

Review Article

Stem Cells in Hemato-Oncology

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Introduction

Stem cells have been utilized for various purposes in medicine ranging from research activities to transplants. A lot of interest has been generated in stem cells because of their regenerative capacity and plasticity. In the area of hematology and oncology stem cells have been used primarily to replace diseased haematopoietic cells or in situations where myeloablative chemotherapy needs to be administered to treat a non-hematological malignancy. Therefore allogeneic stem cell transplants are indicated in situations where the bone marrow is diseased and autologous stem cell transplants are done where the marrow is not diseased.

Autologous Stem Cell Transplants

Autologous transplants can be undertaken for a host of diseases such as lymphomas, multiple myeloma, breast cancer, germ cell tumor, neuroblastoma, lung cancer, ovarian cancer and nephroblastoma. In these diseases the patient is first treated with chemotherapy and a situation of partial remission is attained. This treatment is consolidated further with the use of autologous stem cells. The patient is administered growth factors such as G-CSF to stimulate the bone marrow after which the stem cells are collected from the

peripheral blood using an apheresis machine. These cells are then cryopreserved and stored during which the patient receives a high dose chemotherapy. Post chemotherapy the stem cells are re-infused to the patient and engraftment occurs.

Allogeneic Stem Cell Transplants

Allogeneic transplants can be undertaken for a host of cancerous diseases such as acute myeloid leukemia, acute lymphatic leukemia, chronic myeloid leukemia, myelodysplastic syndrome, lymphomas, and multiple myeloma. In addition allogeneic transplants are useful to cure non-malignant diseases such as thalassemia, sickle cell anemia and aplastic anemia. The patient here receives either myeloablative or non-myeloablative but highly immunosuppressive chemotherapy after which stem cells from a donor are infused. The donor is usually a HLA identical sibling. The donor is administered growth factors such as G-CSF to stimulate the bone marrow after which the stem cells are collected from the peripheral blood using an apheresis machine. These cells are then infused to the patient and engraftment occurs. In allogeneic transplant when a HLA identical sibling is not available a matched unrelated donor or stem cells from a cord blood unit can be used for transplant.

Allogeneic transplant have another complication associated with them called graft versus host disease. These are donor cells reacting against the host tissue and this is controlled with immunosuppressants. However this effect is useful in patients with cancer when it is known as graft versus leukemia effect. This effect helps in prevention of disease relapse after transplant.

Acute and Chronic Leukemia

BMT for acute myelogenous leukemia (AML) is recommended for patients with refractory/resistant leukemia, patients in second clinical remission, and patients with high-risk cytogenetic features in first remission. The Medical Research Council AML10 trial revealed significant differences in long-term disease-free survival when autologous transplantation was compared with consolidative chemotherapy in individuals without an HLA-matched sibling [1]. At least one trial has demonstrated higher long-term survival after allogeneic transplantation compared with autologous transplantation [2], but others have demonstrated equivalence [3, 5]. Allogeneic transplantation has become the standard of care for patients with high-risk cytogenetic features in first remission, patients with resistant or refractory disease and patients in second remission, provided the patient is a candidate for the procedure and a suitable donor is available. Acute lymphoblastic leukemia is treated largely the same way in the adult population.

In chronic phase CML, allogeneic transplantation is currently the curative therapy of choice when a HLA identical sibling is available. However if a donor is not available then patients are treated with imatinib and monitored with quantitative RT-PCR for the bcr-abl transcript. If there is a 2-fold increase in this transcript then a matched unrelated transplant is considered. Autologous transplantation with Philadelphia chromosome-negative-purged marrow or stem cells has recently re-emerged as an investigational treatment option [6], but there is no established benefit of autologous transplantation over interferon-based therapy.

PBSCT has been used most extensively in acute and chronic leukemias. In a prospective, randomized trial comparing allogeneic BMT and PBSCT in 111 patients there was no significantly different overall and leukemia-free survival between PBSCT and BMT groups [7]. The trial did demonstrate the expected significantly decreased time to neutrophil and platelet engraftment after PBSCT. The rate of chronic GVHD was noted to be significantly higher after PBSCT when compared with BMT (30% versus 55%, $p < 0.03$). Another study reported the outcomes of 66 patients with acute or chronic leukemia who received BMT or PBSCT from HLA-matched siblings. The majority of patients entered in this trial had low-risk disease, referring to AML in first remission or CML in chronic, stable phase. The mean time to platelet recovery ($>20 \times 10^9/l$) was reduced by four days after PBSCT when compared to BMT. No differences in rates of GVHD or overall survival were reported in this trial [8].

Multiple Myeloma

Autologous BMT for multiple myeloma has been shown to be superior to traditional chemotherapy, offering both a disease-free and overall survival advantage [9]. However, autologous transplants are frequently contaminated by residual tumor cells when assessed by sensitive molecular techniques [10]. The risk of contamination as well as the demonstration of a pronounced graft-versus-myeloma effect [11, 12] has prompted the study of allogeneic stem cell sources as an alternative to autologous cells. This approach is not without risk; the Cancer and Leukemia Group B recently has had to stop accrual to a trial of non-T cell-depleted allogeneic transplantation in myeloma due to concerns over toxicity.

