group reached the goal of collecting 2x10$^6$ CD34 cells/kg by a median of two days of leukapheresis, while 86% of the relative poor mobilisers reached this CD34 number following three days of leukapheresis. Of the absolute poor mobiliser group, 43% were able to achieve a collection goal of 2.0 x10$^6$ CD34 cells/kg, but a median of four days of leukapheresis were required.

In our centre, patients mobilised with G-CSF and chemotherapy start peripheral PBPC collection when the CD34 cell concentration in their peripheral blood is greater than 10x10$^6$ CD34+ cells/ml and the leukocyte count increases above 5x10$^9$/l. If the CD34+ cell concentration is 5–10x10$^6$ CD34+ cells/l and the leukocyte count is greater than 10x10$^9$/l, the patient is considered a poor mobiliser, since in these cases the minimal number of 2x10$^6$ CD34+ cells/kg is frequently not reached following three days of leukapheresis.

By using plerixafor in a compassionate use setting we have learned how to optimally time the addition of plerixafor to patients mobilised with a combination of chemotherapy and G-CSF upfront. From the first three patients it appeared that when the leukocyte count increased over 5–10x10$^9$ cells/l but the CD34+ cell concentration was still low, between 5 and 10x10$^6$/l, mobilisation was successful. In the last two patients CD34+ cell concentration and leukocyte counts in blood were low, suggesting that G-CSF and plerixafor were started too early or not continued for long enough.

The definition of poor mobilisers in patients mobilised with G-CSF and when to start plerixafor upfront in such patients needs to be agreed. Based on our limited experiences, it appears that the CD34+ cell concentration at day five is an important indicator of patients who could fall into the poor mobiliser group. However, the level of CD34+ cells required in the blood prior to commencing plerixafor therapy needs to be determined.

In previous reports there was lower overall survival among patients with lymphoma who were poor mobilisers than among good mobilisers.[34,56] We have also previously shown that lymphoma patients infused with >6x10$^6$ CD34+ cells/kg have improved progression-free survival, while those below this threshold derive less benefit from high-dose therapy.[57] Moreover, in this report we also describe a correlation between absolute lymphocyte recovery following high-dose therapy and survival.[57]

In view of these findings it might be important to take advantage of the significant synergistic effect of plerixafor and mobilise a higher number of CD34 cells/kg in those patients who mobilise a minimal number of CD34 cells/kg with G-CSF alone or in combination with chemotherapy. Whether this produces a more rapid absolute lymphocyte recovery and, consequently, an improved survival rate remains to be seen.

Recently, plerixafor has been approved for use in combination with G-CSF to mobilise haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and MM whose cells mobilise poorly. We, like others, conclude that plerixafor is an important novel drug to be used to reduce the failure rates in PBPC mobilisation. As outlined in this review, we need to gain more clinical experiences on how to use this drug upfront in poor mobilisers and to avoid remobilisation of our patients. ■


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