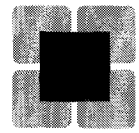

WILLIAM S. WILKE, MD, EDITOR

BONE MARROW TRANSPLANTATION: UPDATED INDICATIONS

In the past 15 years, bone marrow transplantation has proven curative for a variety of malignancies and acquired disorders of hematopoiesis. Allogeneic bone marrow transplantation (using a matched donor as the source of bone marrow) is the treatment of choice for aplastic anemia and for chronic myelogenous leukemia (CML). In certain instances, this modality is indicated for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplasia.

Autologous bone marrow transplantation (using one's own previously harvested marrow as the source of bone marrow for transplantation) is the treatment of choice for relapsed non-Hodgkin's lymphoma and Hodgkin's disease. It may also be beneficial in a variety of other malignancies. New immunosuppressive agents, new prophylactic and therapeutic antibiotics, and improved use of cytotoxic therapy have yielded improved results. Additionally, the National Marrow Donor Program is becoming increasingly valuable in locating unrelated HLA-identical donors for patients in need of allogeneic bone marrow transplantation.

RATIONALE FOR TRANSPLANTATION

In sufficient doses, chemotherapy and radiation therapy, alone or in combination, can eradicate a given tumor; however, the dose of antitumor agents is largely limited by their toxicity to the patient's normal bone marrow. If normal bone marrow is available for transplantation, higher and potentially curative antitumor doses of chemotherapy, radiation therapy, or both, can be administered and the donor marrow can save the patient from iatrogenic death.

A typical protocol involves 3 to 10 days of treatment with chemotherapy and/or radiation therapy followed by infusion of bone marrow. A minimum of 1×10^8 nucleated cells/kg of recipient body weight is required for adequate engraftment. The marrow is infused intravenously and within several weeks becomes engrafted to restore hematopoietic function. If the source of marrow is a matched sibling or matched unrelated donor, immunosuppressive agents to prevent graft vs host disease (GVHD) are begun 1 to 2 days prior to marrow reinfusion.

COMPLICATIONS

All bone marrow transplant patients are pancytopenic for several weeks prior to transplantation. They generally require inpatient care with intensive transfusion support and treatment of suspected or proven infections. Different preparative regimens may have their own potential toxicities as well. Allogeneic bone marrow transplantation is associated with a variety of additional problems, including acute and chronic GVHD, interstitial pneumonitis, and veno-occlusive disease of the liver. Much of the ongoing research in this area involves minimizing the morbidity of these complications.

SPECIFIC INDICATIONS

Allogeneic bone marrow transplantation is the treatment of choice for acute leukemia in relapse. Many centers consider it the preferred therapy for patients with AML in first remission as well. Patients with acute lymphoblastic leukemia (ALL) have a higher risk of relapse following transplant than those with AML, and only patients with a variety of poor prognostic features are treated with allogeneic bone marrow transplantation in first remission.

The incidence of GVHD increases with age, and generally patients over age 55 are not suitable candidates for allogeneic BMT. Chronic myelogenous leukemia is incurable with conventional therapy, but allogeneic bone marrow transplantation is curative in 60% to 70% of patients, and is the treatment of choice. It is also the treatment of choice for young patients with aplastic anemia and myelodysplasia.

Conventional therapy does not cure aggressive non-Hodgkin's lymphoma in patients in whom initial chemotherapeutic regimens have failed. Many of these cases can be salvaged with autologous bone marrow transplantation, which is now accepted as a therapy of choice for relapsed intermediate grade and aggressive grade non-Hodgkin's lymphomas. This is also true of

patients with relapsed Hodgkin's disease in whom one or two courses of chemotherapy has failed. The role of autologous bone marrow transplantation in other tumors is evolving. Results in patients with breast cancer and multiple myeloma appear promising. The treatment of other solid tumors has shown excellent response rates, but unfortunately, positive response has tended to be of brief duration.

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TURNING BACK GROUP A STREPTOCOCCI

Acute rheumatic fever has become resurgent in this country in the last 5 years, with outbreaks that included an epidemic in Salt Lake City, Utah, and smaller clusters in Columbus and Akron, Ohio. Acute rheumatic fever is the only clearly preventable cause of heart disease; yet, worldwide it causes 15 to 20 million new cases of heart disease every year, and it is responsible for 25% to 40% of all cardiac disease.

Because of the resurgence, it is necessary to maintain a high index of suspicion and re-examine our diagnostic approach to group A beta hemolytic streptococcal infection. In the recent outbreaks, the affected patients were primarily from suburban, middle-class, small families. Only one-third had sore throats that required medical attention in the early stages of the disease, when acute rheumatic fever can be most effectively prevented.

Tests are available for rapid, in-office diagnosis of streptococcal infection; these kits work by direct detection of the antigen in the throat. Although they are highly specific, they have a sensitivity of only 60% to 70%. Therefore, if the test is negative, a throat culture is mandatory.

RISK FACTORS

Only upper respiratory streptococcal infection is associated with acute rheumatic fever. High antistreptolysin O (ASO) titers (200 Todd units/mL) and prolonged exudative pharyngitis increase the risk, and there appears to be a familial predisposition to the disease.

In an epidemic setting, acute rheumatic fever may develop in 3% of individuals with streptococcal pharyngitis. The risk is much lower in a nonepidemic setting—about 0.3%. Because the prevalence—even in an epidemic setting—is only 3%, a positive throat culture alone does not necessarily provide useful information about the likelihood of acute rheumatic fever. Carriers without active infection further confound the picture.

DIAGNOSIS

The diagnosis of acute rheumatic fever may be elusive, especially to younger clinicians who have never seen a case. The manifestations are diverse and there is no specific diagnostic test, although the T. Duckett Jones criteria are generally accepted. The presence of two major criteria *or* one major criterion and two minor criteria along with evidence of preceding streptococcal infection makes the diagnosis probable.

The major criteria are carditis (the only feature with a potential for long-term disability or death), chorea, polyarthritis, erythema marginatum, and subcutaneous nodules. Minor criteria are previous acute rheumatic fever or rheumatic heart disease, arthralgia, fever, and acute phase reactions that include elevated sedimentation rate, positive CRP, elevated white blood cell count, and prolonged P-R interval.

In adults, carditis occurs in only 15% of patients and tends to be mild and transient. Even when carditis does occur, it is often asymptomatic, although manifestations may range from just a widened P-R interval up to and including congestive heart failure.

Arthritis is a major feature in adults and usually involves large, lower-extremity joints. Severity ranges from subacute arthralgias to frank arthritis. Synovial fluid analysis yields no findings specific to rheumatic fever, but is useful to rule out other types of arthritis.

Erythema marginatum is an unusual finding that presents as evanescent, primarily vasomotor lesions and may continue for several weeks. Subcutaneous nodules are associated with severe carditis and persist for a few weeks after the onset of disease.

Sydenham's chorea, although rare, is by itself thought