Allogeneic Hematopoietic Stem Cell Transplantation

Complications and Results

Imad A. Tabbara, MD; Kathy Zimmerman, RN; Connie Morgan; Zeina Nahleh, MD

Acute complications such as veno-occlusive disease of the liver, acute and chronic graft-vs-host disease (GVHD), and infectious conditions remain major obstacles for the success of allogeneic hematopoietic stem cell transplantation (HSCT). Progress in allogeneic HSCT depends on several factors, including the adequate prevention and management of associated complications, advances in the conventional management of diseases currently treated with allogeneic HSCT, expansion of the donor pool, selective control of GVHD, development of more effective preparative regimens to eradicate the neoplastic cell population, characterization of a new generation of hematopoietic growth factors and cytokines, and development of newer techniques for ex vivo manipulation of stem cells. Hematopoietic growth factor–mobilized donor progenitor cells collected from peripheral blood have been shown to be associated with rapid hematopoietic engraftment without an increase in the incidence of acute GVHD compared with allogeneic bone marrow transplantation. Implementation of this approach will enhance donor acceptance, eliminate the risk of general anesthesia, decrease cost, and reduce the risk of infectious complications by reducing the duration of neutropenia. Nonmyeloablative allogeneic stem cell transplantation represents a novel treatment approach that may lead to reduced toxic effects and extended use of this treatment in older patients and in those with malignant and nonmalignant disorders. However, GVHD and disease recurrence remain a challenge. Promising results have been reported in patients with refractory hematologic malignancies and in metastatic renal cell cancer. Because late complications are commonly encountered in patients receiving allogeneic HSCT, lifelong observation is needed.
tic benefit of allogeneic transplantation is related to an immune graft-vs-malignancy effect. Donor lymphocyte infusions induce durable remissions in patients with chronic myelogenous leukemia (CML) who relapse after allogeneic HSCT. Several studies are ongoing to assess the role of nonmyeloablative conditioning regimens and induction of the immune graft-vs-malignancy effect. This approach may allow the use of allogeneic HSCT in older patients and in patients with multiple medical problems because it may be associated with decreased toxic effects.

MYELOABLATIVE PREPARATIVE REGIMENS

The myeloablative conditioning regimens used in allogeneic HSCT have 3 main purposes: eradication of malignant disease; suppression of the recipient’s immune system, thereby decreasing the chance for graft rejection; and creation of space in the bone marrow microenvironment to allow engraftment of the donor stem cells. Many myeloablative conditioning regimens have been used, but no single regimen has been shown to be superior. In patients with aplastic anemia, high-dose cyclophosphamide therapy alone or in combination with either low doses of total body irradiation (TBI) or thoracoabdominal irradiation was used to induce a complete state of immunosuppression. Uncontrolled trials showed that combination therapy with cyclophosphamide and antithymocyte globulin leads to a decreased incidence of graft failure. However, randomized studies are needed to confirm this benefit. In patients with acute myeloid or lymphoid leukemias, CML in the chronic, accelerated, or blast phase, high-dose cyclophosphamide in combination with TBI has been widely used, although randomized studies showed that use of combined cyclophosphamide and busulfan, without TBI, has comparable efficacy.

The chemoradiotherapy regimens may be associated with substantial acute adverse effects, including nausea, vomiting, diarrhea, and alopecia. Mucositis can be severe, requiring systemic narcotic therapy for pain control. Hemorrhagic cystitis induced by high-dose cyclophosphamide administration is infrequent and can be prevented by vigorous hydration and diuresis combined with continuous bladder irrigation or by the prophylactic use of mesna. Other early-onset toxic effects may include cardiomyopathy and acute renal failure.

The current pretransplant preparative regimens have been intensified to their maximal potential. New conditioning regimens that can target malignant cells selectively without causing serious nonhematopoietic toxic effects are being investigated. Two approaches to designing conditioning regimens have been studied in animals. In the first approach, radiolabeled monoclonal antibodies have been shown to produce fatal marrow aplasia, which could be reversed by infusing marrow 8 days later, when minimal radioactivity remains. The use of high-energy β-emitting isotopes with short linear energy transfer may lead to fewer toxic effects, improved control of the malignancy, and decreased graft failure. The second approach involves the use of bone-localizing isotopes. Initial data in animals using samarium 153 showed that marrow ablation could be achieved with limited toxic effects to other organs. The ultimate role and long-term efficacy of these approaches in humans remain to be determined.

