Open Journal of
Clinical & Medical
Case Reports

Volume 4 (2018)
Issue 8

ISSN 2379-1039

Successful mobilization of peripheral blood stem cells with early plerixafor and chemomobilization in a very poor mobilizer non-hodgkin diffuse large B cell lymphoma patient

Giulia Tolomelli*; Cristina Clissa; Maria Rosa Motta; Simonetta Rizzi; Elisa Dan; Barbara Sinigaglia; Gabriella Chirumbolo; Francesca Ulbar; Mario Arpinati; Valeria Giudice; Roberto M Lemoli; Michele Cavo; Antonio Curti

***Giulia Tolomelli, MD**

Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology "L. and A. Seràgnoli", University of Bologna, Via Massarenti, 9, 40138, Bologna, Italy
Tel +39-051-6364074, Fax +39-051-6364037; Email: giulia.tolomelli@gmail.com

Abstract

Background: The optimal schedule of plerixafor administration for collection of peripheral blood stem cells (PBSC) in very poor mobilizers (i.e. patients with <5 $CD34^+$ cells/μL PB) has not been clearly defined yet as they may have a different kinetic of mobilization as compared to healthy donors and good mobilizers.

Case report: An adult woman with a "Double Hit" Non Hodgkin diffuse large B-cell Lymphoma, refractory to 6 cycles of R-CHOP chemotherapy, was treated with 6 cycles of R-BFM as salvage chemotherapy. In the attempt to collect PBSC, granulocyte colony- stimulating factor (G-CSF) 10 μg/Kg/daily was administered during the aplastic phase after salvage chemotherapy. However, the number of $CD34^+$ cells/μL remained very low (peak value =3/μL), identifying the patient as proven very poor mobilizer according to Gruppo Italiano Trapianto Midollo Osseo (GITMO) criteria.

Results: Plerixafor, 240 μg/Kg, was administered just four hours before the apheresis procedure. PB $CD34^+$ cells raised to 28 /μL and the patient successfully collected a total of 2.24 x 10^6 $CD34^+$ cells/Kg in two days. Of note, circulating $CD34^+$ cells in the afternoon of the day of the aphereses were almost undetectable. Subsequently, the patient underwent high dose chemotherapy followed by the reinfusion of plerixafor-mobilized $CD34^+$ cells which induced a rapid and durable hematopoietic recovery.

Conclusion: This case report supports the hypothesis that very poor mobilizers may benefit from early administration of plerixafor, even after chemo mobilization, few hours before apheresis. This strategy may result in decreasing resource utilization, thus maximizing stem cells yields and avoiding harvest failures.

Keywords

plerixafor; poor mobilize; peripheral blood stem cells collection

Abbreviations

HSCT: Hematopoietic Stem Cell Transplantation; PB: Peripheral blood; NHL: Non Hodgkin's

Introduction

Autologous hematopoietic stem cell transplantation (HSCT) is widely used to reconstitute hematopoiesis after high dose chemotherapy in multiple myeloma and lymphoma patients [1]. Although mobilized peripheral blood (PB) has become the preferred source for hematopoietic stem cells, failure to mobilize the minimum number $CD34^+$ cells (i.e. 2-2.5 x 10^6 cells/Kg) cells to proceed to transplantation is still a major problem [2,3]. In December 2008, the FDA approved the use of plerixafor, a CXCR4 antagonist that blocks the binding of its ligand CXCL12 enhancing stem cells mobilization, in combination with G-CSF. The use of plerixafor has a strong rationale in the subset of "predicted poor mobilizers", who are heavily pre-treated and/or have already failed a first mobilization attempt, and in the subset of "proven poor mobilizers", who have a peak PB $CD34^+$ cell count <20/μL[4,5]. Current guidelines recommend the injection of plerixafor 10-11 hours before the first leukapheresis, and its efficacy and safety have been demonstrated in many studies [6-9]. However, previous studies have demonstrated that very poor mobilizers (i.e. patients with <5 $CD34^+$ cells/μL) may have a different kinetic of mobilization as compared to healthy donors and patients good mobilizers[10]. In particular, early administration of plerixafor resulted in the successful collection of stem cells in this hard-to-mobilize patient group when combined to G-CSF. Here, we suggest that a similar approach (i.e. plerixafor administered 3-4 hours before apheresis regardless of $CD34^+$ cell count) can be applied to patients undergoing chemo mobilization. In addition, we reinforce the concept [9] that plerixafor can be used "on demand" during the mobilization phase once established that the patient is a very poor mobilizer.

