Biology of Bone Marrow Transplantation

Kamal Mehta
Asst. Professor, P.G Department of Zoology,
Jagdish Chandra D.A.V College, Dasuya (Punjab)-144205, India.
Email: kamal.davzoo@yahoo.in

Abstract-- ***Bone marrow transplantation technique involves the application of immunological principles and procedures for the treatment of a variety of neoplastic and hematological disorders involving bone marrow elements, including severe combined immunodeficiency disorders, leukemias, osteoporosis, various inherited disorders and solid tumors. In addition to this, bone marrow stem cells have been successfully transformed into functional neural cells and can also potentially be used to treat illnesses such as inflammatory bowel disease. No doubt this technique has undergone marvelous advancements in the past thirty years; still there is an urgent need for its improvement as reflected by its complications such as graft versus host disease and graft rejection reaction.***

Key Words-- ***Bone Marrow, Haemopoietic stem cells, Graft versus host disease, Graft rejection.***

I. INTRODUCTION

Bone marrow is the semi-solid fatty vascular tissue present within the bone marrow cavity of the spongy or cancellous portions of bones such as ribs, vertebrae, sternum and pelvis [1, 2]. It acts as haemopoietic tissue producing approximately 500 billion blood cells per day in human body, which join the systemic circulation via permeable vasculature sinusoids within the medullary cavity [3, 4]. Bone marrow produces all types of haemopoietic cells including both myeloid and lymphoid lineages. In humans, 4% of the total body mass is contributed by bone marrow that approximately equals to 2.6 kg. of body mass in an adult having 65 kilograms of body weight [5]. The fatty and vascular composition of bone marrow is not constant and varies with age as well as in response to systemic factors. On the basis of composition, bone marrow is of two types-red bone marrow (medulla ossium rubra) and yellow bone marrow (ossium flava medulla).Red bone marrow is rich in vascular component whereas yellow bone marrow is rich in fatty component. The proportion of red bone marrow is high in a newborn baby's bones that progressively transits into yellow bone marrow with advancing age [6]. In adults, red marrow is found mainly in the central skeleton, such as the pelvis, sternum, cranium, ribs, vertebrae and scapulae and variably found in the proximal epiphyseal ends of long bones such as the femur and humerus. Under special circumstances such as chronic hypoxia, reversion of yellow to red bone marrow takes place to increase blood cell production for increasing respiratory efficiency [7]. Bone marrow contains hematopoietic stem cells which give rise to all types of blood cells like red blood cells, white blood cells along with Platelets that are found in circulation [8]. Pathological conditions of bone marrow may lead to disorders such as aplastic anemia, leukemia, malignancies such as multiple myeloma, or infections such as tuberculosis, leading to a decrease in the production of blood cells and blood platelets [9].Even the radiation exposure as well as chemotherapy may affect bone marrow due to killing of haemopoietic stem cells leading to various immune related diseases. Bone marrow transplantation therapy is the solution to such severe diseases of the bone marrow, including certain forms of cancer such as leukemia. In addition to this, bone marrow stem cells have been successfully transformed into functional neural cells and can also potentially be used to treat illnesses such as inflammatory bowel disease [10,11].

II. METHODOLOGY OF BONE MARROW TRANSPLANTATION

Bone marrow aspiration is generally performed to assess the diseases involving the bone marrow in which a sample of red bone marrow is harvested from the top of the hip girdle (the iliac crest) under general or local anesthesia [12]. Generally, 10 ml/kg of the recipient's body weight is required. The aspiration is done using heparinised needles, the marrow being placed in heparinised, buffered culture medium. The mixture is filtered through fine meshes to produce a single cell suspension and nucleated cell counts are obtained. Blood group compatible recipients are given 2-6x10^8 nucleated cells/kg of body weight by intravenous infusion. Erythrocytes are given simultaneously. If the blood group of donor and recipient are not compatible, either the recipient undergoes plasmapheresis to remove anti-A or anti-B antibodies or the donor marrow is treated in vitro to remove the erythrocytes. The immune system of most recipients must be destroyed in order to prevent rejection of the marrow and to allow the development of new haemopoietic system. This is achieved by treating the recipient with cyclophosphamide (50-60 mg/kg, for 2 or 4 days) and by total body irradiation administrated over 3-5 days. This combination of therapies eliminates the immune system and has antineoplastic effect in most cancer patients.

