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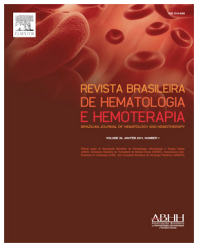

Review article

Hematopoietic progenitor cell mobilization for autologous transplantation – a literature review

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ABSTRACT

The use of high-dose chemotherapy with autologous support of hematopoietic progenitor cells is an effective strategy to treat various hematologic neoplasms, such as non-Hodgkin lymphomas and multiple myeloma. Mobilized peripheral blood progenitor cells are the main source of support for autologous transplants, and collection of an adequate number of hematopoietic progenitor cells is a critical step in the autologous transplant procedure. Traditional strategies, based on the use of growth factors with or without chemotherapy, have limitations even when remobilizations are performed. Granulocyte colony-stimulating factor is the most widely used agent for progenitor cell mobilization. The association of plerixafor, a C-X-C Chemokine receptor type 4 (CXCR4) inhibitor, to granulocyte colony stimulating factor generates rapid mobilization of hematopoietic progenitor cells. A literature review was performed of randomized studies comparing different mobilization schemes in the treatment of multiple myeloma and lymphomas to analyze their limitations and effectiveness in hematopoietic progenitor cell mobilization for autologous transplant. This analysis showed that the addition of plerixafor to granulocyte colony stimulating factor is well tolerated and results in a greater proportion of patients with non-Hodgkin lymphomas or multiple myeloma reaching optimal $CD34^+$ cell collections with a smaller number of apheresis compared the use of granulocyte colony stimulating factor alone.

High-dose chemotherapy with autologous hematopoietic stem cell transplantation is an effective strategy to treat various hematologic neoplasms, such as chemosensitive relapsed Hodgkin's lymphomas,[1,2] non-Hodgkin lymphomas (NHL)[3,4] and multiple myeloma (MM).[5] Several clinical guidelines and consensus recommend the procedure as standard treatment in these conditions.[6–11] According to the Center for International Blood and Marrow Transplant Research (CIBMTR), 12,047 autologous hematopoietic stem cell transplantations (AHSCT) were carried out in the United States in 2011, with MM and NHL being the main indications.[12] In Brazil, data from the Brazilian Transplant Registry show that 1144 AHSCT were performed in 2013, slightly higher than the year before.[13]

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The CIBMTR shows that peripheral blood progenitor cells are the main source used to support autologous transplants.[12] In addition to the possible chemoresistance of the cancer, mobilization of hematopoietic progenitor cells (HPC) is another potentially limiting step for AHSCT, with high failure rates (between 5% and 40%) associated with historically used mobilization strategies.[14]

A consensus published by the American Society for Blood and Marrow Transplantation (ASBMT) recommends collecting a minimum dose of 2×10^6 $CD34^+$ cells/kg to perform AHSCT, but the decision to accept collections of between 1×10^6 and 2×10^6 $CD34^+$ cells/kg can be individualized according to the circumstances of each patient. On the other hand, larger target numbers are needed if multiple transplants are planned.[15]

Although the minimum dose of progenitor cells to be collected is well defined, the ideal target or the desirable maximum dose is less clear. Some data show that the use of $\geq 5 \times 10^6$ $CD34^+$ cells/kg leads to quicker and more predictable grafting, achieving platelet transfusions independence significantly earlier with potential reductions in transplant costs.[16,17] Thus, adequate progenitor cell mobilization is a key step when planning an AHSCT.

