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Perspective

Plerixafor use for peripheral blood stem cell mobilization in Korea

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Peripheral blood stem cell (PBSC) mobilization is a prerequisite for the success of autologous stem cell transplantation (ASCT), and the infusion of adequate number of CD34+ hematopoietic progenitor cells is correlated with successful engraftment [1]. Traditionally, chemotherapeutic agents such as cyclophosphamide in combination with granulocyte-colony stimulating factor (G-CSF) have been used for mobilization of hematopoietic stem cells from bone marrow into peripheral blood. However, approximately 10–30% of patients who are at risk of mobilization failure are unable to mobilize minimum required number of PBSCs ($\geq 2.0\times10^6$ CD34+ cells/kg) for the success of ASCT [2], and consequently fail to undergo ASCT. Plerixafor (AMD3100), a small molecule inhibitor of stromal cell-derived factor-1 α binding to the CXCR4 receptor, was introduced as a solution for patients who show inadequate mobilization of CD34+ PBSCs. Results of Phase I/II trials demonstrated the efficacy of plerixafor, and a subsequent Phase III study showed that the use of plerixafor in combination with G-CSF significantly increased the number of CD34+ PBSCs, compared to G-CSF alone [3]. Plerixafor has been approved for patients with lymphoma and multiple myeloma who show poor PBSC mobilization, and its use is expected to increase the likelihood of successful ASCT. However, it is still difficult to define 'poor' mobilization because the total number of CD34+ cells can be influenced by the number of apheresis. There have been variable parameters to evaluate the extent of mobilization, such as cumulative apheresis yield as well as the number of CD34+ cells per apheresis. In addition, the total yield of CD34+ cells depends on the number of courses of apheresis, which is, in turn contingent on physicians' discretion. Recently, the Italian Group for Stem Cell Transplantation (GITMO) proposed consensus criteria for 'proven poor mobilizers' as follows: (a) circulating CD34+ cell peak of less than 20/μL up to 6 days after mobilization with G-CSF or up to 20 days after adequate mobilization such as using G-CSF 10 μg/kg if used alone or 5 μg/kg after chemotherapy, (b) less than 2.0×10^6 CD34+ cells per kg after fewer than three apheresis [4]. In Korea, use of plerixafor in combination with G-CSF is approved in patients with non-Hodgkin lymphoma and multiple myeloma for PBSC mobilization, and reimbursement is provided to those who have failed previous mobilization attempts with chemotherapy and G-CSF. However, the appropriate time for the initiation of plerixafor is still subject to ambiguity due to the lack of consensus on usable criteria for determining mobilization failure. Despite CD34+ PBSC count

being considered the most powerful predictive factor of mobilization failure, the measurement of circulating CD34+ cells is not feasible in a majority of institutes in Korea. Therefore, at the recent meeting of the Consortium for Improving Survival of Lymphoma (CISL), the board members adopted a consensus definition of 'mobilization failure' as a count of less than 2.0×10^6 CD34+ cells/kg after three courses of apheresis. Thus, if the total number of CD34+ cells does not reach the minimum requirement for ASCT, the use of plerixafor should be considered, rather than continuation of apheresis with G-CSF. Furthermore, in specific patient populations which are expected to have low possibility of adequate cell yield such as elderly and heavily-pretreated patients, the board members of CISL discussed early administration of plerixafor. While the risk factors of mobilization failure have not yet been clearly identified, the recent GITMO working group proposed consensus criteria to define 'predicted poor mobilizers' as follows: (1) they failed a previous collection attempt (not otherwise specified); (2) they previously received extensive radiotherapy or full courses of therapy affecting PBSC mobilization; and (3) they met two of the following criteria: advanced disease (≥two lines of chemotherapy), refractory disease, extensive bone marrow involvement or cellularity <30% at the time of mobilization; age ≥65 years (4). A recent study on identifying prognostic factors for prescribing plerixafor-based PBSC mobilization showed that an age of 65 years, a diagnosis of non-Hodgkin's lymphoma, and treatment with four chemotherapy regimens were significantly associated with mobilization failure. Given the congruence between these prognostic factors and GITMO criteria of 'predicted poor mobilizers', it is evident that PBSC mobilization is impacted by the existence of risk factors and hence, the early use of plerixafor for high-risk groups should be carefully considered [5]. Further study is warranted to prevent mobilization failure by maximizing the benefit of plerixafor in Korean clinical setting. Plerixafor is a new class agent with a novel mechanism of action and has the potential to lead to a paradigm shift in PBSC mobilization and success of ASCT. In the era of plerixafor, considerable changes in clinical practices associated with PBSC mobilization can be expected in Korea.

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