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BONE MARROW TRANSPLANTATION: A THERAPY TO EMBRACE LIFE FROMDEATH

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ABSTRACT

Stem cells are the center for regenerative medicine. Given a right signal these undifferentiated cells have a remarkable potential to develop into specialized cell types (blood cells, heart cells etc.) in the human body. Stem cells, therefore, can be used in cell-based therapies to replace/repair damaged tissues and/or organs. Ongoing research in the area of stem cells focuses on their potential application (both embryonic stem cells and adult stem cells) to create specialized cells and replace the damaged ones. Hence, this cutting-edge technology might lead to new ways of detecting and treating diseases. Bone marrow transplantation represents the technical application of basic immunologic principles to the treatment of a variety of neoplastic and allied disorders that originate in the bone marrow. The results have improved during the past 15 years, being most striking for the treatment of the acute and chronic leukemias. The promise of autologous bone marrow transplantation for the treatment of leukemias and solid tumors is awaiting the perfection of techniques for the effective removal of residual neoplastic cells as well as more effective therapy. The use of this technique at its present stage of development for the treatment of benign hematologic disorders, which cause severe morbidity (ie, thalassemia or sickle cell anemia), is controversial, raises serious ethical issues, and cannot be recommended routinely at this time. Complications of bone marrow transplantation such as graft rejection, graft-versus-host disease, and opportunistic infections are discussed. The present review, therefore, focuses on the growing use of stem cell transplantation in regenerative medicine to treat a variety of diseases. This review also provides the current status of the field with a particular emphasis on bone marrow transplantation.

KEYWORDS: BMT, GVHD, MHC, HLA, ALL, AML, CLL, CML, HL, NHL, MDS, MPN, Myeloma.

INTRODUCTION

Bone marrow transplantation (BMT) is the therapeutic modality used in the treatment of many benign or malignant, inherited or acquired hematologic diseases.[1] BMT is characterized by the removal of stem cells from the donor, which may be the patient himself (autologous transplant) or another compatible donor (allogeneic transplant), and the infusion of these cells into the patient after a conditioning period. Progenitor cells infused into the bloodstream are implanted in the bone marrow, promoting hematopoietic reconstitution. The annual frequency of performing BMT with high success rates are growing exponentially due to a greater knowledge of the human histocompatibility system and accurate examinations in the selection of bone marrow donors. However, graft versus host disease (GVHD) still represents one of the most common complications after allogeneic transplant.[3] Bone marrow transplantation is used extensively for the treatment of many disorders involving bone marrowelements, including severe combined immunodeficiency states, leukemias, osteoporosis, various inherited disorders and more recently, solid tumors. 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.[4,5] Following World War II and the initiation of the atomic age, animal experimentation by groups in Chicago, Bethesda, Md, and Oak Ridge, Tenn, demonstrated that the myelosuppressive effects of radiation could be overcome. Jacobson showed that irradiated mice whose spleens were shielded could be protected from the lethal effects of radiation.[6] Lorentz et al showed that lethal radiation effect in mice and guinea pigs could be prevented by transfusing syngeneic guinea pig bone marrow.[7] Other reports also clearly demonstrated the protective effect of bone marrow infusion against lethal irradiation.[8] In 1957, Thomas reported the first series of human bone marrow recipients, demonstrating that large amounts of marrow could be safely infused intravenously and describing transient marrow engraftment in one individual.[9] Mathe then reported on the attempted use of bone marrow transfusions in six victims of radiation accidents.[10] Following these initial attempts, bone

marrow transplantation progressed slowly until the 1960s. Led by Thomas and associates at Seattle, Wash, human marrow transplantation for aplastic anemia was initiated and gradually progressed. Initial attempts at all organ transplants were thwarted by rejection, however, and further progress awaited a clearer understanding of transplantation immunology.[11-13] GVHD is a complication that occurs through the activation of T cells in response to molecules from the major histocompatibility complex (MHC) after an allogeneic histocompatible BMT.

