Turning CD34 Non-Mobilizers into Mobilizers: A Case Report Involving Plerixafor (AMD3100)

Henk S.P. Garritsen\textsuperscript{a} Thomas Gabrysiak\textsuperscript{b} Andreas Sputtek\textsuperscript{c} Bettina Biermann\textsuperscript{a}
Bernhard Wörmann\textsuperscript{b}

\textsuperscript{a}Institute for Clinical Transfusion Medicine, \textsuperscript{b}Department of Hematology/Oncology Städtisches Klinikum Braunschweig gGmbH, Braunschweig, \textsuperscript{c}Institute of Transfusion Medicine, Medical Center Hamburg, Eppendorf, Hamburg, Germany

Key Words
Hematopoietic stem cells · Peripheral blood progenitor cells · Stem cell collection · CD34 · Plerixafor

Summary
Objective: In a significant proportion of patients with hematologic malignancies (5–30%) poor mobilization of hematopoietic stem cells (HSC) is observed. This compromises the application of effective and potentially curative high-dose chemotherapy (HDC) treatment. Case Report: Here we report the case of a 38-year-old female patient who was treated for recurrent follicular B-cell non-Hodgkin’s lymphoma grade III. In this patient, we failed twice to mobilize stem cells using chemotherapy followed by granulocyte-colony stimulating factor (G-CSF). Recently a new chemokine receptor CXCR4 antagonist, AMD3100 (plerixafor), was introduced which can be combined with G-CSF mobilization and has been reported to increase the number of harvested stem cells significantly. Using this protocol, we were able to harvest a HSC product. This product was transplanted 3 weeks after the harvest (after HDC), and the patient had an uncomplicated recovery of granulopoiesis (day 11 after transplantation of autologous HSC). Conclusion: Plerixafor has the potency to become an important tool in mobilizing HSC, especially in those patients in whom HSC cannot be mobilized by the combination of G-CSF and chemotherapy alone.

Schlüsselwörter
Hämatopoetische Stammzellen · Periphere Blutprogenitorzellen · Stammzellentnahme · CD34 · Plerixafor

Zusammenfassung
Introduction

There is a significant proportion of patients with hematologic malignancies (5–30%) [1–6] in which poor mobilization of hematopoietic stem cells (HSC) is observed. This compromises the application of effective and potentially curative high-dose chemotherapy (HDC) treatment. Here we report a case of a 38-year-old female patient who was treated for recurrent follicular B-cell non-Hodgkin’s lymphoma (B-NHL) grade III and in whom we attempted twice to mobilize stem cells unsuccessfully using chemotherapy followed by granulocyte-colony stimulating factor (G-CSF).

Case Report

A 38-year-old female patient was admitted to our hospital for treatment of a recurrent follicular B-NHL grade III. After diagnosis in October 2007 she received 6 chemotherapy cycles (6 × R-CHOP21) and was in complete remission. In September 2008 she relapsed with axillar, mediastinal, retroperitoneal and inguinal lymphoma manifestations and 80% bone marrow infiltration (NHL grade III). During 2008 we attempted twice to harvest autologous HSC during the recovery phase after chemotherapy using G-CSF (Neupogen). Both attempts remained unsuccessful. She never reached levels of more than 2 CD34+ cells/µl (peripheral blood) during these attempts, and therefore she falls within the definition of a poor mobilizer. Because no other curative option besides HDC plus autologous HSC transplantation (HSCT) was within reach for this patient, we discussed the possibility of steady-state G-CSF mobilization in combination with plerixafor, and she agreed.

After a steady-state mobilization with G-CSF (10 µg/kg body weight (BW)), again no CD34+ HSC could be detected in her peripheral blood (day 4). On day 4, plerixafor (Genzyme, Boston, MA, USA) (240 µg/kg BW per day) was applied s.c., 10 h before the planned apheresis. Peripheral blood monitoring showed 8 CD34+ cells/µl (pre-apheresis, day 5). Large-volume apheresis (4 times patient’s blood volume) using a Cobe Spectra (Caridian, Lakewood, CO, USA) resulted in a HSC product of 1 × 10⁶ CD34+ cells/kg BW. We planned to repeat the mobilization procedure including plerixafor the next day. However pre-apheresis monitoring showed only 2 CD34+ cells/µl in the peripheral blood and we decided to refrain from further apheresis. Plerixafor was well tolerated by this patient, we observed no adverse events or systemic allergic reactions. Figure 1 presents a schematic overview of the mobilization procedure, leukocyte counts, and CD34+ counts in the peripheral blood.

