Medical Progress

Bone Marrow Transplantation
Part I—Allogeneic

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Major progress in experimental and clinical research has made allogeneic bone marrow transplantation a highly effective therapy for a variety of malignant and nonmalignant diseases. Allogeneic bone marrow transplantation from histocompatible donors is now the therapy of choice for some of these disorders. We review in part I the history, technical approach, complications, and the results achievable with this therapeutic approach. Further experimentation and future goals are also discussed.

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Bone marrow transplantation has evolved over the past 20 years to an acceptable and "first-line" therapy for certain diseases. This evolution paralleled the description of the human leukocyte antigen system, the development of intensive support systems such as broad-spectrum antibiotics, total parenteral nutrition, and transfusional support with platelets. Furthermore, understanding some of the immunologic aspects involved has helped in controlling distinct facets of transplantation such as graft-versus-host reaction.

The first documented description of bone marrow transplantation was made in 1939, when a woman with gold-induced aplasia was given marrow intravenously from a brother with identical blood group antigens.[1] Engraftment did not take place, and the patient died five days later. The modern era of transplantation began in the 1950s when experiments in animals suggested that mice could be protected from lethal irradiation by an infusion of bone marrow cells and, specifically, the regenerating marrow could be of donor origin.[2,3] Pioneer work by Thomas and co-workers at Seattle showed prolonged disease-free survival in a notable number of patients, even though they generally had relapsed advanced leukemias or multiply transfused aplastic anemia.[4] After these encouraging results, bone marrow transplantation was applied earlier for various diseases rather than in patients with end-stage disease, and results have improved consistently.

Most of the active therapies for malignant diseases are limited by bone marrow toxicity. This limitation can restrict the dosing and scheduling of potentially curative drug combinations. Thus, bone marrow transplantation provides a method where dose escalation can occur and where other physiologic toxicities limit the dose intensity. Higher drug dosing can result, then, in higher tumor cell kill, and, it is hoped, more cures. Finally, a bone marrow graft is a form of adoptive transfer where immunomodulation from the grafted tissue can be clinically significant, as is the case with graft-versus-leukemia effect.[5,6]

Technical Approach

Allogeneic bone marrow transplantation is the grafting of bone marrow from a donor into a recipient who is not an identical twin. At this time most transplants are of donor-recipient pairs who are matched for the HLA loci of the major histocompatibility complex. The chance of an HLA-identical donor-recipient pair being found among siblings is one in four. As the registry for unrelated donors grows, other unrelated persons who match at the HLA region may become donors. Long-term follow-up results and large numbers of patients have not been accumulated in the unrelated donor group, however.

Allogeneic transplantation can be used successfully for all the nononcologic disorders listed in Table 1 and for selected malignant diseases where a match can be found and where it is clinically indicated.

Before patients receive a graft, their endogenous bone marrow must be removed and their immune system suppressed. Immunosuppression is achieved with high doses of chemotherapy—usually accompanied by total body irradiation. Toxicities of the preparative regimen vary, depending on the agents used. Most agents cause notable mucositis, nausea, and vomiting. Other toxic effects include sterility, cataract formation, pulmonary fibrosis, hepatic and renal injury, cardiomyopathy, hemorrhagic cystitis, and neurotoxicity—tremors, seizures. Occasionally these can be fatal.

Once myeloablation and immunosuppression are completed, the recipient is ready to receive the bone marrow graft. The donor is taken to the operating room, and, with the patient under general or spinal anesthesia, the marrow is aspirated from the iliac crests. Particulate matter—bone spicules, fat, or small clots—is removed through a metal screen mesh.[7] The bone marrow is then infused intravenously into the recipient. In cases where there is a major ABO blood group mismatch, incompatible erythrocytes or the circulating isohemagglutinin in the host must be removed. This can be done through sedimentation with dex-

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ABBREVIATIONS USED IN TEXT
CML = chronic myelogenous leukemia
CMV = cytomegalovirus
Ph = Philadelphia [chromosome]

trans, differential centrifugation, ABO immunoabsorption of blood group antigens, or total plasma exchange.[8-10] The infused bone marrow, with its stem cells, migrates throughout the body and establishes itself in the bone marrow cavity and elsewhere, such as the Kupffer's cells in the liver, the microglia of the brain, and the macrophages in the lung.[11,12] The period of aplasia lasts about three weeks before enough newly formed leukocytes can be seen in the peripheral blood. During this period, the recipient is in danger of serious bleeding and sepsis from bacterial and fungal infections. Patients are frequently unable to eat or drink because of substantial mucositis. As the bone marrow engrafts and regenerates, the risk of acute graft-versus-host disease is at its peak.

