Allogeneic and Autologous Bone Marrow Transplant Experiences in Hawaii

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Allogeneic bone marrow transplant (BMT) was first performed successfully at St. Francis Medical Center in 1978. Since that time, 91 BMTs have been performed for aplastic anemia, leukemia, lymphoma, and Stage II, III and IV breast cancers. This article will explain the methods, complications and results of BMT in Hawaii.

Methods

Bone marrow transplant experience in Hawaii has been that of purged or non-purged autologous and allogeneic. Autologous is defined as marrow taken from the patient. It is purged with chemotherapeutic agents or monoclonal antibodies if marrow is involved with tumor, or non-purged if marrow is not involved with tumor. The marrow is stored after being frozen with liquid nitrogen. The patient is treated with total body irradiation, fractionated 225 rads for 5 doses and/or with chemotherapeutic agents such as cyclophamide (CTX), etoposide (VP 16), busulfan (BU), and carmustine (BCNU) in escalated doses (4 to 10 times normal doses). After chemotherapy and/or radiation, the marrow is thawed and re-infused into the patient through a central venous catheter.

Allogeneic transplant is performed between a donor and recipient. The healthy donor usually is an HLA-identical sibling, although HLA-identical unrelated donors recently have been used. The 6th chromosome harboring the HLA locus must be identical or with no more than 1 mismatch in the 6 antigens. The ABO blood type locus in the 9th chromosome can be crossed and a mismatch also may result in similar good results. In Hawaii, a donor is found by HLA typing of family members or through local and national registries. The donor must be free of hepatitis, AIDS, and in good physical condition. The recipient must be young and otherwise healthy with no infectious disease, diabetes, cardiac disease or severe respiratory problems. Once a donor/recipient pair is identified, the recipient undergoes total body irradiation of fractionated 225 rads for 5 doses, and/or receives chemotherapy with CTX,VP 16, BU, or BCNU. Following this, the patient is allowed to rest for 48 hours. The donor marrow is then harvested and infused into the recipient within 24 hours. The amount of marrow given is 3×10^8 of nucleated cells per kilogram of recipient weight.

After infusion of marrow, the recipient is maintained in a special room with Hepafilter air conditioning and 10 mm of positive pressure. The patient is maintained on a specific diet consisting of no fresh fruits or vegetables, and all meals are thoroughly cooked to avoid this source of infection. Specific oral antibiotics and antifungal medications are given prophylactically. Visitors must comply with strict rules for washing their hands and must wear masks and gloves to avoid contaminating these immunosuppressed patients. Hospitalization for 30 to 500 days generally is needed to reconstitute marrow and obtain a WBC > 4,000 cells/mm^3. The patient is given granulocyte-colony stimulating factor (G-CSF) or granulocyte and macrophage-colony stimulating factor (GM-CSF) in order to stimulate WBC production. RBCs are slower to reconstitute and platelets may require 3 to 6 months before the count becomes normal.

Although the WBC count may become normal, the function of these cells can be depressed for as long as a year. These patients will require monthly intravenous immunoglobulin and cyclosporine for 6 months. If all goes well, at the end of the 6 months, these patients are on no medication and can behave almost normally. At the end of 1 year, the majority who survive in a disease-free state are as healthy as any in their age group.

Results

Sixty-seven allogeneic bone marrow transplants have been performed at St. Francis Medical Center (SFMC) for various stages of leukemia, aplastic anemia, and lymphoma since 1978 and the majority of these were for advanced disease. When broken down by age groups, stage of disease, and type of disease, the numbers of patients for each category would be a relatively small 3 to 5 for each category. Comparisons for such small numbers would not be meaningful. At present, 23 are alive, in complete remission and disease-free: One patient is

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alive with recurrent disease; of the 23 who are alive, 19 are back to full employment and activity, 2 are at home and 2 remain hospitalized.

Sixteen autologous harvests have been performed at SFMC, followed by 11 transfusions: Five of these patients are in remission and disease-free and 6 have died. Four autologous purged BMTs have been performed; 2 have survived in complete remission (disease-free). The first was done in conjunction with Kapioloni Medical Center for Women and Children.

Discussion

Autologous BMT, purged or non-purged, has been performed in Hawaii for: Leukemia in remission, lymphoma with minimal or no bone involvement, and breast cancer as an adjutant therapy in those patients with 10 or more positive nodes or metastatic disease. Allogeneic BMT is performed for aplastic anemia, acute leukemias, chronic leukemias, and lymphoma. Currently, there appears to be no benefit of allogeneic BMT in solid tumors.

The results from our center are comparable to many U.S. centers. The success rate for bone marrow transplant is quite variable and depends on: 1) age, 2) disease type: acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), Lymphoma - B-cell, T-cell, Hodgkin's or non-Hodgkin's, 3) stage of disease (first remission, relapse, second remission, second relapse, accelerated disease or blastic crisis), and 4) overall physical condition of the patient.

1) Age. Allogeneic BMTs generally are limited to the younger patient. Those patients under 20 years of age have the best results. Intermediate results occur in 20 to 30-year olds, and BMT is contraindicated in those over 45 years of age because of the high morbidity and mortality.

2) Type of disease. Aplastic anemia has excellent results bordering on 75% complete remission after BMT. Good results are obtained from AML and CML, with long-term disease-free states. BMT for ALL results in high recurrence rates and lower long-term disease-free states. The outcome for lymphoma depends largely on the extent of disease and the presence of chromosomal abnormalities. Extensive disease with chromosomal abnormalities invariably yields poor long-term disease-free states.

3) State of disease. Optimal results for allogeneic BMT occur when done early after diagnosis when the disease is in first remission. Transplantation done in blastic crisis yields 10% or less long-term disease-free remission.

