



Hematopoietic stem cell mobilization: current status and future perspective

Jin Seok Kim, M.D., Ph.D.

Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, Korea

Received on May 25, 2017; Revised on June 16, 2017; Accepted on June 19, 2017

Introduction

Autologous stem cell transplantation (ASCT), high-dose chemotherapy followed by hematopoietic stem cell rescue, is a widely used therapeutic strategy especially for some patients with hematological malignancies such as malignant lymphoma or multiple myeloma (MM). Because successful ASCT is crucial in these patients for improving overall survival [1], collection of a sufficient number of hematopoietic stem cells for restoring the bone marrow function is very important. Although most hematopoietic stem cells are located within the bone marrow, BM harvest is accompanied by procedure related risk and relatively lower yield. Therefore, the mobilization of hematopoietic stem cells by using growth factors such as granulocyte colony-stimulating factor (G-CSF) either as a single agent or in combination with chemotherapy (chemo-mobilization) and the collection of mobilized peripheral blood (PB) hematopoietic stem cells are essential processes for using the peripheral blood stem cell (PBSC) as a stem cell source.

However, these classical PBSC mobilization methods fail to collect sufficient number of PBSCs in 5–40% of patients [1]. Plerixafor is a reversible CXCR4 chemokine receptor antagonist and blocks binding of stromal cell-derived factor 1- α , resulting in mobilization of CD34⁺ cells to the PB. The additional use of plerixafor to G-CSF resulted in a significantly higher probability of achieving the optimal PBSC targets in patients who failed at least one PBSC mobilization attempt [1, 2]. Plerixafor gained Food and Drug Administration (FDA) approval in 2008 and has been reimbursed from the Korean Health Insurance Review and Assessment Service (HIRA) since 2012 in Korea. Its Korean reimbursement guideline was expanded in 2015. Plerixafor is used for non-Hodgkin lymphoma (NHL) or MM patients who failed to collect sufficient number of PBSCs at the previous PBSC mobilization attempt in Korea. Therefore, the appropriate use of plerixafor would increase the number of patients receiving ASCT and improve the overall treatment outcomes of these hematological malignancies. Herein, we review the current issues in PBSC mobilization including the definition of mobilization failure and suggest the future perspectives of PBSC mobilization.

Current issues

The generally accepted minimal target PBSC number is 2×10^6 CD34⁺ cells/kg with an optimal number of 5×10^6 CD34⁺ cells/kg [1]. Previously, a consensus definition of ‘mobilization failure’ as a count of $< 2.0 \times 10^6$ CD34⁺ cells/kg after 3 courses of apheresis was made by the board members of the Consortium for Improving Survival of Lymphoma in Korea [2]. However, the target number of CD34⁺ cells should be modified according to the number of ASCT because second ASCT is usually recommended in patients with MM who have sufficient remission duration after first ASCT. In addition, tandem ASCT is still recommended especially for the high risk MM patients. Therefore,

International Myeloma Working Group suggested that a minimum target of 4×10^6 CD34⁺ cells/kg be collected and that if feasible an average of $8\text{--}10 \times 10^6$ CD34⁺ cells/kg be collected in the patients with MM [3]. In the previous phase 3 trials for plerixafor, the primary end point was the percentage of patients who collected 5×10^6 CD34⁺ cells/kg in ≤ 4 apheresis days for NHL [4] and 6×10^6 CD34⁺ cells/kg in ≤ 2 apheresis days for MM [5]. Therefore, the previous definition of mobilization failure and the guideline for using plerixafor should be modified. If collecting for 1 ASCT, mobilization failure would be a count of $< 2.0 \times 10^6$ CD34⁺ cells/kg. On the other hand, if collecting for more than 1 ASCT, at least a count of $< 4.0 \times 10^6$ CD34⁺ cells/kg should be a criterion for mobilization failure.

To determine the appropriate date on which to initiate PBSCs collection, the serial monitoring of PB CD34⁺ cells count is essential. Mobilization with G-CSF alone (usually at a dose of 10 $\mu\text{g}/\text{kg}$ subcutaneously daily) or G-CSF plus plerixafor (240 $\mu\text{g}/\text{kg}$) makes peak circulating PB CD34⁺ cells count between the 4th and 6th days of therapy. Therefore, monitoring of PB CD34⁺ cells usually begins on either the 4th or 5th day. For patients with chemo-mobilization, monitoring of PB CD34⁺ cells usually starts on the 8th–10th days after chemotherapy or white blood cell count $> 1.0 \times 10^9/\text{L}$ because the peak timing of PB CD34⁺ cells count varies according to the specific chemotherapy regimens [1]. In addition, pre-apheresis PB CD34⁺ cells count monitoring is useful for identifying the patients who eventually fail to collect a sufficient number of PBSCs. According to the previous decision-making algorithm for the use of plerixafor, PB CD34⁺ cells $< 10/\mu\text{L}$ for the minimal target PBSC number of 2×10^6 CD34⁺ cells/kg and PB CD34⁺ cells $< 20/\mu\text{L}$ for 4×10^6 CD34⁺ cells/kg would be appropriate for the use of plerixafor [1]. Therefore, the serial monitoring of PB CD34⁺ cell count will be able to select the most appropriate date of PBSCs collection and reduce unnecessary PBSCs collection attempt. Eventually, we can avoid unnecessary use of plerixafor. However, the serial monitoring of PB CD34⁺ cells count during stem cell mobilization is not allowed from the HIRA reimbursement guideline. Therefore, these reimbursement policies of HIRA should be modified and improved in the future.