ACUTE COMPLICATIONS

Immunologic and Infectious Complications

Deficiencies in the cellular and humoral aspects of the immune system occur to some degree in all allogeneic HSCT recipients for a variable duration, and they are more profound and prolonged in patients with GVHD receiving immunosuppressive therapy. Cellular immunodeficiency consists of decreased T-cell response to alloantigens and mitogens, decreased helper CD4+ cell function, and decreased reactivity to intradermal skin tests. Because of thymic involution in the patient, T-cell function depends on the peripheral expansion of the few donor T cells that are present in the graft. The use of live viral vaccine in these patients should be avoided. Humoral immunodeficiency is manifested by a decrease in IgG2 and IgG4, although immunoglobulin levels may be within the reference range. The switch from primary (IgM) to secondary (IgG) production and antigen-specific responses is abnormal, leading to impaired production of antibodies to pathogens. The recovery of the immune system occurs within 6 months to a year of allogeneic HSCT in the absence of GVHD and after discontinuation of immunosuppressive therapy.

Patients receiving allogeneic HSCT are highly susceptible to infections because of immunodeficiency, neutropenia, and the immunosuppressive therapy used to prevent or treat GVHD. Bacterial and fungal infections can occur during the first 2 weeks after allogeneic HSCT, and the mortality from these infections is approximately 3% to 5% despite intensive supportive care and appropriate antimicrobial drug therapy. The prophylactic use of fluconazole has been shown, in a randomized study, to decrease the incidence of systemic and superficial fungal infections. Late-onset fungal infections with invasive candidiasis and aspergillosis can occur several months after transplantation, especially in patients with severe GVHD receiving immunosuppressive therapy. Factors associated with increased susceptibility to late infections in patients with chronic GVHD include impaired mucosal defense, chemotactic defects, functional asplenia, and qualitative and quantitative B- and T-cell abnormalities.

Viral infections with the herpesvirus group are common and are usually caused by reactivation of a latent virus. Infection with the herpes simplex virus may occur 1 to 2 weeks after transplantation in 80% of seropositive patients who are not receiving acyclovir prophylaxis, causing mucocutaneous lesions of the oropharynx, esophagus, or genital tract. Cytomegalovirus (CMV) infection tends to occur 4 to 10 weeks after transplantation, with CMV pneumonitis developing in 20% to 30% of patients with GVHD. The risk of developing CMV infection and disease increases directly with the occurrence and severity of acute GVHD. No such correlation has been found.
for chronic GVHD. The clinical presentation of CMV pneumonitis includes dyspnea, tachypnea, fever, hypoxemia, and diffuse interstitial lung involvement. This condition is associated with high mortality (30%-50%) despite therapy. Effective prevention can be achieved by the use of CMV-negative blood products in CMV-seronegative donor-patient pairs, intravenous immunoglobulin, prestorage leukocyte-depleted blood products, leukocyte-filtered blood products, and prophylactic ganciclovir. Three randomized, placebo-controlled studies showed that prophylaxis with ganciclovir led to a significant reduction in the incidence and severity of CMV infection in CMV-seropositive allogeneic HSCT recipients when (1) starting 1 week before transplantation and resuming when the posttransplantation absolute neutrophil count is 1000/µL until day 100; (2) starting when the absolute neutrophil count is 750/µL until day 120; and (3) starting on day 35 after transplantation if there is evidence of CMV infection by bronchoalveolar lavage. Prolonged neutropenia and increased risk of bacterial infection have been associated with the prophylactic administration of ganciclovir. Because of these complications and because approximately 40% of patients will never excrete CMV or have the disease, it seems that the optimal approach is to give ganciclovir when CMV excretion is detected for the first time.