Case Report

A 54 years-old woman with "double hit" non-Hodking diffuse large B-cell lymphoma with t (8;22) and t (14;18), stage IV due to bone marrow, muscles and skeleton involvement, was admitted to our Institution on January 2013. She underwent six cycles of chemotherapy (R-CHOP schedule) including rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone plus prophylactic intrathecal injection of methotrexate and dexamethasone, which resulted in partial response. Then, early disease progression was documented and she received salvage therapy consisting of six cycles of chemotherapy according to the R-BFM schedule (rituximab, ifosfamide, vincristine, methotrexate, cytarabine, etoposide). After three cycles of therapy a positron emission tomography (PET) scan was performed to evaluate response to therapy, showing a complete remission of disease. Hence, we decided to proceed with the fourth cycle of R-BFM followed by granulocyte colony- stimulating factor (G-CSF), at the daily dose of 10 μg/kg, to mobilize stem cells. The patient had not previously failed any attempt of PB stem cells mobilization, and specifically she had never received plerixafor before.

We monitored stem cell mobilization by measuring circulating $CD34^+$ cells as soon as the white blood cell reached 1.0 X 10^9/L. Although full neutrophil recovery was observed at day +11 after chemotherapy, the $CD34^+$ cell count remained very low with a peak value of 3/μL on day +12. Therefore, we decided to add plerixafor, 240 μg/kg subcutaneous, to chemomobilization in the early morning of day 14, just three hours before performing flow cytometry analysis on peripheral blood. Flow cytometry showed a remarkable increase in the amount of $CD34^+$ circulating cells (figure 1a), up to 28 cells/μL. The patient was then admitted to the stem cell collection facility four hours after plerixafor administration

and underwent standard volume leukapheresis, which allowed the collection of 1.5 x 10^6 $CD34^+$ cells/kg. This leukapheresis was hard to perform, complicated by a low flow and poor perviousness of the femoral central venous catheter previously inserted. So, we preferred to plan a second attempt during the next cycle of chemotherapy. Then, next month, the patient was treated with the fifth cycle of R-BFM therapy followed by G-CSF. Similarly to what observed during the first mobilizing attempt, circulating $CD34^+$ were barely detectable (peak value of 1/μL on day +16). On day +18, we repeated the administration of plerixafor at the standard dose of 240 μg/kg and after 3 hours the $CD34^+$ cell count was 10.5 cells/μL (Figure 1a). Therefore, she underwent the second apheresis with the collection of 0.74 x 10^6 cells/kg. In both cases, in the afternoon of the day of the apheresis the percentage of circulating $CD34^+$ cells, and we observed a decreasing level (0.01 % and 0.012% respectively), as shown in Figure 1b. Altogether, a total of 2.24 x 10^6 $CD34^+$ cells/kg were collected with two aphereses, reaching the minimum target of 2 x 10^6 $CD34^+$ cells/Kg. Overall,

Overall, plerixafor administration was well tolerated without any adverse events.

The patient underwent autologous HSCT after BEAM conditioning regimen (carmustine, etoposide, cytarabine, melfalan) [11]. Neutrophil (ANC>0.5 x 109/L) and platelet (PLTs>20 x 109/L) engraftment occurred 12 and 15 days after stem cell reinfusion, respectively. No severe complications, including infections, occurred during the aplastic phase. After 10 months, she is still in complete remission with full hematological recovery.

