

A BRIEF REVIEW OF BONE MARROW TRANSPLANTATION-1996

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The “Modern Era” of Human Marrow Transplantation

The era of effective clinical marrow transplantation began at the end of the 1960s when the knowledge of human histocompatibility had progressed to the point where human leukocyte antigen (HLA)-matched siblings could be identified within a family. The early evolution of marrow transplantation in both animals and human patients was traced in detail in 1975, and the references in that article provide a review of the early work in the field.⁽¹⁾ This report summarizes some of the progress made over the past 25 years based on data from the Seattle marrow transplant team. There are, of course, many reports by other marrow transplant teams, and the Bone Marrow Transplant Registry has published numerous reports of combined data from many marrow transplant teams that do not include the Seattle data.⁽²⁾

Initially, marrow grafting was carried out in patients with severe combined immunodeficiency disease (SCID), severe aplastic anemia and advanced acute leukemia. The demonstration that some of these patients could be cured of their disease provided impetus for the rapid development of the field.

Acute Leukemia

Patients with acute leukemia were prepared for engraftment with high-dose chemo-irradiation therapy in order to kill leukemic cells and to immunosuppress the patient so that the graft would be accepted. In patients with far advanced disease, cure rates (5 years and beyond) were achieved in only 10 to 15 per cent of the patients. As transplants were carried out earlier in the course of the disease, results improved to 40 to 75 per cent.

Although many children with acute lymphoblastic leukemia (ALL) are cured by chemotherapy, many are not. Currently, in children who relapse after chemotherapy and are put back into remission, transplantation can provide 40 to 60 per cent long-term survivors. Children transplanted in first remission because of poor prognostic indicators for long-term survival after chemotherapy show a long-term survival of approximately 65 per cent. In acute myeloid leukemia (AML) in children or adults, slightly more than one-half of the patients can achieve long-term disease-free survival if transplanted in first remission.

Chronic Myeloid Leukemia

Results in chronic myeloid leukemia (CML) are the most interesting since this disease is not cured by chemotherapy. In Seattle, we carried out a study in patients with CML transplanted in the chronic phase who were randomized to receive a regimen of total body irradiation (TBI) and cyclophosphamide (CY) (the regimen that we had used since 1969), or busulfan (BU) with CY (a regimen first evaluated by Santos and Tutschka) followed by marrow from an HLA-identical sibling.⁽³⁾ The post-grafting

immunosuppression consisted of a short course of methotrexate and cyclosporine. In both arms of the study, long-term disease-free survival was achieved for approximately three-fourths of the patients. The Stanford/City of Hope group have reported a regimen of etoposide and TBI that gives similar results.⁽⁴⁾

Non-Malignant and Genetic Diseases

Non-malignant or genetic diseases can be treated successfully by an allogeneic marrow graft from a matched sibling. For patients with aplastic anemia⁽⁵⁾ or thalassemia major who have not suffered major complications of their disease, long-term survival after marrow grafting is better than 90 per cent. Dr. Lucarelli will present details of the experience with thalassemia.

Marrow Transplants from Donors Other Than HLA Identical Siblings

The above data are derived from transplants using HLA-matched sibling donors. In the past 10 years, there have been impressive advances in the use of donors other than family members. Dr. Anasetti will summarize that experience.

Current Applications of Marrow Grafting

Autologous Marrow Transplantation

The use of autologous marrow grafts for almost every category of disease other than aplastic anemia and genetic diseases is the most rapidly growing area of marrow transplantation. Long-term disease-free survival is being achieved in leukemias, lymphomas, breast cancer, and multiple myeloma.

Peripheral Blood Hematopoietic Progenitors for Transplantation

It is now feasible to carry out autologous marrow grafts using peripheral blood stem cells. The development of continuous flow centrifuges makes it possible to collect large numbers of peripheral blood nucleated cells. Chemotherapy or, preferably, hematopoietic growth factors such as G-CSF can be used to mobilize stem cells into the peripheral blood. Results of allogeneic marrow grafts using peripheral blood stem cells have shown excellent engraftment without excessive graft-vs-host disease (GVHD) despite the large number of T-cells given with the stem cells.⁽⁶⁾ Peripheral blood cells generally give more rapid engraftment than marrow, indicating that transplantation with these cells will probably replace the use of marrow. Dr. To will present details of the use of peripheral blood stem cells for transplantation.