Interstitial pneumonia occurs in 25% to 35% of patients, and half of these cases are due to CMV infection. Cytomegalovirus pneumonitis occurs at a median of 7 weeks after transplantation, with most cases occurring within the first 4 months. Risk factors associated with CMV pneumonitis include acute GVHD, older age, CMV seroconversion and CMV seropositivity of the recipient, transplantation for hematologic malignancy, use of TBI in the conditioning regimen, and use of antithymocyte globulin for the treatment of GVHD. Foscarnet sodium was used prophylactically in a small phase I-II study in CMV-seropositive patients. In this study, the administration of foscarnet 7 days before to 75 days after transplantation was effective in preventing CMV infection in most patients. However, its use was associated with several adverse effects, including renal failure, requiring its discontinuation and initiation of hemodialysis in some patients.

Pneumocystis carinii pneumonitis can occur several weeks to several months after transplantation, but it is now prevented in most patients by the prophylactic use of dapsone, trimethoprim-sulfamethoxazole, or pentamidine.

Veno-occlusive Disease of the Liver

Veno-occlusive disease of the liver is seen in 20% to 50% of patients receiving high-dose chemotherapy and TBI and in patients receiving high-dose cyclophosphamide and busulfan without TBI. This disease is rarely seen in patients with aplastic anemia receiving cyclophosphamide alone. The risk factors include pretransplantation elevation of serum aminotransferase levels (especially aspartate aminotransferase), intensive conditioning therapy (higher TBI and busulfan dose), graft from a mismatched or unrelated donor, and use of antimicrobial therapy with acyclovir, amphotericin B, or vancomycin (possibly reflecting persistent fever). This disease may develop within 3 weeks of allogeneic HSCT, and it is clinically manifested by jaundice, right upper quadrant abdominal pain, hepatomegaly, fluid retention, and weight gain.

The pathogenesis of VOD remains unclear. One of the etiologies is thought to be the obstruction of the terminal hepatic and sublobular central venules by endothelial cell injury and thrombosis, leading to a shift of fluid containing sodium and albumin from the intravascular to the extravascular space. This fluid shift leads to a decrease in renal blood flow and activation of the renin-angiotensin system, resulting in sodium and fluid retention. More recent evidence suggests that an early decrease in protein C and antithrombin III levels may play a role in the pathogenesis of VOD and is predictive of its development and severity. In some cases, VOD may occur at the same time as acute GVHD, making clinical differentiation between the 2 conditions difficult. Transjugular liver biopsies and manometric monitoring of hepatic blood flow can establish the diagnosis. Patients with mild disease, as evidenced by minimal elevation in the bilirubin level and weight gain, have an excellent prognosis. In contrast, patients who have a bilirubin level of 20 mg/dL or higher (≥342 µmol/L) or a weight gain of 15% or more of original weight have a 90% mortality before day 100. Sodium and fluid restriction and the judicial use of diuretics remain the main treatment approaches for this condition. Administration of tissue plasminogen activator is effective in some patients in treating established disease. Defibrotide was used on a compassionate basis in 19 patients with severe VOD. Resolution of VOD was seen in 8 patients (42%), and 6 of the 8 responders survived past day 100.

Attempts at preventing VOD are the subject of many investigative trials. Pentoxifylline, a xanthine derivative capable of down-regulating tumor necrosis factor α production, has been shown in randomized studies to be of no benefit in reducing the incidence of VOD. A randomized trial showed that use of low-dose heparin (100 U/h) was capable of reducing the incidence of VOD without added risk of bleeding. Ursodiol administration reduced the incidence of VOD in a randomized, double-blind, placebo-controlled trial in patients receiving a preparative regimen of cyclophosphamide and busulfan.

Graft-vs-Host Disease

Graft-vs-host disease remains one of the major complications after allogeneic HSCT, especially with the increased use of grafts from mismatched and unrelated donors. This disease is divided into 2 forms based on timing of occurrence and clinical manifestations. The acute form occurs in the first 2 to 3 months after transplantation, and the chronic form manifests later in the posttransplant period.