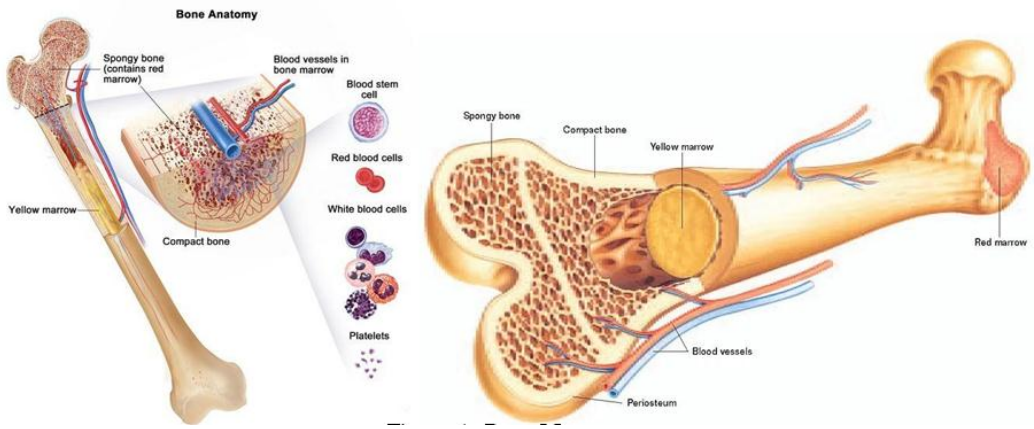

Figure-1: Bone Marrow.

Donated T cells recognize molecules from the host tissue as foreign. The incidence of GVHD varies from 6 to 80% according to patient age, donor type, stem cell source, graft manipulation and use of lymphocyte infusions after the transplant.[3]

The source for the earliest transplants was the marrow of a healthy donor who had the same tissue (human leukocyte antigen [HLA]) type as the patient. Usually, the source was a brother or sister. When a patient needs an allogeneic transplant (stem cells from a donor), his or her doctor turns to a registry of donors—a list of people who are willing to donate to any patient in need—and of donated umbilical cord blood. The Match Registry®, operated by the National Marrow Donor Program®, is the world's largest listing of volunteer donors, more than 9.5 million. Using information about the patient's HLA type, a computer program is used to scan the database of HLA types of volunteer donors.

Disorders treated by boneMarrow transplantation

Acute lymphoblastic leukemia (ALL)

1. The decision to perform a transplant for an adult who has ALL depends on the features of the leukemia, the patient's general health and the patient's age.
2. For patients with high-risk ALL, an allogeneic stem cell transplant may be an option in first remission for a patient who has a suitable donor available.
3. For patients with standard-risk ALL in first remission, the choice between allogeneic transplantation and continued chemotherapy is less clear. Discuss standard and/or reduced-intensity allogeneic stem cell transplantation with your doctor to determine if either is recommended for you.
4. Autologous stem cell transplantation outside of the clinical-trial setting is not commonly used to treat ALL.
5. Most children with ALL (about 75 to 80 percent) do not need stem cell transplantation. A child with refractory disease (a poor response to treatment) or relapsed ALL is considered for transplantation with an allogeneic transplant.

Acute myeloid leukemia (AML)

1. Favorable-risk AML: Stem cell transplantation is generally not recommended with first complete remission.
2. Intermediate-risk AML: Discuss standard and/or reduced-intensity stem cell allogeneic transplantation with your doctor to determine if either is recommended for you.
3. High-risk AML: Allogeneic stem cell transplantation is generally recommended with first remission for patients who are candidates for a transplant and have a suitable allogeneic donor. Reduced-intensity allogeneic stem cell transplantation may be recommended for older patients or patients who have certain co-morbidities.
4. Autologous stem cell transplantation may be recommended for certain patients.

Chronic lymphocytic leukemia (CLL): Allogeneic transplantation (usually reduced-intensity but sometimes standard) is being studied in clinical trials to treat patients who have CLL that has certain high-risk features or has relapsed after standard therapies.

Chronic myeloid leukemia (CML): Oral CML therapies are generally used to treat newly diagnosed CML patients. In cases of advanced or refractory disease (a poor response to treatment), standard allogeneic stem cell transplantation (or reduced-intensity allogeneic stem cell transplantation) may be recommended for patients

who have a suitable allogeneic donor available.

