Annotation

Bone marrow transplantation in India

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Beginning in 1970, last 18 years have witnessed a remarkable growth in the use of bone marrow transplantation (BMT). The procedure has been performed in various hematological disorders, both of malignant (acute and chronic leukemias, malignant lymphomas, multiple myeloma etc.) and non-malignant origin (severe aplastic anemia, thalassemia major, and other hemoglobinopathies), congenital immunologic deficiency diseases like severe combined immunodeficiency diseases and also in inborn errors of metabolism. In fact the list is rapidly increasing and there seems to be no sign of decreasing the enthusiasm. However, in a good number of disorders, the procedure remains largely experimental. But in some conditions, like severe aplastic anemia, acute myeloid leukemia in first remission, chronic myeloid leukemia in chronic phase, it has become the treatment of choice when a suitable donor is available.

Though there are different ways of doing BMT depending on the source of transplanted marrow, allogeneic BMT has become most popular worldwide. Autologous BMT (ABMT) when the patient himself acts as a donor, is also increasingly being applied at various centres. In this setting the patient's marrow is collected before administering high dose chemotherapy and/or radiotherapy and subsequently the marrow is infused to rescue the hematopoietic tissue. At the moment, there are 162 functional BMT centres in 26 different countries of the world performing an approximately 2500 transplants each year.

For allogenic marrow transplantation, suitable donor recipient selection remains the most important factor. Histocompatibility typing by serologic and mixed leukocyte culture technique is used to determine the alleles of the HLA-A, -B, DR, and -D loci. Identical (syngenic) twins are completely matched at all genetic loci and provide an ideal source of donor marrow. The incidence of graft rejection and GVHD is almost non-existent. However, statistical data show that the incidence of leukemic relapse is quite high in these transplants. Unfortunately, for allogeneic transplant, it is difficult to find a genotypically identical donor in a small family.

The conditioning or preparatory regimen ideally consists of high dose alkylating agents (cyclophosphamide, busulfan, melphalan etc.) alone or in combination, and/or total body irradiation (TBI) of 8 to 12 Gy. For majority, this seems to be adequate though for refractory leukemias, blastic phase chronic myeloid leukemia, high grade non-Hodgkin's lymphomas and high risk acute lymphoblastic leukemia, the regimen is largely inadequate as the relapse/failure rates
are very high. We have been using cyclophosphamide and TBI combination for leukemias and cyclophosphamide alone for severe aplastic anemia.

In spite of using fully HLA matched donors and immunosuppressive therapy with drugs like methotrexate, cyclosporin, cyclophosphamide, ATG alone or combination, the incidence of acute graft versus host disease (GVHD) remains high (35-60%). A combination of methotrexate and cyclosporin seems to be effective in reducing the incidence of acute GVHD but its impact on the long term survival is yet to be proved. Chronic GVHD also is quite a difficult condition to treat and the development of it renders the patient immunosuppressed for a prolonged indefinite period when he may succumb to severe opportunistic infections. The use of T-cell depletion procedures from the donor marrow also have failed to increase the success rate, because though the incidence of GVHD may be reduced using this procedure, the incidence of graft failure and relapse are high.

The Tata Memorial Hospital in Bombay initiated the procedure in 1983, for the first time in India. So far, six marrow transplants have been carried out; these include four acute myeloid leukemia in remission one severe aplastic anemia and one chronic phase myeloid leukemia. Two of them have died post-transplant due to acute GVHD and the remaining four alive and disease free between 850+ and 1640+ days. Grafting occurred in all cases. One patient is alive with chronic GVHD. All leukemia patients were prepared with a conditioning regimen of cyclophosphamide 60 mg/kg/day for two days and TBI of 12 Gy over 6 fractions. All transplants were allogenic, the donor being a fully matched sibling. All received post-BMT GVHD prophylaxis with methotrexate and remained in isolated laminar air-flow rooms till recovery. In spite of GVHD prophylaxis, two had developed grade IV GVHD and both succumbed to it. The patient with chronic de novo GVHD continues to be under immunosuppressive therapy, but the primary disease has not relapsed. The severe aplastic anemia patient recovered fully after the procedure.

Apart from GVHD, another complication responsible for high immediate post-BMT mortality is interstitial pneumonia. The exact cause of this complication is not known, but a few factors like the TBI, elderly age, GVHD, log interval between diagnosis and BMT have been shown to influence the incidence.

It is difficult to compare the results of BMT with conventional chemotherapy in acute myeloid leukemia as an ideal randomised trial is not possible. However, it seems that the incidence of immediate post-BMT mortality due to complications somewhat nullifies the ultimate disease-free survival in the patient population as a whole. For severe aplastic anemia, the procedure still remains the treatment of choice, though various centres are trying to compare it with the results of anti-thymocyte globulin.

Improved understanding of the immunobiology of marrow transplantation has led to the decrease in mortality from graft rejection, prevention and treatment of both acute and chronic graft versus host disease (GVHD) and further understanding is expected to provide a clue for eliminating resistant leukemic cells with modification of conditioning regimens. The results of autologous BMT in different leukemias are yet immature.