Acute GVHD. Acute GVHD develops within 2 to 10 weeks of allogeneic HSCT. Clinically relevant grade II to IV acute GVHD occurs in approximately 20% to 50% of patients who receive stem cells from an HLA-
identical sibling donor and in 50% to 80% of those who receive stem cells from an HLA-mismatched sibling or from an HLA-identical unrelated donor. Dermatitis, hepatitis, and enteritis characterize acute GVHD. A maculopapular rash involving the trunk, face, extremities, palms, soles, and ears usually marks the onset of acute GVHD. In severe cases, the rash may progress into bullous lesions, with subsequent development of epidermal necrolysis. Histologically, vacuolar degeneration and lymphocytic infiltration involving the basal cell layer is seen in mild disease, and this picture changes to necrotic dyskeratotic cells with acantholysis and cell membrane separation in moderate disease and to the development of epidermolysis in severe cases. These findings are not pathognomonic of GVHD because chemoradiotherapy and use of other drugs can induce them.

The bilirubin, alkaline phosphatase, and aminotransferase levels may increase with the onset of nausea, vomiting, abdominal pain, and massive watery or bloody diarrhea. In patients with isolated hepatic derangement, a liver biopsy may be needed to confirm the diagnosis of GVHD because liver dysfunction in these patients can be secondary to many processes, such as VOD, infectious hepatitis, and drug-induced liver toxicity. However, liver biopsy is a risky procedure in this patient population and should not be undertaken without adequate assessment of the hemostatic and clinical condition of the patient. The histologic pattern on liver biopsy findings is characterized by lymphocytic infiltration mostly of the portal triads, with the presence of hepatocellular necrosis in some cases similar to that seen in acute hepatitis. Rectal punch biopsies may confirm the diagnosis of GVHD, with the histologic picture showing epithelial cell necrosis, vacuolar degeneration, crypt dropout, and, in advanced cases, epithelial denudation.

The following immunologic factors were defined by Billingham52 in 1966 to be essential for the development of GVHD: (1) the graft must contain immunologically competent lymphocytes; (2) the recipient must express transplantation antigens that are not present in the donor and that can lead to the stimulation of donor lymphocytes; and (3) the recipient has to be incapable of immunologically destroying the graft. However, the recent description of cyclosporine-induced autologous GVHD suggests that other factors may play a role in the development of this syndrome.53,54 Acute GVHD occurs as a result of donor T-cell recognition of recipient HLA antigens as foreign, and it has been reported to cause atrophy of the lymphoid system, thymic regression, delayed B-cell reconstitution, and reversal of the CD4/CD8 ratio, leading to increased predisposition for infection.51 The tissue damage occurring in acute GVHD may be mediated by infiltration of the target organ by natural killer lymphocytes. Cytokines, including interleukin 1 (IL-1), tumor necrosis factor α, and IL-2, are thought to be critical to the development of acute GVHD.55,56 Initial phase 1 and 2 studies56,57 using anti–IL-2 receptor monoclonal antibody and anti–tumor necrosis factor α monoclonal antibody have shown promising results in controlling corticosteroid-resistant acute GVHD. An IL-1 receptor antagonist is being investigated in refractory acute GVHD.58 Acute GVHD is clinically graded (I-IV) based on the extent and severity of involvement of the skin, liver, and gastrointestinal tract. The risk factors for acute GVHD are given here.59,60

Risk Factors for Acute GVHD
Unrelated HLA-identical donor

HLA mismatch
Female donor to a male recipient (previous donor pregnancy)
Increasing donor or recipient age
Ineffective GVHD prophylaxis
Previous recipient infections with herpesviruses