Obviously, patients undergoing bone marrow transplantation to combat severe combined immunodeficiency disease do not require this treatment, since they lack a functioning immune system.Another option in addition to bone marrow aspiration is to administer certain drugs that stimulate the release of stem cells from the bone marrow into circulating blood [13]. An intravenous catheter is inserted into the donor's arm, and the stem cells are then filtered out of the blood. This procedure is similar to that used in blood or platelet donation. In adults, bone marrow may also be taken from the sternum, while the tibia is often used when taking samples from infants [14].In newborns, stem cells may be retrieved from the umbilical cord [15].A number of pathological conditions such as leukemia, multiple myeloma, anemia and pancytopenia can be recognized by bone marrow examination through aspiration technique. Then, the sample is clinically diagnosed for relative proportions of myeloid series and erythroid cells for analysing bone marrow functions as well as haematological disorders such as leukemia and anemia. The normal myeloid-to-erythroid ratio is around 3:1; this ratio may increase in myelogenous leukemias, decrease in polycythemias, and reverse in cases of thalassemia [16].These disorders are treated by bone marrow transplantation technique that involves harvesting of hematopoietic stem cells from one person and thereafter its infusion into another person (allogenic) or into the same person at a later time (autologous). Donors may be an identical twin (syngeneic); another closely related individual, usually a sibling, (allogeneic); or the patient himself (autologous). If compatibility of major histocompatibility antigen (HLA) identity exists between donor and recipient persons, infused cells will then travel to the bone marrow and initiate blood cell production. The bone marrow of the patient is firstly killed off with drugs or radiation, and then the new stem cells are introduced. Historically, the first reported case was that of a 19-year-old female with gold-induced aplasia who received ABO matched marrow transfused intravenously from her brother. In cancer patients, hematopoietic stem cells are sometimes harvested and later infused back when the therapy is finished to restore the immune system [17]. In 2013, following a clinical trial, scientists proposed that bone marrow transplantation could be used to treat HIV in conjunction with antiretroviral drugs however, it was later found that HIV remained in the bodies of the test subjects [18-20].Success of the transplant in indicated by an increasing total leucocytes count (TLC), raised levels of circulating monocytes and the presence of mature neutrophils in the circulation between two to four weeks after transplantation. As these parameters normalize, antibiotic therapy can be stopped and transfusion becomes unnecessary. Unfortunately, the technique is not always successful and graft versus host disease and infections are responsible for 10-30% failure rate in the first 30 days following transplantation. Other causes of transplant failure include interstitial pneumonia, and veno-occlusive liver disease.

III. COMPLICATIONS IN BONE MARROW TRANSPLANTATION

The major complications that may arise during bone marrow transplantation are Graft-versus-Host Disease (GVH) and Graft rejection reaction. Graft-versus-Host Disease involves sensitization of transfused donor immunocompetent lymphocytes that react to host cellular antigens with signs of disease. It is caused by the presence of immunocompetent cells in an organ given to an immunocompromised host. It even occurs in patients, who are HLA identical with their donors, the disease being attributed to minor differences in histocompatibility. The disease presents as a skin rash associated with diarrhea and jaundice. In severe disease, the rash resembles extensive second degree burns and water dirrohoea is associated with malabsorption, cramps and gastrointestinal bleeding. Hyperbilirubinaemia is often seen due to inflammation of small bile ducts as a direct consequence of disease process.It occurs in 25% to 75% of allogeneic transplants and a significant proportion of patients die as a result [33, 34]. Resulting from major histocompatibility (HLA) differences, the phenomenon is apparently due to minor antigen incompatibility when transplants are HLA identical. Modern immunosuppressive therapy involves an array of immunosuppresive agents such as prednisone, azathioprin, chemotherapeutic agents such as cyclophosphamide and methotrexate, antilymphocyte serum, and cyclosporine to limit graft versus host disease [35].It has reduced the risk of acute graft versus host disease to 25%. Established acute graft versus host disease has been treated with infusions of antithymocyte globulin, prednisolone and monoclonal antibodies, however, success was limited. In bone marrow transplants, the donor marrow has been incubated in vitro with T-cell specific monoclonal antibodies, either with complement or conjugated to toxins. These treatments decreased the incidence of graft versus host disease by depleting the marrow of donor T-cell.