Hodgkin lymphoma (HL): Autologous stem cell transplantation is used to treat HL patients whose disease relapses after initial therapy. Standard and reduced-intensity allogeneic stem cell transplantation are under study in clinical trials to treat HL patients who have a suitable allogeneic donor.

Non-Hodgkin lymphoma (NHL): Autologous stem cell transplantation is generally used to treat patients who have relapsed or who have refractory disease; transplantation in first remission is only done in clinical trials with some exceptions—for example, in certain cases of mantle cell lymphoma. Allogeneic transplantation is used to treat selected patients who have NHL.

Myelodysplastic syndromes (MDS): A standard allogeneic stem cell transplant (or a reduced-intensity allogeneic stem cell transplant for older or other selected patients) may be recommended for people who have intermediate- or high-risk MDS and a suitable allogeneic donor available. Autologous stem cell transplants are used infrequently.

Myeloma: Autologous stem cell transplantation is an important part of treatment for certain myeloma patients. Allogeneic stem cell transplantation is not a common treatment for myeloma patients but may be used for selected younger patients who have a suitable allogeneic donor available. Reduced-intensity allogeneic stem cell transplantation is used in some cases following autologous stem cell transplantation for patients who have a suitable allogeneic donor available.

Myeloproliferative neoplasms (MPNs): Myelofibrosis: A standard allogeneic stem cell transplant (or a reduced-intensity allogeneic stem cell transplant for older patients or patients who have certain comorbidities) may be recommended for certain patients who have a suitable allogeneic donor available. Polycythemia vera and essential thrombocythemia: Allogeneic stem cell transplantation and reduced-intensity allogeneic stem cell transplantation are occasionally used to treat the disease.

Figure-2: Bone Marrow Transplantation.

Radiation Accidents: The bone marrow constantly proliferates and is, therefore, among the most sensitive tissues to radiation exposure. Early attempts to transplant marrow were undertaken as a result of radiation accidents during the 1950s.[10] More recently, the immediate medical consequences of high dose radiation exposure and the potential role of allogeneic bone marrow transplantation in its treatment has been made more poignant by the major accident at Chernobyl.[16] Thermal injury from extremely high temperatures as well as injury to other organ systems from high radiation doses makes the prognosis of those exposed extremely poor.[2]

Aplastic Anemia: Aplastic anemia is a rare disorder involving the impairment of hemopoietic stem cells, which ultimately results in a mortality of 90% within three months of diagnosis.[15-17] The disorder is usually refractory to androgen and other drug therapy. Bone marrow transplantation has become the treatment of choice. Syngeneic (homologous twin) transplants have been performed and are the ideal, however, allogeneic transplants have been more common. Problems of allogeneic transplant recipients include marrow rejection (approximately 30%) and GvHD. Rejection is believed to be caused by "minor transplantation antigens" and attempts have been made to increase marrow engraftment and survival by decreasing prior sensitization. Storb et al, for example, have demonstrated an increased rate of marrow recipient survival in patients transplanted before the transfusion of any blood products. Although engraftment and GvHD continue to be problems for aplastic anemia recipients, to date, 70% have had a restoration of marrow function and long-term survival.[2]

Immunodeficiency States: The first successful use of bone marrow transplantation to restore patients with congenital immunodeficiency syndrome was reported in a Swiss-type severe "combined" immunodeficiency patient. Transplantation has been shown to be the treatment of choice for this disorder as well as in Wiscott-Alridge syndrome. In fact, a total of 20 potentially lethal blood disorders have now been corrected using bone marrow transplantation, including osteoporosis, paroxysmal nocturnal hemoglobinuria, and Gaucher's disease.[2]

Hemoglobinopathies and Related Problems: Investigators in bone marrow transplantation have long wanted to transplant patients with hemoglobinopathies. Although animal studies have indicated the applicability of this teohnique to inherited anemias, there are few cases in the literature of its actual successful application in human hereditary anemias. This is because of the relatively long-term survival of most patients with the common hemoglobinopathies, such as sickle cell anemia, despite significant chronic morbidity. Thalassemia major is the only major hemoglobinopathy that has routinely been transplanted owing to its poor prognosis. Only one case of homozygous sickle cell anemia has been "cured" when transplanted for ALL. Further use of this technique awaits the practical development of molecular biology, cloning, and genetic engineering.[2]

Sources of bone marrow stem cells: The basis of bone marrow transplantation is the provision of hematopoietic stem cells to repopulate the bone marrow. Initially bone marrow was considered to be the only source of these cells, but recently alternative sources of stem cells have been recognized.[4]

Bone marrow
Syngeneic-from an identical twin.