Prophylactic immunosuppressive therapy with cyclosporine and methotrexate, cyclosporine alone,61 or cyclosporine with prednisone62 has led to a significant reduction in the incidence of acute GVHD, with improved survival. Use of the combination of prednisone, cyclosporine, and methotrexate was more effective in preventing acute GVHD of grades II to IV than was the combination of cyclosporine and prednisone.62 In a phase III study63 of patients receiving an HLA-identical sibling bone marrow graft, prophylactic therapy with tacrolimus in combination with methotrexate was shown to reduce the incidence of grade II to IV acute GVHD compared with cyclosporine and methotrexate therapy. In this study, there was no difference in the incidence of grade III or IV acute GVHD, chronic GVHD, relapse rates, or disease-free survival (DFS) or overall survival in patients with nonadvanced hematologic malignancy. However, there was a higher frequency of deaths caused by regimen-related toxic effects in patients with advanced disease who received tacrolimus. The use of intravenous immunoglobulins may be associated with a decrease in the severity of acute GVHD.64 Prophylactic decontamination of gut flora and laminer airflow room microbe-free isolation led to a decreased incidence of acute GVHD, with improved survival in patients with aplastic anemia.65 The effectiveness of this approach in other diseases remains to be documented, and its mechanism of action is not fully elucidated. It is postulated that by preventing infections, lymphocytes may not secrete lymphokines that increase the expression of class II histocompatibility antigens on certain cells, rendering them susceptible to the action of donor T lymphocytes. Several methods have been used to deplete ex vivo the T lymphocytes from the graft in an attempt to reduce the incidence and severity of acute GVHD. This approach has been effective in decreasing the incidence of acute and chronic GVHD, but no survival benefit was documented owing to the higher incidence of nonengraftment, leukemia relapse secondary to a decreased graft-vs-malignancy effect, and development of new lymphoproliferative disorders associated with the Epstein-Barr virus.66

The treatment of established acute GVHD includes the use of high-dose methylprednisolone, cyclosporine, and antithymocyte globulin.67,68 Responses can be achieved in approximately 40% of patients receiving high-dose corticosteroid therapy, with only 20% of patients achieving a complete response. Patients who do not respond to this therapy may achieve limited benefit from second-line therapy, and their long-term outcome is poor owing to infectious complications, interstitial pneumonitis, and progression to
chronic GVHD. In a multicenter study, patients with corticosteroid-refractory acute GVHD treated with anti-CD3, rituximab, and anti-CD19 antibody had a better survival rate compared with those treated with antithymocyt globulin.

Patients with acute GVHD have a lower incidence of leukemia relapse owing to a presumed graft-vs-leukemia effect. The risk of relapse is inversely proportional to the severity of acute GVHD. This beneficial effect may not be limited to patients with leukemias because a similar effect was seen in patients with lymphoma receiving allogeneic bone marrow transplantation (BMT).

Chronic GVHD. Chronic GVHD occurs in less than 50% of long-term survivors. It is a complex late complication developing most frequently 3 to 6 months after hematopoietic engraftment. In approximately 20% of the cases, there is no evidence of previous acute GVHD. The pathogenesis of this syndrome is different from that of the acute disease. Current evidence suggests that the syndrome is mediated by donor T lymphocytes that recognize minor histocompatibility complex differences and by T lymphocytes that are primarily autoreactive, with specificity for histocompatibility antigens shared by donor and recipient cells. These activated T lymphocytes are capable of cytolysis and cytokine production. Interleukin 4 and interferon γ are produced by these cells and may be the cause of the immunologic dysfunction associated with this syndrome, including the increased production of autoantibodies. These autoantibodies are frequently detected, and they have been associated, in rare cases, with the development of myasthenia gravis and thrombocytopenia. The increased collagen deposition in the skin seen in this disease is most likely secondary to the stimulation of fibroblast collagen production by a variety of cytokines, including IL-1, tumor necrosis factor α and β, and IL-4. Patients with chronic GVHD and thrombocytopenia have a poor prognosis.

The clinical presentation of chronic GVHD is similar to that of autoimmune disorders, particularly scleroderma. Patients with this disease may experience a variety of manifestations, including the sicca syndrome (dryness of the mouth and eyes), skin lesions (hypopigmentation or hyperpigmentation, decreased elasticity, and loss of hair follicles and sweat glands), keratoconjunctivitis, oral mucositis, esophageal strictures, malabsorption, hepatic involvement with hyperbilirubinemia, and suppressed hematopoietic reconstitution. In 10% to 20% of patients with chronic GVHD, bronchiolitis obliterans is seen and is associated with hypogammaglobulinemia and poor outcome. Skin and oral mucosal biopsies may be helpful in establishing the diagnosis of chronic GVHD.