Discussion

The combination of plerixafor and G-CSF has been shown to improve significantly stem cell mobilization as compared to G-CSF alone, thus reducing the number of aphereses required to collect the optimal number of $CD34^+$ cells and increasing the percentage of patients proceeding to autologous stem cell transplantation[6,12]. Several papers have also demonstrated the capacity of plerixafor to enhance $CD34^+$ collection after chemomobilization [9,13,14].

According to current practice, plerixafor is injected subcutaneously 10-11 hours before the first apheresis session. However, the kinetic of stem cell mobilization after plerixafor has been investigated on normal donors as well as on patients proved to be good mobilizers[10,15]. In healthy donors there is evidence that plerixafor could induce a significant increase in CD34+ cells/μL from 6 hours after injection [16]. Indeed, recent studies, have demonstrated that, in very poor mobilizers, peak values of circulating $CD34^+$ cells occur at earlier time points (i.e. 3-4 hours from administration of plerixafor). Thus, if scheduled according to conventional criteria, many leukaphereses would not result in a successful stem cell collection. In this paper, we report about a patient treated with chemomobilization and "early" plerixafor. We have been able to confirm the peculiar mobilization kinetic of very poor mobilizers with a > 9 fold-increase of circulating $CD34^+$ cells after 3 hours from plerixafor and the rapid clearance of PB stem cells [10]. Of note, the extent of stem cell mobilization declined over time, similarly to previous studies [10]. However, we couldn't exclude a possible additional role of the apheresis procedure in the reduction of the circulating CD34+ cells levels measured by flow cytometry at 10 hours after plerixafor administration. Overall, > 2 x 10^6 $CD34^+$ cells /Kg of recipient body weight have been collected and reinfused after sub-myeloablative chemotherapy inducing rapid and sustained recovery of bone marrow function. Therefore, one may hypothesize that the hematopoietic function of those cells

was maintained. Noteworthy, poor mobilization was defined when the concentration of PB $CD34^+$ cells was lower than 10 cells/μL during the recovery phase after chemotherapy [4,5,9]. The rapid biological activity of plerixafor allowed its administration 'on demand', that is when PBSC mobilization was felt to be inadequate, considering WBCs and $CD34^+$ cell kinetics.

Most important, the collection of the minimum target of 2×10^6 $CD34^+$/Kg cells allowed the patient to undergo the optimal planned therapy (i.e. high dose chemotherapy with autologous transplantation) which resulted in 10 month disease-free survival in a very poor prognosis patient.

Conclusion

In this case-report we describe a feasible novel schedule of plerixafor administration "on demand", in a very poor mobilizer patient undergoing chemomobilization. This approach was cost-effective because we avoided a harvest failure, thus optimizing resources and maximizing stem cells yield. We confirm that the PB $CD34^+$ cell count may peak much earlier in very poor mobilizers. Therefore, the efficient interaction between clinical transplanters, the laboratory and the apheresis facility may be required to adjust our current practice to these hard to-mobilize patients.

With the notable limitation of a single case, our data may serve as a background for identifying a subset of poor and/or very poor mobilizers, who may benefit from an alternative schedule of plerixafor administration. To address this point, specific clinical trials are highly warranted.