Matched allogeneic-from a sibling compatible for major histocompatibility complex ("HLA-identical"); each sibling has a 1:4 chance of being compatible.

Mismatched allogeneic-usually from a family member, but not compatible for major histocompatibility complex.

Unrelated donor-from a donor registry, donor thought to be compatible.

Autologous-patients are their own donors, thus overcoming any compatibility problems.

Peripheral blood stem cells- A relatively recent development in bone marrow transplantation.

Haematopoeitic stem cells are mobilized from the bone marrow and enter the peripheral blood as the marrow regenerates from chemotherapy (usually with the aid of recombinant growth factors). These cells can be collected by a cell separator and processed identically to a marrow donation.

Umbilical cord blood stem cells- The most recently identified source of haematopoietic stem cells. Due to the relatively small numbers of stem cells this source is only applicable to small children.[4]

Most transplants are of matched allogeneic bone marrow, autologous bone marrow, and peripheral blood stem cells.

Timing of Transplantation and Tissue Typing: The points at which transplant options are considered during an individual's disease course vary. Transplantation is recommended for some patients in first remission. For others, it is recommended later on in the course of treatment for relapsed or refractory disease. This decision may depend on the response of the underlying disease to initial therapy and to other factors discussed in the previous section. If allogeneic transplantation is a consideration, it is best to have the patient's tissue typing (HLA typing) done early in the disease course. The patient's siblings should have tissue typing. If the patient does not have a sibling match, then decisions about whether to enter the patient's tissue typing into unrelated donor registries can be made. It is a good idea to do this to determine whether suitable unrelated donor matches or cord blood matches will be available if needed. HLA tissue typing is different from the red blood cell typing used to determine blood transfusion compatibility. Almost every cell in the body displays what are called human leukocyte antigen (HLA) molecules on the cell surface. The immune system uses these molecules to verify that a given cell is part of the body and not a foreign invader. The HLA type can be determined by looking directly at the person's DNA, obtained from the blood or via cells from the inside of the cheek. The best transplant outcomes happen when the patient and the donor are HLA well-matched, meaning they share the same or almost the same HLA molecules. The immune reactions that occur when individuals receive a stem cell transplant are largely determined by the patient's and the donor's human leukocyte antigens; these antigens are cell surface proteins. In general, human cells have 46 chromosomes: pairs of chromosomes numbered from 1 to 22 plus two sex chromosomes (either XX in a female or XY in a male). A person's HLA type is governed by genes on chromosome 6. Testing of potential donors involves obtaining either a blood sample (usually three to four tubes of blood) or a scraping from the cheek inside the mouth (buccal scraping/swab scraping). Both samples yield enough cells for typing at protein and DNA levels. On average, a person has one chance in four of having the same HLA type as his or her sibling, but many patients will not have a sibling with the same tissue type (Figure 3).

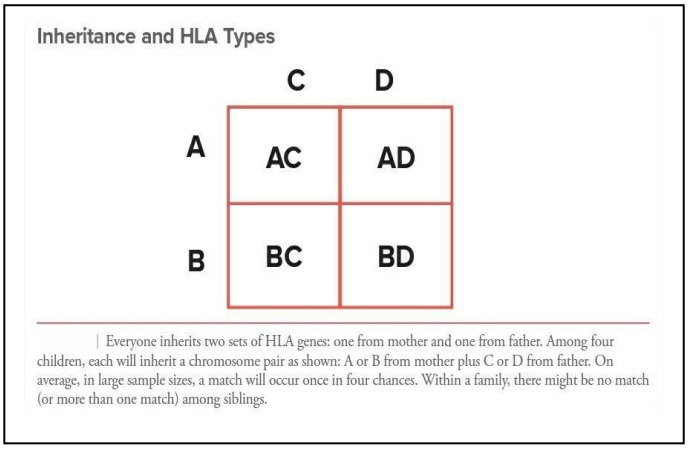

Figure-3: HLA types.