Treatment of chronic GVHD consists of the use of immunosuppressive agents early in the course of the disease, before the onset of functional impairment. Oral cyclosporine therapy every other day, alternating with prednisone therapy, has been associated with improved complete responses and overall survival rates. The addition of azathioprine, UV light, and psoralen–UV-A has been helpful in controlling the disease in some patients. Thalidomide, through the presumed blockade of IL-2 activation, has been shown to be effective in some refractory cases. Mycophenolate mofetil may play a role in the management of these patients, pending further studies.

In 50% of patients, therapy can be discontinued after 9 to 12 months. Self-tolerance occurs usually a few years after allogeneic HSCT, and in most patients, immunosuppressive therapy can be tapered and discontinued at that time. Infections caused mainly by encapsulated gram-positive bacteria may occur in patients with chronic GVHD and may be associated with significant mortality. The prophylactic administration of antibacterial agents such as co-trimoxazole or penicillin is indicated in these patients.

Factors associated with an increased incidence of chronic GVHD are (1) acute GVHD greater than grade II, (2) female donor to a male recipient (previous donor pregnancies), (3) increasing donor or recipient age, (4) transfusion of donor buffy coat, and (5) use of blood stem cells. Poor prognostic factors in patients with chronic GVHD include older patient age, resistant disease, persistent thrombocytopenia, inability to achieve a response after 9 months of therapy, hyperbilirubinemia, and lichenoid histologic findings on skin biopsy specimens.

GRAFT FAILURE AFTER ALLOGENEIC HSCT

Graft failure can be early, as evidenced by lack of initial hematopoietic recovery, or late, in association with recurrence of the disease or reappearance of host cells after initial donor cell engraftment. The incidence of failure of sustained marrow engraftment is rare (<2%) in patients with hematologic malignancies receiving a complete HLA-compatible marrow. However, this complication is more commonly seen in patients with aplastic anemia receiving allogeneic BMT, especially in patients who received many transfusions. The use of TBI or antithymocyte globulin as part of the conditioning regimen, or infusing donor buffy coat after transplantation, led to a reduction in the incidence of graft failure from 30% to 60% to less than 10% in patients with aplastic anemia. Patients with myelofibrosis or mixed hematopoietic chimerism also have an increased incidence of graft failure. Other factors that are associated with increased risk of nonengraftment include a low number of infused mononuclear cells, previous bone transplants, manipulation of the graft for T-cell depletion, and HLA incompatibility between the donor and the recipient. The pathophysiologic characteristics of failure of sustained and complete engraftment are not completely elucidated. There is some evidence to suggest that this failure may result from a graft-vs-marrow (recipient’s marrow microenvironment) effect or from an abnormal microenvironment. In patients receiving T-cell-depleted marrow transplants, graft failure is thought to be secondary to disequilibrium between donor and recipient immunocompetent cells. It is important to differentiate between graft failure and severe marrow suppression secondary to infections (CMV), administration of
certain drugs (ganciclovir), and chronic GVHD causing thrombocytopenia. Treatment of graft failure consists of administration of a second conditioning regimen and HSCT if donor hematopoietic cells are not detected by cytogenetic or DNA studies. However, the outcome of these patients is extremely poor. When donor cells are present in the recipient's bone marrow, treatment may include either a second stem cell infusion without conditioning or administration of hematopoietic growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor.

LATE COMPLICATIONS

Several delayed toxic effects occur after HSCT and require long-term follow-up and care. Thyroid function remains unaffected in patients conditioned with chemotherapy alone. Clinical hypothyroidism is rare but may occur as early as 1 year and as late as 15 years after transplantation. The incidence of compensated hypothyroidism is higher in patients receiving single-dose TBI than in those receiving fractionated TBI (15%-25%). In some patients with chronic GVHD, hyperthyroidism has been reported. Growth hormone deficiency has been noted in approximately 60% of children conditioned with high-dose TBI and in 90% of children who had previous cranial irradiation. The growth and development of children receiving only chemotherapy is usually normal.

Risk factors for delayed and impaired sexual maturity in boys and girls include the use of single-dose TBI and older age at the time of transplantation. Approximately 50% of children receiving fractionated TBI and 90% of those receiving chemotherapy alone will experience normal sexual and reproductive development. Most men and women treated with TBI become infertile. However, a few women were reported to have been able to become pregnant, but recovery of spermatogenesis in men is unlikely. In women younger than 25 years who received high-dose cyclophosphamide alone, recovery of ovarian function has been documented. Most men treated with cyclophosphamide alone experienced recovery of spermatogenesis.