Re-mobilization using plerixafor after the failure of first PBSC mobilization attempt has been usually recommended and reimbursed in Korea for patients who cannot collect

sufficient number of PBSC for ASCT. After at least 7-day rest period, G-CSF plus plerixafor is usually applied for re-mobilization. However, it will take a lot of time to collect an appropriate number of CD34⁺ cells for subsequent ASCT and delaying the schedule of ASCT may be related to poor treatment outcomes. Therefore, the immediate salvage use of plerixafor (just in time plerixafor) for patients with suboptimal mobilization according to the PB CD34⁺ cells count or the apheresis results of the first day of apheresis should be considered [6]. The immediate salvage use of plerixafor is the additional use of plerixafor during mobilization when the PB CD34⁺ cells count is $< 10/\mu\text{L}$ for 1 ASCT, and $< 20/\mu\text{L}$ for more than 1 ASCT. In addition, the first-day apheresis yield of $< 1.5 \times 10^6$ CD34⁺ cells/kg or subsequent day apheresis yield of $< 0.5 \times 10^6$ CD34⁺ cells/kg also should be indicated for the immediate salvage use of plerixafor [6]. The strategy of immediate salvage use of plerixafor will increase the rates of successful PBSC mobilization, reduce the number of apheresis attempt and save the total cost of mobilization [7–9] (Table 1).

The HIRA reimburses only two doses of plerixafor administration per patient in Korea. It was basically because the median use of plerixafor was two doses in the previous phase 3 trial [4, 5]. However, the plerixafor is continuously used until the target number of CD34⁺ cells is collected and the probability of successfully achieving the target number of CD34⁺ cells continuously increases after the 3rd PBSC apheresis using plerixafor [4, 5]. Therefore, the limitation on the number of plerixafor usage is inappropriate and the guideline should be revised.

Future perspectives

The goals of PBSCs mobilization should be collecting sufficient amount of PBSCs, to minimize mobilization related morbidities, and to reduce the use of the resources. Therefore, appropriate use of plerixafor in patients who likely to benefit from ASCT and reduced trials of unnecessary PBSCs collection attempt should be the main policies of PBSC mobilization. To achieve these goals, the definition of mobilization failure should be modified according to the number of ASCT. In addition, the serial monitoring of PB CD34⁺ cells count during stem cell mobilization should be allowed. Although plerixafor-based re-mobilization after first mobilization failure is widely used, immediate salvage

Table 1. Mobilization outcomes of immediate salvage use of plerixafor.

	Underlying disease	Mobilization regimen	Plerixafor use	Failure of mobilization
Veltri L <i>et al.</i> 2015 [7]	Lymphoma & MM	G-CSF only	36/60 (60%)	2/60 (3.3%)
Micallef IN <i>et al.</i> 2013 [8]	Lymphoma & MM	G-CSF only	57/98 (58%)	1/98 (1.0%)
Milone G <i>et al.</i> 2014 [9]	Lymphoma & MM	CTX 4 g/m ² or DHAP+G-CSF	9/102 (8.8%)	4/102 (4.0%)

Abbreviations: CTX, cyclophosphamide; DHAP, dexamethasone, cytosine arabinoside, and cisplatin; G-CSF, granulocyte colony-stimulating factor; MM, multiple myeloma.

use of plerixafor (just in time plerixafor) for patients with suboptimal mobilization should be considered. In the future, the pre-emptive use of plerixafor for the first mobilization attempt should be applied in patients with predicted poor mobilization. The use of plerixafor for the first mobilization attempt is also tried because greater numbers of CD34⁺ cells may provide faster engraftment and, potentially, better long-term outcomes. Many new molecules for PBSC mobilization such as a high-affinity CXCR4 antagonist and a sphingosine-1-phosphate agonist have been under trials [10]. Therefore, mobilization failure and poor mobilization would not be an essential problem in the near future.

Author's Disclosure of Potential Conflict of Interest

The author has no potential conflict of interest relevant to this article.

REFERENCES

1. Giralt S, Costa L, Schriber 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.
2. Kim SJ, Yoon DH, Yang DH, et al. Plerixafor use for peripheral blood stem cell mobilization in Korea. *Blood Res* 2013;48:72-3.
3. Giralt S, Stadtmauer EA, Harousseau JL, et al. International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). *Leukemia* 2009;23:1904-12.
4. DiPersio JF, Micallef IN, Stiff PJ, 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.
5. DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood* 2009;113:5720-6.
6. To LB, Levesque JP, Herbert KE. How I treat patients who mobilize hematopoietic stem cells poorly. *Blood* 2011;118:4530-40.
7. Veltri L, Cumpston A, Shillingburg A, et al. Hematopoietic progenitor cell mobilization with "just-in-time" plerixafor approach is a cost-effective alternative to routine plerixafor use. *Cytotherapy* 2015;17:1785-92.
8. Micallef IN, Sinha S, Gastineau DA, et al. Cost-effectiveness analysis of a risk-adapted algorithm of plerixafor use for autologous peripheral blood stem cell mobilization. *Biol Blood Marrow Transplant* 2013;19:87-93.
9. Milone G, Martino M, Spadaro A, 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.
10. Ataca Atilla P, Bakanay Ozturk SM, Demirer T. How to manage poor mobilizers for high dose chemotherapy and autologous stem cell transplantation? *Transfus Apher Sci* 2017;56:190-8.