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SECTION V

BLOOD AND NEOPLASTIC DISORDERS

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1 • BONE MARROW TRANSPLANTATION IN THE TREATMENT OF SEVERE APLASTIC ANEMIA

Wayne Spruce
SCRIPPS CLINIC AND RESEARCH FOUNDATION

ETIOLOGIC CONSIDERATIONS

Until the advent of bone marrow transplantation, severe aplastic anemia was associated with a high mortality rate. Most patients would succumb within the first six months of the onset of their disease. Treatment with anabolic steroids and corticosteroids had, in most cases, been disappointing and most patients died of hemorrhagic or infectious complications. The presenting symptoms of marrow aplasia are a result of the marrow failure and are usually easy bruising, spontaneous bleeding, and/or infection.

Severe aplastic anemia is a relatively uncommon disorder with an incidence of about 65 per million in adults over 65 years of age and 4 per million in children. Approximately 25% of cases occur in individuals under the age of 20 years and 30% in patients over the age of 60 years. Males and females are equally affected. While there are well-described congenital forms of marrow aplasia including Fanconi's anemia, the majority of the cases are acquired. A variety of etiologic agents including chemicals, drugs, ionizing radiation, and infections has been implicated. Occasionally pregnancy and thymomas have been associated with marrow failure, and paroxysmal nocturnal hemoglobinurea may occasionally present with pancytopenia. The best known drug association is the rare but often fatal association with chloramphenicol. Benzine and insecticides are chemical agents that have been implicated in cases of aplastic anemia. In spite of the multitude of possible etiologic agents, the majority of patients present with no clear-cut cause of their marrow failure.

DIAGNOSTIC CRITERIA

The criteria for severe marrow aplasia include a markedly hypocellular marrow and peripheral blood with any two of the three following findings: a neutrophil count of less than 500/dl, a platelet count of less than 20,000/dl, and a corrected reticulocyte count of less than 1%. Bone marrow aspirations are not adequate to make the diagnosis and a bone marrow biopsy is mandatory.

PATHOPHYSIOLOGY

Since aplastic anemia is not a single disease, the pathophysiology cannot be explained with a single concept. Theoretically, marrow failure could be explained as failure of the pleuripotential stem cell, or a failure of its microenvironment. Until recently it was felt that most cases of marrow failure resulted from an isolated failure of the stem cell. However, clinical experience in human marrow transplantation indicates that at least in some cases the cause may reside in the immune system. There are many well-documented cases of spontaneous autologous marrow recovery after unsuccessful attempts at marrow grafting. In addition, at least half of identical twin transplants have failed when no immunosuppression was used. Also, a growing number of individuals have been successfully treated with antithymocyte globulin (ATG). These observations implicate an immune mechanism in at least some patients.

PHARMACOLOGIC AND IMMUNOLOGIC THERAPY

Most of this chapter will deal with bone marrow transplantation as the treatment for severe aplastic anemia; however, a brief description of other forms of therapy will also be presented.

STEROIDS

Treatment with androgens such as testosterone and oxymetholone was reported to result in remission of severe marrow aplasia in small numbers of patients in the early 1960s. These reports were not confirmed in larger numbers of patients, and more recent studies in the 1970s showed that they provided no advantage over modern supportive care. Likewise, corticosteroids in

conventional doses (1 to 2 mg/kg) and immunosuppressive drugs such as cyclophosphamide have been reported to be effective in small numbers of patients. Confirmation in larger numbers of patients is lacking.

ANTITHYMOCYTE GLOBULIN

Since Mathe's original report on autologous marrow recovery in three out of seven patients treated with antithymocyte globulin (ATG) in 1970, there have been many other studies confirming its efficacy used alone, with haplo-identical marrow, or with androgens. The doses of ATG and the source of the material have varied greatly from study to study. However, the response rate in most series is between 40% and 70%. Many patients do not respond completely; however, the majority of them are transfusion free. The role of haplo-identical marrow and androgens remains unclear. The use of large doses of methylpredisolone (20 mg/kg) along with ATG by the Swiss group has shown responses in 15 of 16 patients so treated. In most series of patients, the time to response has varied from a few weeks to several months and relapses have been seen in up to 10% of patients.