The incidence of cataracts is 80% in patients receiving single-dose TBI, 50% in patients receiving fractionated TBI (>1200 rad [>12 Gy]), and 34% in patients receiving lower-dose fractionated TBI (≤1200 rad [≤12 Gy]). Patients receiving chemotherapy alone had a 19% incidence of cataracts. The use of glucocorticoids to treat GVHD is associated with an increased incidence of cataracts. Obstructive pulmonary defects occur in 10% of patients with chronic GVHD approximately 1 year after transplantation. Bronchiolitis obliterans has been reported to occur in 10% of patients with chronic GVHD up to 2 years after transplantation. Neurologic toxic effects include leukoencephalopathy, cerebellar ataxia, seizures, and motor spinal cord syndromes. Children undergoing irradiation and intrathecal chemotherapy tend to experience a variable degree of decreased neuropsychologic performance. Aseptic necrosis of the hip is seen, probably related to corticosteroid therapy and TBI. An increased incidence of late secondary malignancies has been documented in long-term survivors. The risk of a secondary malignancy was 8 times higher than in the healthy population 10 years after transplantation. The incidence is cumulative over time, and the most common malignancies include leukemia, cancer of the buccal cavity, hepatocellular carcinoma, brain and central nervous system tumors, and thyroid, bone, and connective tissue cancers. The risk of secondary malignancy increases over time after transplantation and is greater among younger patients, necessitating lifelong surveillance. Patients with aplastic anemia who receive conditioning therapy with cyclophosphamide and thoracoabdominal irradiation have a 22% risk of developing secondary malignancies at 10-year follow-up. In T-cell-depleted and HLA-mismatched transplants, an increased risk for secondary lymphoproliferative disorders, which often occurred in donor cells and was associated with the Epstein-Barr virus, has been documented. In addition, the use of TBI and treatment of GVHD with antithymocyte globulin or anti-CD3 monoclonal antibody were found to be risk factors for the development of secondary malignancies.

RESULTS OF ALLOGENEIC HSCT

The long-term results of allogeneic BMT for acute and chronic leukemias, aplastic anemia, thalassemia major, congenital immunodeficiency disorders, non-Hodgkin lymphoma, and multiple myeloma are summarized in the Table.

In acute myeloid leukemia, allogeneic BMT in young adults with HLA-matched donors in first complete remission (CR) is associated with long-term DFS of 40% to 70%. The DFS in patients who undergo transplantation at the time of early first relapse is approximately 30%. Patients who have refractory disease or who undergo transplantation in second or subsequent remission have DFS of 10% to 40%.

In acute lymphocytic leukemia, allogeneic BMT is recommended in second remission. The DFS is comparable in patients with low-risk acute lymphocytic leukemia whether they underwent transplantation in first or second remission. Reported long-term DFS was approximately 50% to 55% for patients receiving HLA-identical sibling transplants in first remission and 40% to 45% in second or subsequent remission. In patients with high-risk disease, such as those with Philadelphia chromosome-positive acute lymphocytic leukemia, allogeneic BMT may be indicated in first remission.

In CML, allogeneic BMT within a year of diagnosis and during the chronic phase is associated with DFS of approximately 70%, 91,92 The use of hydroxyurea rather than busulfan as initial treatment for these patients seems to be associated with better prognosis. Allogeneic BMT
is considered to be the treatment of choice in young patients with myelodysplastic syndrome who have an HLA-matched sibling donor. Limited data suggest long-term DFS of 30% to 40%.94

Allogeneic BMT in patients with multiple myeloma is associated with approximately 40% CR and 20% DFS at 2 years follow-up. The overall relapse-free survival of patients who achieve a CR after BMT is 35% at 6 years.93 Transplant-related mortality is approximately 50%, with infections, interstitial pneumonitis, and acute and chronic GVHD accounting for most of the causes of death. Favorable pretreatment prognostic factors include female sex, stage 1 disease at diagnosis, one line of previous treatment, and being in CR before allogeneic BMT. The most important posttransplantation prognostic factor is the achievement of a CR.

