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Review

What is the role of apheresis technology in stem cell transplantation?

Ilhami Kiki*

Atatürk University, Medical School, Department of Internal Medicine, Division of Hematology, Erzurum, Turkey

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ABSTRACT

Since the demonstration that hematopoietic cells are present in circulating blood, peripheral blood stem cell transplantation (PBSCT) has become an area of interest. The invention of growth factors such as the granulocyte colony-stimulating factor (G-CSF) and the availability of apheresis techniques allowed the wide application of peripheral blood stem cells (PBSC) in both autologous and allogeneic hematopoietic stem cell transplantation settings. It has been since 1986 that clinically introduced, peripheral blood stem cells replaced bone marrow as a stem-cell source to nearly 100% in the autologous and to approximately 75% in the allogeneic transplantation setting. During this period of time, remarkable development occurred in both stem cell mobilizing agents (i.e. CXCR4 antagonists) and apheresis techniques. Currently, apheresis technology is being increasingly used in not only for collection of PBSC or blood product support, but also for treatment and/or prevention of several transplantations related complications. Apheresis technology also allows to manipulate stem cells and thus provides opportunity to curative treatment of certain diseases.

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* Corresponding author at: Medical School, Department of Internal Medicine, Division of Hematology, 25240 Yakutiye, Erzurum, Turkey.
E-mail address: kikiilhami@yahoo.com

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1. Peripheral blood stem cells

In earlier studies, peripheral blood derived cells were shown to be capable of division and differentiation and could restore bone marrow function in lethally irradiated animals such as mice [1], dogs [2], and baboons [3]. First experimental studies using autologous and allogeneic leukocyte concentrates in animal models suggested that, bone marrow recovery could be achieved; however, were not pursued at a clinical level due to the rarity of peripheral blood stem cells [4,5].

2. Development of apheresis technology

In the early 1960s, continuous flow apheresis technology was developed and clinically utilized. The invention of the NCI-IBM blood cell separator allowed to process large volume of blood (2–3 times of patient's blood volume) and to collect substantial amount of white blood cells. This achievement suggested that adequate amount of PBSCs could be collected by using apheresis technique [6].

In the early 1970s, McCredie at al successfully collected PBSC by continuous flow apheresis and showed their grown in-vitro by use of soft agar gel technique. They also claimed that repeat leukapheresis of the same donor does not reduce the number of PBSCs [7].

In the mid-1970s, some authors proposed that PBSCs have limited capacity for self-renewal and proliferation. Furthermore, a couple of unsuccessful clinical experiences of PBSC transplantation were further raised this concern. In these reports, authors concluded that, the reasons for failed marrow recovery were either low quality or inadequate amount of peripheral blood derived cells [8–10].

First successful autologous PBSCTs were achieved after the development of cryopreservation techniques that allow repeat apheresis and preserve PBSCs until an engraftment dose was achieved [11]. In 1986, Körbling at al. reported successful PBSCT in a patient with Burkitt's lymphoma who underwent a myeloablative conditioning regimen [12]. Subsequently, similar successful PBSCT applications were reported. In all of these reports PBSCs were collected by multiple apheresis procedures without using PBSC increasing methods. There was a great need of PBSC augmentation techniques.

3. Attempts to increase peripheral blood stem cells

The results of an initial study reported by Richman et al., showed that, PBSCs are markedly increased in patients who were recovering from intensive chemotherapy [13]. Subsequently, Cline et al. reported that PBSCs could be 4 fold increased by the administration of small amounts of pseudomonas endotoxin [14]. However, the most prominent progress in this area was achieved by the utilization of recombinant hematopoietic growth factors, the granulocyte macrophage colony stimulating factor (GM-CSF) and the G-CSF [15,16]. Since the demonstration of clearly superior stem cell mobilization by G-CSF than GM-CSF (up to 100 fold vs 60 fold over baseline respectively), G-CSF alone or following chemotherapy has become a standard approach to mobilize autologous PBSCs [17].

The surrogate marker of peripheral blood stem cells is CD34. Between 2 to 5 million CD34+ mononuclear cells/kg body weight is considered as adequate number of stem cells to proceed to transplantation. The adhesion and release of CD34+ cells from bone marrow is dependent of the interaction between chemokine receptor 4 (CXCR4) and its ligand stromal cell-derived factor 1-alpha (also known as CXCL12). A novel agent plerixafor reversibly inhibits this binding and when administered combined with G-CSF, more effectively increases PBSC than G-CSF alone. This agent is successfully used in poorly mobilized patients [18].

4. Role of Apheresis Technology in Autologous Peripheral Stem Cell Transplantation

4.1. PBSC versus BM

As described above, before the introduction of successful autologous PBSCT, the main source of stem cell was BM and there were some concerns about the quality of PBSCs. After the utilization of growth factors and apheresis techniques, PBSCs have become increasingly popular stem cell source in the world. The question of which is the preferred source for an autologous graft, bone marrow or peripheral blood, has been answered, at least in the treatment of lymphoma. In two studies, autologous PBSCT was compared to autologous BMT in patients with relapsed lymphoma. PBSCs were found to be superior in terms of neutrophil and platelet engraftment time, need of blood product support, quality of life, and cost mainly due to the use of antibiotics and prolonged hospital stay [19,20]. Today, PBSCs are used for autologous SCT in almost all adult cases.

4.2. Peripheral Blood Stem Cell Mobilization

4.2.1. G-CSF Mobilization

Although several different approaches have been applied, the optimal methodology for mobilizing PBPCs has yet to be defined. In one randomized study, divided doses of 5 mcg/kg twice per day G-CSF ensured a higher yield of CD34+ cells and required fewer apheresis procedures than a single daily dose of 10 mcg/kg in healthy donors [21]. Although not widely used, single dose of pegfilgrastim has also been shown to be equivalent efficacy to daily G-CSF in a series of 64 cases of lymphoma patients [22]. In another study, higher doses of G-CSF (i.e, 30 mcg/kg per day) increased the CD34+ cell yield and reduced the need for apheresis to reach the collection goal of more than 2.5 or 5×10^6 CD34 + cells/kg [23].

4.2.2. Mobilization after chemotherapy

PBSC mobilization is also observed after recovery from chemotherapy. Concomitant use of G-CSF, results in a synergistic effect. Although different methods of hematopoietic stem cell mobilization are in use, administration of cyclophosphamide (typically 3–4 g/m^2) plus G-CSF (10 mcg/kg) has become a standard approach in the autologous transplant setting [24,25].

4.2.3. Mobilization with other agents

In some cases, especially who have a history of exposure to chemo-radiotherapy, standard approach for mobilization with G-

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