Prophylactic measures are taken to minimize the occurrence of these complications. Red cells and platelets are transfused prophylactically or therapeutically, as necessary. Gut decontaminants are used to reduce endogenous flora. Broad-spectrum antibiotics are given to patients who have fever. If defervescence does not occur promptly, antifungal therapy such as amphotericin B is given. Cytomegalovirus (CMV) is another pathogen of concern because of the high mortality it can cause if pneumonia develops.[13-16] High-titer anti-CMV immunoglobulins may be used, and patients need to be monitored closely both clinically and radiographically for any pulmonary symptoms. Total parenteral nutrition is also frequently and effectively used to meet the increased caloric demands as a result of the therapy.[17,18] Finally, graft-versus-host reaction should be prevented, again because of the severe morbidity and possible death. The graft-versus-host reaction may be prevented by combinations of prednisone, cyclosporine, and methotrexate sodium.[19-21] Ongoing clinical studies should determine the best prophylaxis for cytomegalovirus and graft-versus-host reaction.

Complications

There are three major problems associated with allogeneic bone marrow transplantation. As previously mentioned, graft-versus-host reaction creates a serious barrier to effective transplantation. The graft-versus-host reaction can lead to graft-versus-host disease, which occurs as an acute reaction—arbitrarily defined as occurring within the first 100 days and associated with skin, gut, and liver dysfunction,[22] or as a chronic reaction that occurs after the first 100 days as a syndrome resembling various autoimmune phenomena.[23-29] Although the recipient and donor are matched at the HLA loci and intensive immunosuppression is used, the incidence of graft-versus-host disease varies from 26% to 76%, with an average of approximately 30%.[22,30-32] This can result in substantial morbidity and mortality—as much as 50%. Both forms of graft-versus-host disease can cause direct morbid effects, such as gastrointestinal bleeding, and death or increased morbidity and mortality from its treatment, resulting in an increased incidence of opportunistic infection.[33-35]

Efforts to understand and prevent graft-versus-host disease are a large fraction of allogeneic bone marrow transplant research. Permutations of combinations of methotrexate, cyclosporine, and prednisone are part of ongoing clinical trials. Promising results are being reported for a variety of T-cell depletion techniques.[36-40] Whether the lower incidence of graft-versus-host disease will result in improved survival rates is unclear. There are drawbacks to T-cell depletion, such as graft failure or higher relapse rates, which may negate the benefits of a lower incidence of graft-versus-host disease.[41-44] These data will become available as current studies mature. Preventing graft-versus-host disease will be of greater importance, especially with the increase in the number of unrelated donor transplants.

TABLE 1.—*Disorders and Clinical Conditions in Which Allogeneic Bone Marrow Transplantation Has Been Used Successfully*

Acute leukemia, de novo and secondary	Severe hemoglobin abnormalities
Chronic granulocytic leukemia	Congenital pure red cell aplasia
Acute "malignant" myelosclerosis	Paroxysmal nocturnal hemoglobinuria
Myelodysplastic syndromes	Severe combined immunodeficiency
Non-Hodgkin's lymphoma*	Osteopetrosis
Hodgkin's disease*	Wiskott-Aldrich syndrome
Multiple myeloma	Congenital leukocyte dysfunction syndromes
Hairy-cell leukemia	Hereditary storage disorders
Aplastic anemia	Glanzmann's disease
Thalassemia major	
Fanconi's anemia	

*Most centers use autologous bone marrow transplants.

A second obstacle in bone marrow transplantation is opportunistic infections. The most prominent example is interstitial pneumonia, caused by cytomegalovirus. Before current treatment regimens were developed, the mortality from CMV interstitial pneumonia approached almost 90%, affecting approximately 15% to 20% of allogeneic transplant patients.[14,34] Recently, notable strides have been made in the therapy for this disease. The use of the antiviral agent DHPG:9-(1,3-dihydroxy-2-propymethyl)guanine, or ganciclovir, in combination with high-titer anti-CMV immunoglobulin G has resulted in substantial improvement in survival rates—approximately 50% to 70%.[45-47] There is great interest in using these agents in the prophylaxis of CMV pneumonias.