In patients with intermediate- or high-grade non-Hodgkin lymphoma, DFS with allogeneic BMT at 2 to 3 years of follow-up is superior to that seen with autologous BMT most likely because of a graft-vs-lymphoma effect.90,97 However, randomized trials are needed to confirm these results and to assess the long-term outcome of these patients. Good prognostic factors include transplantation early in the course of the disease, sensitive disease, good performance status, and the absence of bulky disease.

In aplastic anemia, previous transfusion therapy has a significant negative impact on transplantation outcome. In these patients, allogeneic BMT is superior to other immunosuppressive therapies in producing a complete hematologic remission. However, in older patients and in those with milder disease, an initial trial of immunosuppressive therapy may be indicated.65

Allogeneic BMT has been shown to be highly effective in patients with thalassemia major. The most important negative prognostic factor seems to be the presence of hepatic cirrhosis.98

Allogeneic BMT has been used in sickle cell disease.99 In the United States, 5 patients were first reported to receive HLA-matched sibling donor marrow grafts. With a median follow-up of 16 months (range, 8 months to 9.3 years), all 5 patients were alive and demonstrated donor engraftment and the donor’s hemoglobin electrophoretic pattern. Later, a multicenter collaborative study103 investigated BMT for sickle cell disease in 34 patients younger than 16 years. With a median follow-up of 26.5 months (range, 0.2–66.9 months), 32 of the 34 patients survived, and 28 patients demonstrated stable engraftment of donor hematopoietic cells.

Graft rejection or recurrence of sickle cell disease occurred in 4 patients, and 2 patients died of intracranial hemorrhage or GVHD.100

In a European study,101 42 patients with sickle cell disease underwent allogeneic BMT from sibling donors. With follow-up of 1 to 75 months, 1 patient died of GVHD, and had sustained engraftment and demonstrated the donor’s hemoglobin electrophoretic pattern, and 6 had chronic GVHD.102 These limited experimental data indicate that allogeneic BMT may cure sickle cell disease in selected patients. However, concerns about short- and long-term toxic effects, lack of suitable donors, and limited access to this treatment currently make it an infrequently used treatment for sickle cell disease.102

Allogeneic HSCT has been investigated in patients with autoimmune diseases. Several animal studies93 have shown that autoimmune diseases are stem cell disorders and that transplantation of normal hematopoietic stem cells after myeloablative therapy can be used to treat these diseases. Similarly, remissions of autoimmune diseases have been reported in patients with concomitant malignancies for which they were treated with myeloablative chemotherapy followed by HSCT. Autologous HSCT is being increasingly used worldwide in patients with severe autoimmune diseases.104 Favorable results have been reported in multiple sclerosis105 and in systemic lupus erythematosus.106,107 Allogeneic HSCT may be more promising than autologous HSCT because it may exert a graft-vs-autoimmunity effect by gradually eradicating the recipient’s lymphopoiesis. However, the transplant-related mortality rate is considered too high to routinely recommend this approach. New nonmyeloablative conditioning regimens with allogeneic HSCT are associated with fewer toxic effects and may be used in refractory autoimmune disorders.

**LEUKEMIC RELAPSE AFTER ALLOGENEIC BMT**

Treatment of recurrent leukemia after allogeneic BMT has had limited success.108 Withdrawal of cyclosporine therapy in patients with mini-
mal disease recurrence and no GVHD has been shown to reduce remis-
son in certain cases, particularly in patients with CML and cytogenetic
lesions. Interferon α, IL-2, and in-
fusion of donor buffy coat have all been shown to reduce remission in
some cases of relapsed acute leuke-
ia and CML after allogeneic BMT. 80 Granulocyte colony-stimulating fac-
tor administration induced remis-
sion in 3 of 7 patients who relapsed
within a year of allogeneic BMT. 81 In
patients whose relapse occurs later than 12 months after allogeneic BMT,
a second transplantation may be as-
terminated with lethal cytoreduc-
tion for the treatment of malignant and nonma-
lignant hematologic disease. 82


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