One study has described the molecular remission status of 51 patients after autografting or allogeneic transplantation with either BM or PBSCs [13]. All 17 patients who received allografts entered a CR state after transplantation. In patients with molecular markers available, there was a significantly increased proportion of patients who achieved

a molecular remission after allogeneic transplantation compared to autologous transplantation. Furthermore, only one of five allogeneic BMT patients became polymerase chain reaction-negative for clonal immunoglobulin gene rearrangements compared with six of nine patients who received allogeneic PBSCT. Similarly another study described five patients who had both complete clinical and molecular remissions after PBSCT from HLA-matched siblings [14].

Myelodysplasia

Allogeneic transplantation is the only therapy for myelodysplastic syndromes (MDS) with curative potential available today. Patients with fewer cytogenetic abnormalities [15], less latency since the time of diagnosis [16], and patients with refractory anemia or refractory anemia with ringed sideroblasts [17, 18] have better outcomes after transplantation. The International Prognostic Scoring System score is also useful for predicting outcome after transplantation [19]. The optimal timing of stem cell transplantation for this disease is not yet known.

The experience in transplantation with PBSC for MDS is more limited than that for the acute and chronic leukemias. However with reduced intensity conditioning regimens available more and more elderly patients are undergoing transplants for MDS with PBSC as the stem cell source.

Non-Hodgkin's Lymphoma (NHL)

Autologous transplantation for relapsed intermediate and high-grade NHL has clear survival advantages over chemotherapy [20]. Allogeneic transplantation has been used for patients with relapse after BMT or refractory disease. [21].

Khouri et al. studied the effects of allogeneic transplantation in patients with mantle cell lymphoma, an intermediate-grade lymphoma with a uniformly poor prognosis [22]. Sixteen patients were studied, 11 of who received allogeneic PBSCs as a stem cell source. Nine patients remained alive at the time of publication, with eight patients in CR. Molecular minimal residual disease was assessed in seven patients. Five of the seven

patients had no evidence of molecular residual disease between 3 and 30 months after transplantation. Five of seven patients had evidence of chronic GVHD. Other case reports have documented the efficacy of allogeneic PBSCT for NHL [23,24].

A graft-versus-lymphoma effect has been noted in both animal models [25] and human studies [22-24]. In a murine model of NHL, a unique graft-versus-lymphoma activity was demonstrated, which was separable from GVHD effects and mediated by CD8⁺ T cells and perforin-dependent cytotoxicity [25].

BM Aplasia and Donor Lymphocyte Infusion (DLI)

The use of unstimulated PB buffy coat cells for aplastic anemia was first reported by in 1982 [26]. At this time, the addition of buffy coat cells to BMT increased the risk of GVHD, likely as a result of the immense T cell load in the buffy coat compared with the relative sparse concentration of progenitor cells. Graft rejection was diminished and survival for patients treated with both marrow and buffy coat cells was improved compared with marrow alone; however, it was not clear whether this improvement could be attributed to the stem cells infused or prevention of graft rejection by the infusion of large numbers of allogeneic T cells [27].

More recently, infusions of buffy coat cells, referred to as DLI have been used as post-transplantation immunotherapy for malignant disease. Given at variable times after transplantation of allogeneic BM or PBSC, DLI can induce potent graft-versus-tumor effects and is useful as treatment for relapsed malignancies or pre-emptive therapy for prevention of relapse. The procedure is associated with a 50% risk in acute GVHD and a 20% risk of marrow aplasia [28]. The effects of DLI are most prominent in CML, where single infusions of donor lymphocytes have induced long-lasting remissions in relapsed patients [29].

Despite the infusion of hematopoietic progenitor cells with the lymphocyte population, even rHuGM-CSF-mobilized donor lymphocytes are not completely

protective against marrow aplasia when used in relapsed CML [29]. This implies that aplasia seen after DLI may not be solely due to destruction of native hematopoietic elements, but also involves suppression of donor engraftment and hematopoiesis.

Nonmyeloablative Transplantation and PBSCs
The DLI experience led to the notion that a transplantation could rely primarily on the immune system of the donor to eradicate the leukemia and that sublethal conditioning might allow stable engraftment. Clearly, depending on whether the targeted disease was a stem cell disorder (e.g., CML) or a disease in which stem cells are not involved (e.g., NHL), it may or may not be necessary to establish complete chimerism of hematopoiesis. The first trial of nonmyeloablative or reduced-intensity conditioning followed by allogeneic PBSCT was reported in 1998 [30]. This technique employs the graft-versus-tumor effect as the primary therapeutic modality and omits high-dose conditioning regimens. Instead, low-dose immunosuppressive regimens containing drugs such as the nucleoside analogue fludarabine, generally in combination with cyclophosphamide or busulfan, are used to permit donor progenitor cell engraftment even without host myeloablation. The graft-versus-host/graft-versus-leukemia response might result in eradication of host hematopoiesis, therefore it is necessary to include a source of stem cells to sustain hematopoiesis.

Potential advantages of a nonmyeloablative approach to allogeneic transplantation include the inclusion of an older patient population and patients with other comorbid conditions that would be otherwise excluded from allogeneic transplantation. As well, the procedure itself is not limited by chemotherapy-induced toxicity and can often be performed in an outpatient setting. Rates of GVHD after nonmyeloablative transplantation are similar to those seen after myeloablative transplantation.

Conclusion

The role of stem cells in haemto-oncology has been continually expanding with coverage of

more disease entities. The source of stem cells also has now increased with the availability of cord blood units for transplantation. These naïve stem cells in cord blood units overcome the barrier of HLA disparity and also produce lesser rates of GVHD. Due to smaller number of stem cells these transplants were primarily done in children with leukemia but with cell expansion methods and use of multiple cord blood units this benefit has also been passed on to adults

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