Each parent's contribution to the HLA type is referred to as a "haplotype." The term "haploidentical" indicates that the potential donor shares half the HLA type of the potential recipient. The HLA system is broken down into two groups of cell surface antigens: class I and class II. Class I antigens are determined by genes referred to as "A," "B" and "C." Class II antigens are determined by genes referred to as "D." A, B, C and D have many variations called "alleles" that make each individual unique. For example, one person may have A1, another A2, another A3 and so on. In families, these variations are minimized, making it more likely to find a match among siblings.

About 70 percent of patients who need an allogeneic stem cell transplant do not have a suitable donor in their family. Efforts are being made to develop methods to permit a transplant between individuals who are only partially matched. For example, the ability to transplant from parent to child would make the availability of transplantation nearly universal for childhood disorders. Children's bodies are more tolerant of deviations from ideal matching, and it is hoped that with better control of the immune reactions involved, moderately mismatched transplants may be feasible.

Pre-transplant tests

Several tests are performed before the bone marrow transplant, to identify any potential problems.
Tests include:

- Tissue typing and a variety of blood tests
- Chest X-ray
- Pulmonary function tests
- CT or CAT scans
- Heart function tests including an electrocardiogram and echocardiogram (ECG)
- Bone marrow biopsy
- Skeletal survey

In addition, a complete dental exam is needed before a bone marrow transplant, to reduce the risk of infection. Other precautions will also be taken before the transplant to reduce the patient's risk of infection.

Harvesting bone marrow

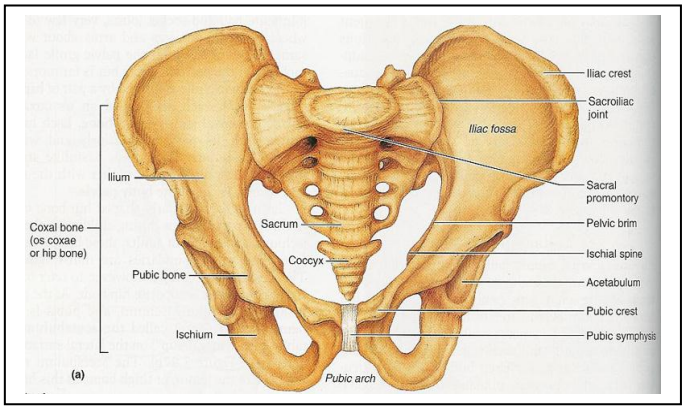

Figure-4: Pelvic Girdle.

he concentration of red marrow is highest in the bones of the hips (ilium). The doctor will insert a needle into the bone and withdraw some of the bone marrow, which is then stored and frozen. Bone marrow can be obtained for examination by bone marrow biopsy and bone marrow aspiration. Bone marrow harvesting has become a relatively routine procedure. It is generally aspirated from the posterior iliac crests while the donor is under either regional or general anesthesia.[17]

It can also be taken from the sternum, and from the upper tibia in children, because it still contains a substantial amount of red bone marrow. The doctor will insert a needle into the bone, usually in the hip, and withdraw some of the bone marrow. It is then stored and frozen. Guidelines established by the National Marrow Donor Program (NMDP) limit the volume of bone marrow removed to 15 mL/kg of donor weight. A dose of 1 X 103 and 2 X 108 marrow mononuclear cells per kilogram are required to establish engraftment in autologous and allogeneic marrow transplants, respectively. Complications related to bone marrow harvesting are rare. They involve problems related to anesthesia, infection and bleeding. Another way to evaluate bone marrow function is to give certain drugs that stimulate the release of stem cells from the bone marrow into circulating blood. The blood sample is then obtained, and stem cells are isolated for microscopic examination. In newborns, stem cells may be retrieved from the umbilical cord.