Graft rejection reaction has been indicated in bone marrow transplantation done for treatment of aplastic anemia in 30% cases. Unfortunately, the technique is not always successful and graft versus host disease and infections are responsible for 10-30% failure rate in the first 30 days following transplantation. Other causes of transplant failure include interstitial pneumonia, and veno-occlusive liver disease.

IV. CLINICAL APPLICATIONS OF BONE MARROW TRANSPLANTATION

Bone marrow transplantation technique has vast medical applications especially in the treatment of bone marrow associated disorders such as radiation accidents, aplastic anemia, acute leukemias, chronic myelogenous leukemia, immunodeficiency diseases, hemoglobinopathies and related problems. Bone marrow is highly susceptible to radiation damage as evident by Chernobyl disaster and Hiroshima Nagasaki atomic bomb episodes. Early attempts to transplant marrow were undertaken as a result of radiation accidents during the 1950s and were found to be effective [21]. Aplastic anemia is a rare disorder of haemopoietic stem cells of the bone marrow. It may results into death of the possessor within three months [22-24]. Generally, this disorder is treated by administration of androgen and other drugs but bone marrow transplantation has been found to be more effective in this case [25-27]. Normally allogeneic transplants are done but they may suffer from rejection (approximately 30%) due to Graft versus host rejection disorder. Syngeneic (homologous twin) transplants are found to be more successful [28]. Success rate for bone marrow transplantation done to treat aplastic anemia is 70% with restoration of normal marrow function and long-term survival. Acute leukemias are the cancers of the bone marrow stem cells which show uncontrolled proliferation, thus, inhibiting the multiplication of normal marrow constituents. It leads to abundance of relatively nonfunctional circulating and in situ bone marrow cells resulting in life-threatening problems of hemorrhage and infection. The patient of acute leukemia can survive up to five years with dependence on chemotherapy. If bone marrow transplantation technique is used for treatment of acute leukemia, it can increase the survival rate up to 60% [29, 30]. More recently, investigators have employed autologous bone marrow transplantation for the treatment of acute leukemia. Perfection of this technique promises an unlimited marrow supply and a solution to the problem of a limited availability of suitable donors for allogeneic transplantation. A translocation of genes between chromosomes 12 and 9 leads to the development of chronic myelogenous leukemia that involves a neoplastic change in precursor stem cells giving rise to all of the non-lymphocytic marrow cell lines. The success rate of bone marrow transplantation in this case is only 15%. In addition to this, bone marrow transplantation technique has been used extensively for the treatment of Immunodeficiency disorders like severe combined immunodeficiency disorder (SCID), Wiscott-Alridge syndrome, osteoporosis, paroxysmal nocturnal hemoglobinuria, and Gaucher's disease[31,32]. Continuous efforts and improvements are being made for increasing the efficacy of bone marrow transplantation in conjunction with genetic engineering and molecular biology to treat common hemoglobinopathies like sickle cell anemia and thalassemia major. Autologous bone marrow transplantation that involves transplantation of cryopreserved bone marrow from the recipient and subsequent infusion for complete marrow reconstitution has been extensively used for treatment of variety of tumours like breast cancer, melanoma, neuroblastoma, Ewing's sarcoma, lymphoma, and small cell carcinoma of the lung. The autologous bone marrow transplantation method overcomes the immunologic problems of graft-versus-host disease and graft rejection. In addition, the marrow may be treated with monoclonal antibodies to remove potential neoplastic cells, yhus extending the use of this technique.

V. CONCLUSION

The bone marrow transplantation implies the application of principles of immunology for the treatment of diseases associated directly or indirectly with haemopoietic stem cells of bone marrow. No doubt this technique has undergone marvelous advancements in the past 30 years; still there is an urgent need for its improvement as reflected by its complications such as Graft-versus-Host Disease and Graft rejection reaction. The steady development of new methods of immunomodulation, microbial therapy, cell stimulating growth factors and genetic engineering along with further prospective evaluation of high dose therapy promise to benefit patients with a wide variety of hematologic, immunologic, and neoplastic disorders. Immunologic problems and microbial infections remain formidable challenges to be overcome [36].

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