Finally, leukemic relapse remains a major obstacle. New combinations of active agents have been developed. Traditionally, the conditioning regimen has consisted of total body irradiation and administering of cyclophosphamide.[48,49] Newer regimens replace a single-fraction total body irradiation with fractionated applications and substitute etoposide (VP-16-213) for cyclophosphamide.[50] Other regimens do not use radiation, employing instead a two-drug combination such as busulfan and cyclophosphamide.[19,51] As the toxicities of each high-dose agent become better understood, such combinations may lead to a lower incidence of relapse and potentially less host organ damage. Methods to control graft-versus-host disease without affecting a beneficial graft-versus-leukemia effect may have a positive effect in preventing leukemic relapse following transplantation.[52,53]

Results

What, then, are the results of such cost- and labor-intensive procedures? Overall, bone marrow transplants offer the hope of true cures to a large number of patients. Although cures are measured only as survival on Kaplan-Meier

curves, equally important is the quality of life for these patients following transplant. Only recently has attention been focused on this issue. A study of 203 patients at the City of Hope National Medical Center (Duarte, California) and Stanford University Medical Center (Stanford, California), with a median follow-up period of 3.6 years, reveals that more than 80% of patients graded their quality of life greater than 8 on a scale of 1 to 10, with 10 being the best. Their overall Karnofsky score was greater than 80%.[54] Data such as these document the favorable outcome for patients following allogeneic bone marrow transplantation.

Acute Lymphoblastic Leukemia

Allogeneic bone marrow transplantation has been done for all remission and relapse states in acute lymphoblastic leukemia. Clearly, as for any therapeutic modality, the variation in response rates is directly related to the disease status of the patients. For adult patients in their first complete remission, allogeneic bone marrow transplantation has been carried out successfully, with an actual survival rate of 63% after two to eight years.[55,56] Intensive chemotherapy without bone marrow transplant also results in significant actuarial disease-free survival and, presumably, cures.[57-59] This disease-free survival is more common in the pediatric population.[60] Randomized studies are necessary to establish whether adult patients with acute lymphoblastic leukemia and histocompatible marrow donors should receive allogeneic bone marrow transplants while in first complete remission rather than continued chemotherapy, with transplantation of those who relapse. Once a patient relapses, the effectiveness of allogeneic bone marrow transplantation is more pronounced. Transplantation for a second or subsequent complete remission or transplantation at the time of relapse has a significant survival advantage in favor of transplantation (Table 2), since long-term disease-free survival even in children given chemotherapy is less than 20%. In children with remissions of less than 18 months, there were no survivors.[60] A randomized study for patients not in their first complete remission, with randomization based on the availability of a histocompatible donor, has been carried out in Seattle. The results strongly favor the use of bone marrow transplants.[61,62] New combinations of chemotherapy such as etoposide and fractionated total body irradiation result in an actuarial disease-free survival rate at three years of 43% to 56%, even in patients not in first remission.[56,63]

Acute Nonlymphoblastic Leukemia

Patients with acute nonlymphoblastic leukemia or acute myelogenous leukemia clearly benefit from transplantation. Randomized studies comparing allogeneic bone marrow transplantation with intensive chemotherapy show improved results with transplantation.[64-66] When allogeneic transplantation is carried out in patients younger than 40 in first complete remission, they can expect an actuarial disease-free survival of 45% to 65% at five years and are probably cured.[67-69] Again, where transplantation is carried out during the second or subsequent complete remissions or in relapse, bone marrow transplantation is clearly superior to chemotherapy (Table 2).

Chronic Myelogenous Leukemia

Allogeneic bone marrow transplantation has been carried out for chronic myelogenous leukemia (CML) for more than a decade. Although early results of transplantation for CML in the blast phase were discouraging,[70] when transplantation is done during earlier stages, namely the chronic phase, the results have been promising. Long-term remission can be achieved in 55% to 75% of these patients.[48,70-72] There are several features unique to CML. The definition and clinical significance of relapse are unclear. That is, a patient with the Philadelphia (Ph) chromosome before a transplant may, after transplant, be Ph-negative and remain so; remain Ph-positive in clinical remission, or subsequently relapse; or remain Ph-negative initially, and then become Ph-positive with or without a clinical relapse.[73-77] Even when a relapse is established histologically, the disease can sometimes behave indolently. Prospective studies with long-term follow-up of patients are needed to establish the importance of these findings.