How is bone marrow transplanted?

Before the transplant, chemotherapy, radiation, or both may be given. This may be done in two ways:

Ablative (myeloablative) treatment: High-dose chemotherapy, radiation, or both are given to kill any cancer cells. This also kills all healthy bone marrow that remains, and allows new stem cells to grow in the bone marrow. Reduced intensity treatment, or a mini transplant: Patients receive lower doses of chemotherapy and radiation before a transplant. This allows older patients and those with other health problems to have a transplant. A stem cell transplant is usually done after chemotherapy and radiation are complete. The infusion of either bone marrow or peripheral blood is a relatively simple process that is performed at the bedside. The bone marrow product is infused through a central vein through an IV tube over a period of several hours. Autologous products are almost always cryopreserved; they are thawed at the bedside and infused rapidly over a period of several minutes. After entering the bloodstream, the hematopoietic stem cells travel to the bone marrow. There, they begin to produce new white blood cells, red blood cells, and platelets in a process known as engraftment. Engraftment usually occurs 2 to 4 weeks after transplantation. Minimal toxicity has been observed in most cases. ABO-mismatched bone marrow infusions can sometimes lead to hemolytic reactions. Dimethyl sulfoxide (DMSO), which is used for the cryopreservation of stem cells, may give rise to facial flushing, a tickling sensation in the throat, and a strong taste in the mouth (the taste of garlic). Rarely, DMSO can cause bradycardia, abdominal pain, encephalopathy or seizures, and renal failure. To avoid the risk of encephalopathy, which occurs with doses above 2 g/kg/day of DMSO, stem cell infusions exceeding 500 mL are infused over 2 days, and the rate of infusion is limited to 20 mL/min.

Doctors regularly check blood counts. Complete recovery of immune function can take several months for autologous transplant recipients and 1 to 2 years for patients receiving allogeneic or syngeneic transplants. Blood tests will confirm that new blood cells are being produced and that any cancer has not returned. Bone marrow aspiration can also help doctors determine how well the new marrow is working.

Early complications: Complications may be seen in the first few weeks after transplantation, many arising from the chemoradiotherapy conditioning regimen.[18]

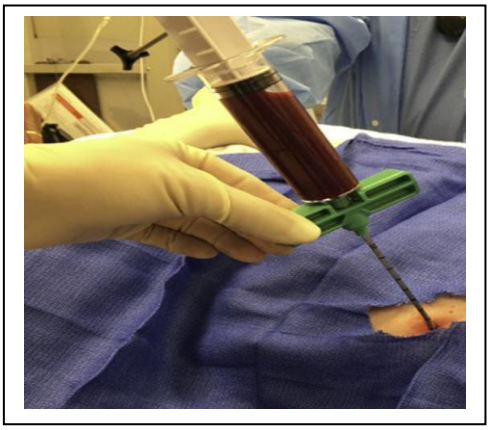

Figure-5: Transplantation of bone marrow.

Reconstitution by donor marrow generally begins 3-4 weeks after transplantation, but patients remain immunosuppressed for many months, even once blood counts have recovered, owing to factors such as lymphocyte subset imbalance and impaired mucosal defense. Infectious disease is a major cause of morbidity and mortality in patients who have received bone marrow transplants. Distinct phases of the post-transplant period are associated with distinct infections. The initial neutropenic period is characterized by reactivation of herpes simplex virus and bacterial and fungal infections. These require prompt treatment with broad spectrum intravenous antibiotics and antiviral and antifungal agents. Treatment often has to be empirical, while the results of specific cultures are awaited. In the post engraftment phase, cytomegalovirus and Pneumocystis carinii are common infections. By 100 days after transplantation, infection rates are falling; however, late infections with varicella zoster virus and encapsulated organism are not uncommon. Interstitial pneumonitis is a dreaded complication. It has a mortality of about 80% and the potential for rapid progression to respiratory failure. Its etiology is complex, and clinically it is characterized by fever and cough. Treatment is supportive, although steroids are also commonly given.[4]

Graft versus host disease occurs when the donated marrow recognizes the recipient tissue as foreign.