The toxic effect of ATG is considerable and includes fever, chills, urticaria, and hypotension. In addition, platelet counts usually drop and may be difficult to support. Many of these side effects can be modified with the use of antihistamines and corticosteroids. Many patients will develop serum sickness, which can usually be prevented or treated with corticosteroids.

Bone Marrow Transplantation

HISTOCOMPATIBILITY

HLA System. Early clinical work, primarily in murine systems, showed that marrow could be successfully transplanted in lethally irradiated animals only when they were histocompatible as determined by the H2 complex. The human equivalent is called the human leukocyte antigen (HLA) system. There is a series of closely related loci on the number six chromosome designated HLA-A, B, C, and D, which make up the human histocompatibility complex. Because of their close proximity on the chromosome, they are inherited as a unit in a mendelian codominant manner. Thus siblings have a 25% chance of being HLA identical. The A, B, C, and DR (D-related) loci are determined by anti-HLA antisera, and the D loci by the mixed lymphocyte culture. HLA testing can be done at all transplant centers and by most major blood banks. By and large, the majority of successful transplants have been performed between individuals who are HLA identical. At present, a patient must have siblings to have a marrow transplant for aplastic anemia. There have been occasional reports of successful transplants using parental or unrelated donors who are phenotypically identical to the patient, but these are rare.

PATIENT EVALUATION PRIOR TO TRANSPLANTATION

Once the diagnosis has been established, a decision needs to be made as to whether the patient is a candidate for transplantation. HLA typing of the patient and family should be done as soon as possible. The results of the HLA typing and mixed lymphocyte culture can usually be available within a week. Transplantation in patients over the age of 40 years is not usually successful, and these individuals should be considered for other forms of treatment.

During the evaluation period, blood product transfusions should be given very judiciously to avoid exposure of the patient to foreign antigens that might lead to graft rejection. Donors who are family members should be especially avoided. However, if the patient is extremely anemic or bleeding, transfusions should be given. The use of washed or frozen red cells and single donor, unrelated platelets may help to minimize sensitization. Infections should be treated vigorously; however, it may be necessary to go ahead with the transplant even in the face of active infections.

PREPARATIVE REGIMENS

Work done in animal systems showed that some form of immunosuppression was necessary in order for a marrow transplant to be successful. This has proved to be true in the human situation as well. Currently most centers, including our own, employ cyclophosphamide as the backbone of the preparative regimen. The dose is 50 mg/kg of lean body weight given intravenously over one hour daily for four days (total dose is 200 mg/kg). Most patients experience intense nausea and vomiting with the drug that lasts from several hours to several days. Other prominent side effects of the drug include an antidiuretic effect, hemorrhagic cystitis, and very rarely cardiac toxicity. Because of the antidiuretic effect and risk of hemorrhagic cystitis, a high urine flow must be maintained. A balanced electrolyte solution containing sodium bicarbonate, potassium, and furosemide (10 mg/L) is infused at a rate of 3000 ml/24 hours/m^2. In addition, we use continuous bladder irrigation with urologic saline at 1 liter per hour beginning at the time of the first cyclophosphamide infusion and continuing for 24 to 48 hours after the last dose of the drug.

In patients who have not been sensitized by prior blood product transfusions, this preparative regimen is usually adequate to allow engraftment. However, the majority of patients with aplastic anemia have required some blood component support either with packed cells or with platelets prior to coming to transplant. In these patients there is a definite risk of graft rejection, which may be as high as 30%, and additional immunosuppression appears to be necessary. Several methods have been used to provide additional immunosuppression. Our group currently employs total lymph node irradiation as suggested by the transplant group at the University of Minnesota. It involves the delivery of 750 rads of irradiation to all the major lymph node–bearing areas at a rate of approximately 25 rads per minute. The total nodal irradiation is delivered 24 hours after the last dose of cyclophosphamide. Other centers have used total body irradiation from 300 to 600 rads, and others have employed additional drugs such as Myleran and procarbazine; all of these methods have been successful in reducing the graft rejection rate to less than 10%. The Seattle group employs unirradiated donor buffy coat transfusions after the marrow transplant for four to five days. Recently cyclosporine has been reported by sev-

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