Cord Blood Hematopoietic Progenitors for Transplantation

Cord blood stem cells are of great interest since they may induce less GVHD than grafts of adult marrow.⁽⁷⁾ Cord blood cells, essentially a by-product of normal pregnancies, are being cryopreserved to assemble banks of cells for transplantation.⁽⁸⁾

Supportive Care

Major improvements in the survival of marrow-grafted patients are occurring because of research in supportive care. Reduction of mortality and morbidity from

cytomegalovirus (CMV) disease through the use of ganciclovir has been impressive.⁽⁹⁾ Few patients now die of bacterial disease, thanks to modern antibiotics. Control of fungal infections and prevention of venoocclusive disease of the liver are still major problems.

Hematopoietic Growth Factors

The use of hematopoietic growth factors has accelerated the time to recovery of granulocytes,⁽¹⁰⁾ resulting in earlier discharge from the hospital with consequent reduction in costs. There is, as yet, no evidence that G-CSF or GM-CSF reduces the incidence of infection. Many new cytokines and combinations of cytokines are currently under study.

Contamination of Marrow with Malignant Cells

A major concern in the application of intensive chemo-irradiation and autologous marrow grafting to patients with leukemia or other malignancies is the question of whether or not small numbers of malignant cells are present in the marrow but undetected among the large number of normal cells. In autologous marrow from patients with leukemia in remission or patients with breast cancer, these cells might bring about a recurrence of disease. Efforts to “purge” these cells by *in vitro* treatment with chemotherapeutic agents or antibodies are being studied. A technique for detecting very small numbers of leukemic cells in the marrow of patients apparently in remission after chemotherapy would make possible a decision about whether further treatment with marrow transplantation is necessary.

Minimal Residual Disease

At present the polymerase chain reaction (PCR) (for amplification and identification of DNA or RNA from minute numbers of cells (less than one in 100,000) possessing a deletion or translocation characteristic of the malignant cell) provides a technique for detection of minimal residual disease. For example, in a recent study of patients who had a marrow transplant for CML, a negative PCR test for the 9:22 translocation 6 to 12 months after transplant was a strong predictor of long-term disease-free survival.⁽¹¹⁾ A positive PCR result predicted almost certain relapse. These patients became candidates for a second transplant, treatment with interferon or infusion of additional donor cells to create a graft-versus-leukemia effect.⁽¹²⁾

Graft-versus-Host Disease and Tolerance

GVHD can range from absent to very mild to life-threatening, presumably due to unrecognized minor histocompatibility differences, even when the donor is an HLA-identical sibling. Although prevention or treatment with immunosuppressive agents is usually effective, some patients develop uncontrollable disease or progress to chronic GVHD. Unlike patients receiving solid organ grafts, most marrow graft recipients can discontinue immunosuppressive treatment in a few months. They then demonstrate a state of “tolerance,” that is, they have cells of donor origin living in the presence of the cells and organs of the host. Many current studies are designed to evaluate the nature of the immunologic reactions between donor and host cells and, particularly, the nature of the tolerance that develops.

In Vitro Expansion of Hematopoietic Progenitor Cells

Our expanding knowledge of the nature of the stem cell, the characterization of the stem cell–microenvironmental cell interaction and the availability of hematopoietic cytokines make it feasible to grow stem cells in vitro. Such cells obtained from small amounts of peripheral blood could be used for transplantation. Alternatively, by adjusting culture conditions, abnormal cells (e.g., leukemic cells) might die off, thus accomplishing a form of in vitro purging. Functional stem cells can be maintained in culture for a few months, but growth of these cells still constitutes a formidable research challenge.

Gene Transfer

The hematopoietic stem cell is generally considered an ideal candidate for gene therapy. Many genetic diseases involve the stem cell, and many of the relevant genes have been cloned. Techniques for gene transfer make it possible to begin studies of gene transfer in human patients. However, the problem of cloning some of the larger genes, the problem of efficient gene transfer, the problem of gene expression and the problem of sustained gene expression represent major challenges. A recently recognized problem is that genetically modified cells may be recognized by the immune system of the host with subsequent rejection.

Summary

In summary, marrow grafting, now more appropriately called hematopoietic stem cell grafting, has advanced from early laboratory studies and desperate bedside therapeutic attempts in terminal patients to be considered standard therapy for selected diseases and stages of disease. Increasing application on an outpatient basis is rapidly lowering the cost of the procedure. The combined efforts of the many clinical marrow transplant teams and the interested basic science laboratories will undoubtedly make the coming decade an exciting and productive time for transplantation and cell biology and for the well-being of patients with otherwise incurable diseases.

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