Early complications of bone marrow transplantation
Regimen related toxicity
Mucositis, Cystitis, Cardiac dysfunction Renal dysfunction
Neurologic dysfunction, Hepatic veno-occlusive disease, Marrow graft failure, Immunodeficiency
Infection, Interstitial pneumonitis
Acute graft versus host disease [4]

Acute graft versus host disease (within 100 days of transplantation) is the major life-threatening complication of allogeneic bone marrow transplantation and is characterized by fever, rash, diarrhoea, liver dysfunction, and immune compromise of varying severity. The diagnosis of graft versus host disease can be confirmed histologically by appropriate biopsy. It is highly unlikely that primary care physicians would be involved in this early complication of bone marrow transplantation. Treatment consists of immunosuppressive agents such as corticosteroids, cyclosporin, and lymphocyte directed monoclonal antibodies. Invivo immunosuppression is given for three to six months after allogeneic transplantation in an attempt to prevent, or ameliorate, graft versus host disease; it is generally in the form of methotrexate and cyclosporin. Alternatively, the donor marrow can be depleted of Tcells in vitro. This is effective in preventing graft versus host disease, but it seems to increase relapse rates, presumably because the graft versus leukaemia effect is also lost.[18]

Chronic graft versus host disease (occurring later than 100 days after transplantation) is an autoimmune like condition that affects 25-50% of long term survivors of allogeneic bone marrow transplantation. Chronic graft versus host disease has features that can resemble systemic sclerosis, lichen planus, systemiclupus erythematosis, Sjogrens syndrome, primary biliary cirrhosis, or bronchiolitis obliterans.[19]

The principal manifestations of chronic graft versus host disease are
Skin changes: Dry eyes
Dryness Infections
Changes in pigmentation Weight loss
Thickening Contractures
Abnormal liver function tests
Oesophagitis
Dry mouth or mucositis
Treatment is complicated but generally consists of immunosuppression with steroids, azathioprine, and cyclosporin.

Long term complications: Even if they are cured of their disease, patients who have undergone bone marrow transplantation are prone to a series of long-term complications. As the results of bone marrow transplantation improve, these become increasingly important. Complications include cataracts (from the radiotherapy), abnormalities of pulmonary function, endocrine abnormalities (hypothyroidism, reduced growth), secondary malignancies, gonadal dysfunction, endocrine dysfunction, neurologic impairment, immunodeficiency, infection, chronic graft versus host disease, infertility.[20] Infertility is an almost inevitable consequence of total body irradiation and very common after high dose chemotherapy. In view of the young patient age infertility, together with the fear of disease relapse, probably represents the major long-term problem that patients face. For men, semen donation is possible before chemotherapy, although patients are often either too ill to donate or the semen is of inadequate quality to be of use. For women, egg donation is generally not logistically possible, and it is now possible to store only human embryos, not eggs. Although most patients adapt well after bone marrow transplantation, studies have documented that25-50% of patients will have difficulties with sexual function, returning to employment, and psychosocial functioning.[21-23] Children require revaccination after bone marrow transplantation, generally after one year, initially with inactivated vaccines. Vaccination before this time may beineffective and possibly dangerous.[4]

CONCLUSION

Bone marrow transplantation represents the technical application of immunology to the treatment of human disease. The sophistication of the technique has improved considerably over the past 30 years. It has become the treatment of choice for aplastic anemia and congenital severe combined immunodeficiency disease. Bone marrow transplantation has been used rarely for hemoglobinopathies and associated marrow stem cell disease. Future applications await technical advances in molecular biology and genetic engineering. Mixed results have been found in the treatment of acute and chronic leukemias where transplantation is complicated by GvHD and relapse in addition to opportunistic infections. The promise of syngeneic transplants has also been tempered by increased relapse rates.

Allogeneic transplantation early during the first remission for ANLL and early during the second remission in ALL is associated with significant survival rates which, thus far, have been superior to chemotherapy. The use of autologous marrow transplantation promises an unlimited source of marrow if problems of marrow infiltration in the case of solid tumors or blastic contamination in leukemic remissions can be overcome. Immunologic problems and microbial infections remain formidable challenges to be overcome. 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.

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