Blood cell transplantation: past, present and future

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Abstract

Blood cell transplantation is rapidly replacing bone marrow transplantation for restoration of hematopoiesis after high-dose chemotherapy in both the autologous and allogeneic settings. Future developments of BCT will be discussed.

Blood cell transplantation (BCT) now represents about 75% of autologous stem cell transplants performed for solid tumors, non-Hodgkin lymphomas (NHL), Hodgkin's disease and multiple myeloma. It is increasingly used to restore hematopoiesis following high-dose chemotherapy in patients with acute or chronic leukemias, both in the autologous and allogeneic setting. Blood stem cells (BSC) will be extensively used in the next decade as source of stem cells for evolving applications of transplantation such as stem cell expansion, gene transfer and immunotherapy. This review will analyse the main biological and clinical arguments for the use of BCT instead of bone marrow transplantation (BMT) ("the past"), summarize the current results of blood cell mobilisation, collection and transplantation ("the present") and discuss coming developments ("the future").

The past

The presence of hematopoietic progenitors in the peripheral blood was hypothesized for many years from experimental studies in animal models. In mice [1], guinea pigs [2], and dogs [3] treated with sublethal radiotherapy and chemotherapy, it was reported that reinfusion of previously harvested blood cells could reduce mortality due to the myeloablative treatment and efficiently reconstitute trilineage hematopoiesis. At the same time, the development of culture assays led to the conclusion that circulating hematopoietic precursors ("committed cells" such as colony forming units - granulocyte macrophage: CFU-GM) exist in normal individuals but at very low concentration [4]. However, when collected during the steady state from normal syngeneic donors, and transfused into recipients with aplastic anemia, these cells were unable to improve hematopoiesis [5, 6]. The first to be transplanted with blood cells were patients with chronic myeloid leukemia (CML), as very high numbers of CFU-GM could be collected at the time of original diagnosis and subsequently used for autologous transplantation after transformation [7, 8].

In fact, the BCT saga really starts when Richman et al, then Lohrmann et al reported that blood CFU-GM concentration was dramatically increased during the recovery phase of chemotherapy-induced marrow aplasia (reviewed in [4]). It was then proposed that these cells could be collected by a series of leukaphereses during the recirculation phase, and during the mid-80s the first patients to be successfully transplanted with chemotherapy-mobilized autologous blood cells were reported [9, 10]. When a sufficient number of patients had been transplanted, it became possible to identify some factors which were associated with poor or delayed engraftment. Such factors included low numbers of transfused CFU-GM cells, the length and intensity
of previous chemotherapy or radiotherapy, the use of drugs which brought about long-lasting bone marrow damage and the use of certain drugs in the conditioning regimen [11]. The Australian group led by Juttner also reported that patients with acute myeloid leukemia (AML) had slower hematopoietic recovery than patients with lymphomas or solid tumors and that engraftment could be unstable in some patients, especially those transplanted with < 25 x 10⁴ CFU-GM/kg [9]. These data have suggested that, following BCT, the first phase (or wave) of engraftment is due to transplanted mature precursors but that long-term reconstitution is brought about by the presence of very primitive progenitors in the infused cells, brought into the circulation by the conditioning regimen.

Most of the patients undergoing autologous BCT during the 1985-1990 period had hematological malignancies as it was hypothesized that blood cells might be less contaminated by residual malignant cells than BM [12]; the hope was that BCT might lead to a lower risk of relapse than BMT. Despite much effort, this hypothesis has not been confirmed. However, an unexpected advantage of BCT over BMT soon became evident: hematopoietic recovery occurred more quickly. For example, the time to reach an absolute neutrophil count of 500/mm³ (ANC 500) was about two weeks, compared with the three and four weeks usually observed after unpurged or purged BMT respectively. Some investigators were able to show that this rapid engraftment could lead to a decrease in the number of days of fever, intravenous antibiotics use, hospitalization and medical expenses. Because of these advantages, it has been predicted that BCT will become the standard for autologous stem cell transplantation.

When hematopoietic growth factors (HGF) became available, further advantages of BCT became apparent. Granulocyte-macrophage colony stimulating factor (GM-CSF) then granulocyte colony stimulating factor (G-CSF) were shown to be able to dramatically (10 to 50 fold) increase blood cell recirculation when administered following mobilising chemotherapy. Thus, the numbers of leukaphereses needed to collect a sufficient number of CFU-GM or CD34 positive cells could be reduced from 4-9 to a median of 2 or 3. Subsequently it was shown that the time to ANC 500 was shorter after transplantation with cells collected after chemotherapy plus G- or GM-CSF mobilisation than after chemotherapy mobilisation alone. More interestingly, the duration of thrombocytopenia following BCT was also significantly reduced when HGF were used together with chemotherapy for mobilisation [13]. Thus, in most autologous transplant programs, BCT progressively is replacing BMT.

The present

To summarize the present status of BCT, we will divide this section in three parts: collection and mobilisation, biology of blood stem cells and hematopoietic reconstitution, and clinical results.

Collection and mobilisation

Blood stem cells are usually collected on a out-patient basis. Semi-continuous or continuous flow cell separators (such as the Fenwall CS 3000 or the Cobe-Spectra) permit processing of about 10 l of patient volume in approximately 3 h. The blood cells are then cryopreserved and are available for reinfusion. Codified standards ("Good Medical Practice") are (or soon will be) available in many countries for collection, cryopreservation, quality control, transportation and reinfusion.

The timing of blood cell collection depends on the type of mobilization used. However, in most cases, leukaphereses are started early when the white blood cell (WBC) count is around 1,000-2,500/mm³. In patients mobilized with HGF (with or without chemotherapy), thrombocytopenia requiring prophylactic platelet transfusions may occur. In some centers, leukaphereses are started according to the level of circulating CD34 positive cells (5-10/µl). Leukaphereses are continued until the target number of progenitor cells is reached. In most studies there is a dose correlation between CD34 positive cells and CFU-GM; as CD34 positive cell evaluation is possible in real time (using flow cytometry) it is usually performed with a target number of 1-2 x 10⁶ CD34+ cells/kg. The minimum number of CFU-GM for safe transplantation is usually put in the range 0.8-1 x 10⁴/kg. These are considered as the thresholds to ensure complete and quick hematopoietic recovery,