Another feature unique to chronic myelogenous leukemia is the timing of the transplant. Because CML is a chronic and heterogeneous disease, patients may stay in the chronic phase for years. Research efforts have been directed to establish the optimal time for a bone marrow transplant. Data from the Seattle group and the International Bone Marrow Registry suggest that the sooner a patient has a transplant following diagnosis, the better the outcome.[71,72] There are also new methods with the potential to select those patients whose clinical characteristics at presentation to medical care put them at a higher risk. There are data to suggest that the position of the breakpoint cluster region (bcr) may have prognostic significance.[78-80] Finally, with the recent introduction of interferon-α and the observation that it can in rare instances even induce Ph chromosome negativity, the timing of allogeneic bone marrow transplantation again has been called into question.[81] Several investigators have proposed a trial of interferon-α as a reasonable alternative path.

Severe Aplastic Anemia

Allogeneic bone marrow transplantation for severe aplastic anemia has become the standard of care for young patients with HLA-matched donors. Results from the Seattle group show a disease-free survival rate of 80% for those patients with severe aplastic anemia who were not transfused

TABLE 2.—*Long-Term, Disease-Free Survival in Continued Complete Remission Following Bone Marrow Transplantation in Relation to Pretransplant Remission Status*

Allogeneic Bone Marrow Transplants			*Autologous Bone Marrow Transplants*	
ANLL, %	*ALL, %*	*CML, %*	*Hodgkin's Disease, %*	*Non-Hodgkin's Lymphoma, %*
1st CR, 45-65	1st CR, 50-65	1st and 2nd chronic phase, 55-75	"Good risk" relapse, 60-70	"Sensitive relapse," 65-70
2nd CR, 1st relapse, 20-45	2nd CR, 1st relapse, 30-45	Accelerated phase, 30-40	"Poor risk" relapse, 15-20	"Resistant relapse," 10-15
3rd and subsequent CR, advanced relapse, 10-25	3rd and subsequent CR, advanced relapse, 15-25	Blastic phase, 5-15		

ALL=acute lymphoblastic leukemia, ANLL=acute nonlymphoblastic leukemia, CML=chronic myelogenous leukemia, CR=complete response

before having an allogeneic bone marrow transplant, compared with 45% to 50% for those who were transfused. The maximum follow-up time has now reached 17 years.[82] Certain criteria have been established to identify a population of patients with a poor prognosis:

- A marrow cellularity of less than 25% of normal, or less than 50% of normal with less than 30% hematopoietic cells;
- At least two of these blood values: granulocyte count of less than 0.50×10^9 per liter (500 per μl), a platelet count of less than 20×10^9 per liter (20,000 per μl), or anemia with a corrected reticulocyte count of less than 0.01 (1%).[83]

In contrast to allogeneic bone marrow transplants for malignant diseases, in transplantation for severe aplastic anemia, graft rejection is more frequent.[84,85] This is related partly to patients' sensitization by previous transfusions and to the preparative regimen, which usually consists of using only cyclophosphamide. Cyclophosphamide as a single agent is probably not sufficiently myelosuppressive for all patients with severe aplastic anemia. There have been some reports of autologous recovery of bone marrow following rejection.

Other Diseases

A small number of patients have received transplants for various malignant and nonmalignant disorders. With the recognition that immune cells arose from the bone marrow, transplantation became an attractive method to correct immunodeficiencies such as severe combined immunodeficiency,[36,37,86] Wiskott-Aldrich syndrome,[87] congenital leukocyte dysfunction syndromes,[88,89] and osteopetrosis.[90-93] Unique to the group of patients with immunodeficiency is the realization that HLA-mismatched grafts can be done successfully, especially in those patients who lack a T-cell response toward allogeneic targets.