Biology related to mobilization of hematopoietic progenitor cells and therapeutic targets

Although mature hematopoietic cells are physiologically released from the bone marrow to the peripheral blood, immature cells are found in the circulation at a very low frequency. About 0.05% or less of the total circulating leukocytes are HPC and express the $CD34^+$ surface marker.[18] HPC adhere to the bone marrow microenvironment by a variety of adhesive interactions.[19] Furthermore, they express a wide range of surface receptors, such as adhesion molecules associated with angiopoietin-1 lymphocytes, very late antigen 4 (VLA4), and Mac-1, C-X-C chemokine receptors type 4 (CXCR4) and type 2 (CXCR2), the surface glycoproteins CD44 and CD62L, and tyrosine kinase receptor c-kit.[19] The bone marrow stroma contains stromal cell-derived factor 1 (SDF-1), CXC chemokine GRO-β, vascular cell adhesion molecule (VCAM-1), KIT-ligand, P-selectin glycoprotein ligand and hyaluronic acid, all of which are ligands for the stem cell adhesion molecules.[20] Preclinical data show that inhibition of these receptor–ligand interactions results in increased mobilization of progenitor cells.[19–21]

Growth factors [granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)] are the most widely used agents for progenitor cell mobilization; they have two main mechanisms of action. The first is the production of proteases by hyperplastic myelomonocytic series, which induces the cleavage of SDF-1 by preventing its binding to CXCR4. The most studied protease is matrix metallopeptidase 9 (MMP-9), although dipeptidase CD26 seems to have a greater role in this process.[22,23] The second main mechanism is also proteolysis induced and is responsible for degradation of VCAM-1, osteopontin and fibronectin, leading to reduced adhesion of progenitor cells through its VLA-4 receptor in bone marrow stroma.[23]

The addition of a chemotherapeutic agent to a cytokine in the mobilization regimen has effects which are not fully elucidated.[19] It is speculated that the addition of cyclophosphamide to growth factors has a synergistic effect on the release of granulocytic proteases in the bone marrow as its administration in isolation leads to cleavage of SDF-1, CXCR4 and c-kit adhesion molecules.[19] Furthermore, the toxicity of chemotherapeutic agents on bone marrow stroma can release HPC as a result of damage to the functional ability of stromal cells in supporting them.[19]

Plerixafor (AMD3100) is a reversibly bicyclam inhibitor of CXCR4 that breaks the binding between SDF-1 and CXCR4 receptors, blocking the chemotactic signaling with stromal cells.[23] Among the hypotheses for its mobilization mechanism is the loss of sensitivity of progenitor cells to SDF-1 caused by the inhibition of CXCR4. Consequently, these cells are attracted to the circulation through signaling probably related to sphingosine-1-phosphate (S1P), a sphingolipid implicated in the chemotaxis control of progenitor cells from bone marrow, blood and other tissues.[23] Studies also suggest that plerixafor keeps the progenitor cells in the circulation by binding to CXCR4, leading to a loss of chemoattraction to SDF-1, decreasing HPC homing, which also contributes to mobilization.[24]

Mobilization of hematopoietic progenitor cells for multiple myeloma and lymphoma: results of the historically most used strategies show limitations

Traditionally, the most widely used mobilization strategies have been the use of growth factors alone (G-CSF/GM-CSF) or in combination with chemotherapeutic agents. Among the available growth factors, the most commonly used is recombinant G-CSF filgrastim, while others, such as, G-CSF pegfilgrastim, G-CSF lenograstim and GM-CSF molgramostim, are used less frequently.[14]

G-CSF alone as first-line mobilization is an attractive option owing to the predictable mobilization kinetics, which in turn allows predictable apheresis scheduling and staffing while decreasing costs of growth factors and the collection procedure compared with cyclophosphamide (CY).[25–27]

GM-CSF has been shown to be inferior to G-CSF in terms of number of stem cells collected and in post-transplantation outcomes related to hematopoietic recovery, transfusion and antibiotic support, febrile episodes and hospitalizations.[28,29] It is most often used in remobilization strategies, alone or in combination with other cytokines or chemotherapy.[28,29] Data on the use of pegfilgrastim in steady-state mobilization are both limited and mixed, but one study demonstrated predictable mobilization kinetics and similar collection yields and apheresis days compared with a separate G-CSF cohort.[30]

CY may be incorporated into the initial induction or salvage therapy cycles, or may be administered as a standalone cycle separately from standard therapy. The most common stand-alone regimens include cyclophosphamide at a range of doses between 2 and 7 g/m^2. CY is associated with higher cell yields, lower or similar failure rates,[25–27,31–34] and improved