Figure

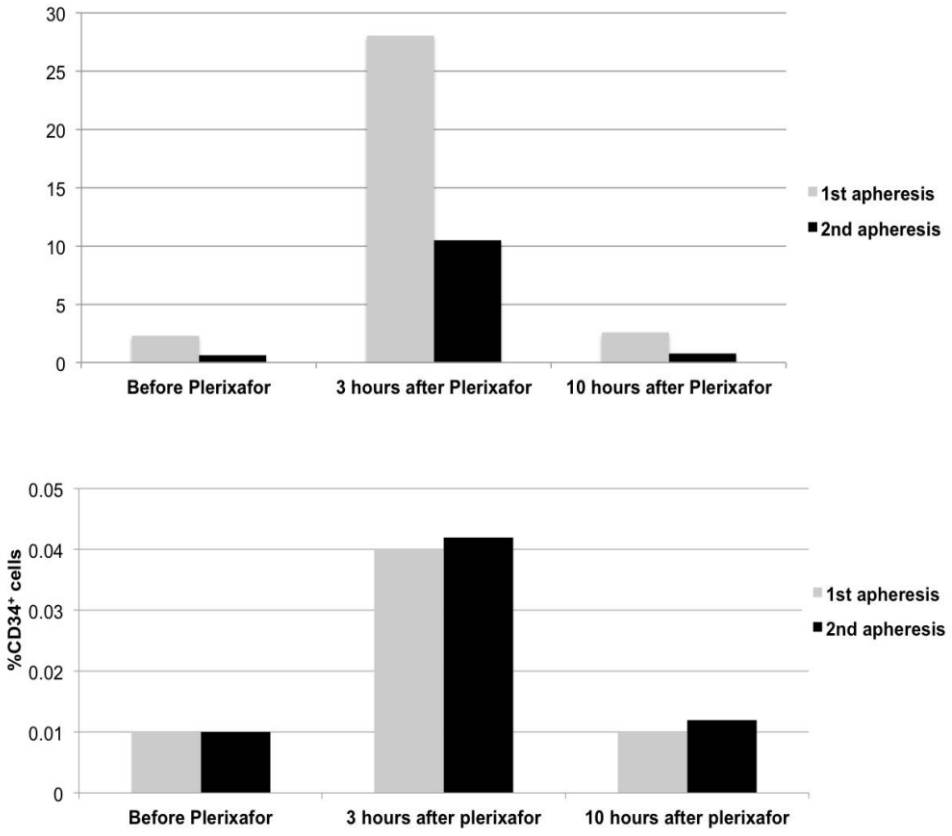

Figure 1: Evaluation of $CD34^+$ cells before and after plerixafor administration. $CD34^+$ cells are expressed as total number of circulating cells (A) and as percentage of total nucleated cells (B). Analysis was performed before plerixafor and after both apheresis.

References

1. Bensinger W, DiPersio JF, McCarty JM. Improving stem cell mobilization strategies: future directions. Bone Marrow Transplant. 2009; 43: 181-95.

2. Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant. 2008;14: 1045-56.

3. Milone G, Poidomani M, Leotta S, Avola G, Camuglia MG, Privitera A, et al. Prognostic value of CD34+ peak in peripheral blood during mobilization in intermediate-risk AML patients treated in first CR by autologous or allogeneic transplantation. Bone Marrow Transplant. 2012;47: 24-32.

4. Attolico I, Pavone V, Ostuni A, Rossini B, Musso M, Crescimanno A, et al. Plerixafor added to chemotherapy plus G-CSF is safe and allows adequate PBSC collection in predicted poor mobilizer patients with multiple myeloma or lymphoma. Biol Blood Marrow Transplant. 2012;18: 241-9.

5. Olivieri A, Marchetti M, Lemoli R, Tarella C, Iacone A, Lanza F, et al. Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytic hierarchy process by ad hoc working group Gruppo Italiano Trapianto di Midollo Osseo. Bone Marrow Transplant. 2012;47: 342-51.

6. Milone G, Martino M, Spadaro A, Leotta S, Di Marco A, Scalzulli P, et al. Plerixafor on-demand combined with chemotherapy and granulocyte colony-stimulating factor: significant improvement in peripheral blood stem cells mobilization and harvest with no increase in costs. Br J Haematol. 2014;164: 113-23.