With the knowledge that the reconstitution of bone marrow resulted in a correction of immunodeficiencies and that bone marrow cells led to the long-lived macrophages, interest grew in using allogeneic bone marrow transplantation for correcting lipidoses, such as Gaucher's disease[94] or Wolman disease,[95] and also the possibility of replacing the missing enzymes in severe combined immunodeficiency disorders such as adenosine deaminase-deficiency,[96] Fabry's disease,[97] Hurler's syndrome, and other mucopolysaccharidoses.[98-102]

Transplantation is also carried out successfully for other hematologic disorders. Lucarelli and colleagues in Italy have reported excellent results in young patients with thalassemia major.[103] Transplantation has also been done for other hematologic disorders such as hemoglobinopathies,[104] paroxysmal nocturnal hemoglobinuria,[105-108] congenital pure red cell aplasia,[109] Diamond-Blackfan anemia,[110] and Fanconi's anemia.[111,112] The results of transplantation for Fanconi's anemia are not as encouraging. These patients seem to have a systemic constitutional defect resulting in poor tolerance of high-dose chemotherapy. Finally, small numbers of transplants have been carried out with encouraging results for myelodysplastic syndromes, secondary leukemia, and acute "malignant myelosclerosis."[113-115]

Future Directions

As marrow transplantation in humans enters its third decade, a review of past achievements is rewarding. Progress has been slow and cumbersome, but allogeneic bone marrow transplant is now a well-accepted form of therapy for a number of diseases. Although progress for the third decade should be more rapid as large numbers of patients undergo transplantation, the procedure should still be part of well-designed and carefully conducted cooperative clinical trials, especially as it is done in a larger number of small centers.

There are several exciting prospects for research and development:

Graft-Versus-Host Disease

T-cell depletion may be a reasonable option for preventing graft-versus-host disease if there is no significant graft failure or late recurrences of malignant disease with longer follow-up. To date, most of the T-cell depletion studies have reported a higher recurrence rate or graft failure. Most likely the data from animal models, where a titrated number of specific T cells are returned, may allow investigators to prevent graft-versus-host disease without the loss of a graft-versus-leukemia effect or an increase in graft rejection.[53]

Monoclonal Antibodies

One of the methods developed for T-cell depletion and therapy for graft-versus-host disease is monoclonal antibodies. These can be coupled to toxins or radioisotopes and directed against specific targets. Monoclonal antibodies may also be used as a cytoreductive method before transplantation. Manipulation of the immune system, by using a monoclonal anti-idiotype of a tumor, may enhance immunity against the tumor before or after transplantation.

Interstitial Pneumonia

Cytomegalovirus, which previously led to lethal pneumonias, may now be adequately treated with a combination of ganciclovir and immunoglobulin G. More exciting is the prospect that the use of these agents prophylactically may significantly reduce the mortality from interstitial pneumonia.

Unrelated Donors

As the number of registered volunteer donors grows, the chances of finding an unrelated HLA-matched donor will increase substantially. The increased chance of locating a matched donor, in conjunction with newer methods to prevent graft-versus-host disease, may allow allogeneic transplantation to be accomplished safely in a larger number of patients.

New Regimens

As discussed previously, new combinations of active agents such as fractionated total body irradiation and etoposide have lowered the rate of relapse from leukemias. As the understanding of human immunology improves and the cellular communication mechanisms are understood, new agents may become useful in transplantation. These include direct toxins such as interferon or interleukin-2 and adoptive cell transfers such as lymphocyte-activated killer cells or tumor-infiltrating lymphocytes. With the advent of molecular cloning, various growth factors have been introduced into clinical trials. Whether these will prove to be useful in marrow transplantation will have to await the results of ongoing randomized clinical trials.

Gene Transfer

Gene transfer is widely done in the laboratory. There has been a great interest in using gene transfer in animals and ultimately as therapy for human diseases. The use of appropriately altered retroviral vectors may provide the ultimate correction of certain genetic diseases—thalassemia major, for example—in conjunction with transplanted bone marrow. Clearly, concerns for the infectivity of the virus and oncogenicity will have to be allayed before this approach can be used in humans.

Stem Cell Isolation

With the murine pluripotent stem cell isolated by Weissman's group,[116] there is a great deal of excitement, with notable efforts being made to isolate the human stem cell. Partially purified "stem cells" have been used for transplant in baboons, with limited success.[117] When this is feasible in humans, various difficulties with allogeneic bone marrow transplants should be lessened.

Finally, as molecular biology and genetic engineering, immunology, pharmacology, and clinical medicine develop, bone marrow transplantation is a field where all can contribute and merge meaningful data for the best outcome for patients.

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