4) Patient condition. The overall physical condition of the patient is important to the success of BMT. Patients with other diseases such as diabetes, cardiac problems, cerebrovascular disease, hepatitis, and AIDS are disqualified from allogeneic BMT because of the associated high morbidity and mortality.

Thus, the ideal candidate for BMT would be an otherwise healthy 20 year-old with AML in first remission. This would yield the lowest mortality and 50% to 60% long-term disease-free state. Likewise, a 30-year old with CML who is transplanted before the third year of diagnosis and not in accelerated phase or blastic crisis also would be a good candidate.

Complications from BMT are numerous; the more frequent ones are listed here:

1. Graft versus host disease (GVHD). This occurs when the graft views the body as foreign and attempts to reject either the body as a whole or specific organs. This process is a function of activated T-lymphocytes which attack the liver, gastrointestinal tract, lungs, and skin. GVHD can be fatal even in HLA-identical donors and mortality can be as high as 10% and varies with age. Younger patients experience GVHD less than older patients. GVHD also brings about GVL (Graft versus Leukemia), a beneficial response. Radiation and chemotherapy are a Log kill of leukemic cells. The probability of all tumor being eliminated by chemotherapy or radiation is small. With GVL, in all likelihood, the graft will be able to eradicate any remaining leukemic cells.

2. Pharyngitis. Severe pharyngitis is caused by high-dose chemotherapy and total body irradiation. This pharyngitis lasts for 2 to 3 weeks and keeps the patient from being able to swallow, drink, or eat; total parenteral nutrition is needed during this period.

3. Infections. Bacterial infections are common early complications; however, long-term antibiotic therapy for these may result in later fungal infections. Viral infection such as cytomegalovirus, adenovirus, and herpes zoster tend to occur years later. Appropriate therapy is needed to prevent and treat each of the specific organisms.

4. Rejection. Rejection of the graft can occur causing prolonged aplasia and accompanying complications. A second graft could be required to achieve good engraftment.

5. Sterility. High-dose chemotherapy and/or fractionated Total Body Irradiation will cause sterility, although male and female hormones will be produced in the usual amounts.

6. Drug effects. Use of immunosuppressive medications can result in many untoward effects. Use of steroids can result in Cushingoid appearance, peptic ulcer disease, and cataracts. Cyclosporine in high doses can result in seizures, hypertension, headaches, and nephrotoxicity.

7. Other complications. There are many other complications that occur less frequently: Hypothyroidism, veno-occlusive disease, de novo tumors such as lymphoma and leukemias, and interstitial pneumonia.

The program in Hawaii has been approved for Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and Pediatric Oncology Group (POG) protocols. Site visits have been performed by SWOG and ECOG, and they have provided full approval for allogeneic and autologous BMT under research protocol.

Under the leadership of Y.K. Paik MD, this program has developed a National Marrow Donor Pool (NMDP) of local donors. Donor marrow has been collected in Hawaii and sent to Canada, Washington, Tennessee, and California.

➤ *Continued on page 84*

Table 2 Donors. Cause of Brain Death

Head Trauma	MVA	8
	GSW	5
	Fall	1
Intracranial Bleeding		5
Brain Tumor		1

MVA=Motor Vehicle accident
GSW=Gunshot Wound

the whole plasma volume as plasmapheresis does. This treatment modality has been used in the recent past, and there are no reports with large experiences available. We have shown that it is an effective way of treating this devastating complication. In one patient, we stopped the azathioprine and substituted it with cyclophosphamide which has more specific effect on the antibody production limb of the immune response. This change seems to have controlled the humoral rejection in a better way.

A serious problem in long-term survivors is the appearance of graft coronary atherosclerosis. Stanford reports a 25% incidence at 5 years,[2] and it seems to correlate with CMV infections. Currently, there is no effective way of preventing this complication. The only effective treatment once it is advanced is retransplantation. Fortunately, we have not seen this problem frequently in our patients. Only one patient has had significant coronary artery obstruction which had no clinical manifestations.

Infectious complications have not been a major problem in our patient population. It is well known that opportunistic infections, mostly fungal and viral, are prevalent in transplanted patients. With one exception, all infectious episodes have been adequately treated.

Cardiac transplantation is an expensive procedure. Nonetheless, studies have shown this operation to be cost-effective. It is clear that most patients with end-stage cardiac disease are disabled, many of them being unable to work with resultant loss of income, and others have repeated or prolonged hospitalizations with accumulating health care costs. A transplant operation often reverses this downhill trend and can return the patient to a functional status. The results are not optimal yet and further improvements are expected as more experience accumulates, but great advances have been made in the past 3 decades. This endeavor requires a monumental effort from different institutions and many individuals. The main reward that professionals involved in transplantation receive is seeing a patient recover from a devastating disease.

Addendum

Since the completion of this study, one more patient, our longest survivor (who lived more than 6 years) died in January 1994. The cause of death has not been determined, however his death does not alter the 1-year, 3-year or 5-year survival statistics.

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Allogenic and Autologous Bone Marrow Transplant Experiences in Hawaii

➤ *Continued from page 73*

The Hawaii BMT program also has been investigated by NMDP. Approval has been given for St. Francis Medical Center as one of 72 hospitals capable of performing unrelated allogeneic BMT transplants from the world's pool of potential donors.

Summary

Allogeneic and autologous bone marrow transplantation has been performed in Hawaii since 1978 for leukemia, lymphoma, aplastic anemia, and advanced breast cancer. The numbers for each group are relatively small and the disease stages are diverse. Our program has been recognized and approved by the various national organizations, and we hope to continue to provide this treatment alternative to appropriate candidates.

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