7. Fruehauf S. Current clinical indications for plerixafor. Transfus Med Hemother. 2013;40: 246-50.

8. Micallef IN, Stiff PJ, Stadtmauer EA, Bolwell BJ, Nademanee AP, Maziarz RT, et al. Safety and efficacy of upfront plerixafor + G-CSF versus placebo + G-CSF for mobilization of Cd34(+) hematopoietic progenitor cells in patients >/=60 and <60 years of age with non-Hodgkin's lymphoma or multiple myeloma. Am J Hematol. 2013; 88: 1017-23.

9. D'Addio A, Curti A, Worel N, Douglas K, Motta MR, Rizzi S, et al. The addition of plerixafor is safe and allows adequate PBSC collection in multiple myeloma and lymphoma patients poor mobilizers after chemotherapy and G-CSF. Bone Marrow Transplant. 2011; 46: 356-63.

10. Lefrere F, Mauge L, Rea D, Ribeil JA, Dal Cortivo L, Brignier AC, et al. A specific time course for mobilization of peripheral blood CD34+ cells after plerixafor injection in very poor mobilizer patients: impact on the timing of the apheresis procedure. Transfusion. 2013; 53: 564-9.

11. Martin N, Borchiellini D, Coso D, Gastaud L, Boscagli A, Saudes L, et al. High-dose chemotherapy with carmustine, etoposide, cytarabine and melphalan followed by autologous stem cell transplant is an effective treatment for elderly patients with poor-prognosis lymphoma. Leuk Lymphoma. 2015; 20: 1-9.

12. Russell N, Douglas K, Ho AD, Mohty M, Carlson K, Ossenkoppele GJ, et al. Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: results of the prospective PREDICT trial. Haematologica. 2013;98: 172-8.

13. Haverkos BM, McBride A, O'Donnell L, Scholl D, Whittaker B, Vasu S, et al. An effective mobilization strategy for lymphoma patients after failed upfront mobilization with plerixafor. Bone Marrow Transplant. 2014 Aug;49: 1052-5.

14. Giralt S, Costa L, Schriber J, Dipersio J, Maziarz R, McCarty J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant. 2014; 20:295-308.

15. DiPersio JF, Micallef IN, Stiff PJ, Bolwell BJ, Maziarz RT, Jacobsen E, et al. Phase III prospective randomized

double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol. 2009;27: 4767-73.

16. Liles WC, Broxmeyer HE, Rodger E, Wood B, Hübel K, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist. Blood. 2003;102: 2728-30.

Manuscript Information: Received: December 12, 2017; Accepted: April 23, 2018; Published: April 30, 2018

Authors Information: Giulia Tolomelli[1*]; Cristina Clissa[1,2]; Maria Rosa Motta[1]; Simonetta Rizzi[1]; Elisa Dan[1]; Barbara Sinigaglia[1]; Gabriella Chirumbolo[1]; Francesca Ulbar[1]; Mario Arpinati[1]; Valeria Giudice[3]; Roberto M Lemoli[4]; Michele Cavo[1]; Antonio Curti[1]

[1]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology "L. and A. Seràgnoli", University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy.
[2]Haematology and Haematopoietic Stem Cell Transplant Center, AORMN Marche Nord Hospital, Pesaro, Italy.
[3]Immunohematology Service and Blood Bank, S.Orsola-Malpighi Hospital, Bologna, Italy.
[4]Chair of Hematology, Department of Internal Medicine (DiMI), University of Genoa, IRCCS Azienda Ospedaliera Universitaria S. Martino-IST, Genoa, Italy.

Citation: Tolomelli G, Clissa C, Motta MR, Rizzi S, Dan E, Sinigaglia B, et al. Successful mobilization of peripheral blood stem cells with early plerixafor and chemomobilization in a very poor mobilizer non-hodgkin diffuse large B cell lymphoma patient. Open J Clin Med Case Rep. 2018; 1404.

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at **www.jclinmedcasereports.com**
For reprints and other information, contact editorial office at **info@jclinmedcasereports.com**