Functional assays (colony assays of thawed cryoconserved samples) showed 0.6 × 10⁵ CFU/kg BW (goal >1 × 10⁵ CFU/kg BW). Three weeks after the mobilization the patient was transplanted with the cryoconserved autologous HSC product after HD-BEAM chemotherapy. The patient showed uncomplicated recovery of granulopoiesis within the normal time frame (day 11 after HSCT). Probably as a consequence of the low numbers of transplanted CD34+ cells/kg BW, recovery of megakaryopoiesis (>20,000 platelets/µl) took more time (day 18 after HSCT). 28 days after HSCT, no further blood products were required.

Discussion

Why some patients do not mobilize adequate numbers of CD34+ cells is still not completely understood. High-risk factors for poor mobilization of CD34+ cells certainly include extent of prior therapy, disease status, and extensive irradiation.
CD34+ HSC are normally located in the bone marrow. Through interactions of integrins such as LFA-1 and adhesion molecules such as ICAM-1 they are bound to endothelial osteoblasts and to stromal cells [7, 8].

Recent studies point out the crucial pathway in which the chemokine stromal-cell-derived factor-1 (SDF-1) in combination with its ligand, the CXCR4 receptor on CD34+ cells, has a high impact on the release of CD34+ HSC from the bone marrow to the peripheral blood [9, 10]. Plerixafor disrupts the physiological binding of SDF-1 to CXCR4 by acting as a competitive antagonist. In combination with G-CSF, a synergistic effect has been observed [11, 12]. One explanation could be that G-CSF decreases the expression and secretion of SDF-1 in marrow stromal cells [13].

Recent clinical trials in multiple myeloma and non-Hodgkin’s lymphoma patients compare the mobilization of HSC using G-CSF with or without plerixafor [14, 15]. In both trials plerixafor is enhancing the mobilization of HSC quantitative- ly without serious adverse effects. The investigators included good and poor HSC mobilizers in these trials. We feel that the separation of good and poor or non-mobilizers is important in this context. In patients defined as good HSC mobilizers we are quite comfortable in continuing the classical mobilization approach with G-CSF (plus chemotherapy) because we see no significant advantage compared to mobilization using plerixafor additionally. In poor non-mobilizers however plerixafor has the potential to enable autologous HSCT, and therefore approaches that have the potential to enable autologous HSCT, and therefore are quite comfortable in continuing the classical mobilization approach with G-CSF (plus chemotherapy) because we see no significant advantage compared to mobilization using plerixafor additionally. In poor non-mobilizers however plerixafor has the potential to enable autologous HSCT, and therefore must be regarded as an important novel therapeutic tool in this patient group. An important point in this context is that in case of non-mobilizers, these patients never reach the apheresis units because they are ‘of the list’ already because of low CD34+ counts in their CD34+ monitoring. This could be an explanation of the wide variability of reported poor mobilizers in different institutions.

Although plerixafor is only available as a compassionate-use drug in Germany at present, we are convinced about its effectiveness in the case described here.

To date we performed G-CSF plus plerixafor mobilization in 2 additional non-mobilizers. One was successful, and we were able to harvest a therapeutic unit (2 × 10^6 CD34+ cells/kg BW), the other not.

The patient in whom mobilization was not successful had a history of extensive irradiation treatments (34 procedures) and chemotherapy. However, we observed a discrete increase in CD34+ HSC in the peripheral blood (maximally 3 CD34+ cells/μl) in this patient after additional application of plerixafor. In our opinion these cases demonstrate that a critical minimal stem cell pool must be present in the bone marrow. If this critical mass is not available, CD34 mobilization with either G-CSF alone or in combination with plerixafor will be not successful.

**Conclusion**

Plerixafor has the potency to become an important tool in mobilizing HSC, especially in those patients in whom HSC cannot be mobilized by giving G-CSF and chemotherapy alone. HDC treatment in combination with autologous HSC transplantation is extremely important for this group of patients because of limited alternative curative treatment options. Performing HSC apheresis using the combination of plerixafor and G-CSF in non-mobilizers means an ‘all hands on deck’ approach. Because the increase in HSC is very discrete and short-lasting; intensive (daily) CD34 monitoring and large-volume apheresis are a prerogative for successful harvesting in these patients.

**References**


Turning CD34 Non-Mobilizers into Mobilizers

Transfus Med Hemother 2009;36:325–328

327

