Treatment of Aplastic Anemia

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**Key Words.** Aplastic anemia · Treatment · Bone marrow transplantation · Immunosuppression

**ABSTRACT**

There is general agreement that in children and adolescents with an HLA-identical or syngeneic sibling, bone marrow transplantation (BMT) should be performed without delay. More controversial are young-to-middle-aged adults with an HLA-identical sibling. Because of comparable survival rates, some centers advocate BMT; others advocate immunosuppression as primary treatment. BMT cures severe aplastic anemia (SAA), but has a higher early mortality. Immunosuppression usually induces hematopoietic improvement and has hardly any early mortality. However, there are late problems. After immunosuppression, there may be relapse and clonal hematopoietic disease. After BMT, there may be late graft failure, severe or even fatal chronic graft-versus-host-disease (GVHD).

Both procedures are followed by a slight increase in second malignancies. Retrospective studies show no significant differences in long-term survival between the two treatment modalities. In patients over the age of 40, immunosuppression is favored by most centers because in this age group there is a very high transplant-related mortality with BMT. Androgens and hematopoietic growth factors have hardly any role in therapy of SAA. Splenectomy helps some patients with severe thrombocytopenia and problems with supportive care, but does not improve the overall prognosis. BMT with unrelated donors has usually been performed in late stages of the disease with disappointing results. *The Oncologist* 1996;1:367-370

**INTRODUCTION**

The severity of aplastic anemia (AA) varies widely from total hematopoietic failure to mild chronic pancytopenia. Whatever the severity of the disease, optimal initial management is of great importance for the clinical course. Transfusion policy is crucial and deserves special attention.

**SUPPORTIVE CARE**

Transfusion policy must be carefully considered in order to avoid sensitization to transplantation antigens and transmission of viral disease. These patients are likely to have a long period of pancytopenia and may require many transfusions.

Whenever possible, AA patients should be referred to a specialized center before being given blood products. Only leukocyte-poor transfusions from single donors should be used. HLA-typing should be performed immediately.

Each patient under the age of 40 is a potential candidate for bone marrow transplantation (BMT). Sensitization by transfusions has a deleterious effect on the outcome of this procedure, in particular if blood products from family members are used [1, 2]. Transfusions in general should be kept at a minimum, but should not be withheld if clinically indicated.

If the patient is febrile or has objective signs of infection, broad-spectrum antibiotics should be administered i.v. without delay. If fever persists, antifungal drugs should be added and herpetic lesions should be treated i.v. with Acyclovir.

**TREATMENT OF SEVERE APLASTIC ANEMIA (SAA)**

The criteria for SAA are well-defined: granulocytes <0.5 × 10^9/l, thrombocytes <20 × 10^9/l and reticulocytes <20 × 10^9/l and an aplastic bone marrow proven by biopsy. In very severe aplastic anemia, the granulocyte count is <0.2 × 10^9/l. Patients who fulfill these criteria are very unlikely to have a spontaneous remission. Two entirely different treatment modalities are currently used.

**BMT**

This procedure is largely limited to young patients who have an HLA-matched sibling donor. Only about 25%-30% of the patients have such a donor; in addition, in our center the upper age limit is 40 years. The standard preparative regimen consists of high-dose cyclophosphamide 30 mg/kg i.v. on four successive days. In recent studies, cyclophosphamide has been combined with antilymphocyte globulin...

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(ALG) or antithymocyte globulin (ATG) [3]. The addition of total lymphoid irradiation or thoraco-abdominal irradiation has been shown to enhance engraftment. However, this has been at the expense of an increased incidence of late radiation-induced problems [4].

For prevention of graft-versus-host-disease (GVHD), the best results are achieved with cyclosporine-A (CsA) or a combination of CsA and short methotrexate (MTX). From the day before BMT, 2-5 mg/kg CsA are given as a continuous infusion. Later, the patient is switched to an oral dose of 5-10 mg/kg per day [5]. The dose is adapted to the serum creatinine level, severity of GVHD, and blood concentration of CsA. Late rejections can occur when CsA is stopped [6]; therefore we administer it for 6-12 months after BMT and decrease the dosage very slowly before stopping it.

Actuarial survival has improved from about 45% to 72%, to 90% in the most recent studies [7, 8]. Rejection and chronic GVHD remain problems. Even in the most recent studies, chronic GVHD is frequent among long-term survivors. GVHD increases in frequency and severity with age. This contributes to poor survival in older patients. Better survival and low morbidity in young patients make autologous BMT the treatment of choice for children and adolescents [9, 10]. Between 20 and 40 years of age, there is an intermediate group with a reasonable chance for cure but with more complications than younger patients. Beyond the age of 40, there is a high risk of transplant-related mortality. Besides age, multiple transfusions, serious infections before grafting, and a prolonged interval between diagnosis and transplant are risk factors for treatment failure [9].

Immunosuppression

In an experimental model of AA in rabbits, we documented that autologous marrow reconstitution followed conditioning with ALG and infusion of mismatched bone marrow [11, 12]. These results were confirmed in patients with SAA. Later we documented that ALG was the active principle [13]. The marrow infusion is not necessary in patients with AA. Obviously, immune mechanisms are involved in the pathophysiology of AA. Improvement of marrow function can be induced with immunosuppression in 50%-80% of patients. For those who are not eligible for BMT, immunosuppression is the treatment of choice. Currently, most centers use a combination of ALG or ATG with CsA [14, 15]. This appears to be beneficial for inducing remission and for prevention of relapse. For many years, we used equine antihuman thoracic duct lymphocyte globulin. This preparation is no longer available, but we now achieve equally good results with equine ATG [16, 17]. The addition of methylprednisolone prevents, or at least ameliorates, serum sickness. It does not improve overall results and can be associated with significant toxicity, such as aseptic necrosis of the femur or the humerus. One of the drawbacks of ALG therapy is that hemopoietic recovery usually is slow, often taking months. Relapse occurs in about 35% of cases, but most of them respond to a second immunosuppressive therapy [18].

Evolution of AA to paroxysmal nocturnal hemoglobinuria (PNH) has been described in 10% to 57% of the patients [19-21]. It is usually subclinical but can be associated with severe hemolysis and thrombo-embolic events. More serious is the evolution into myelodysplasia (MDS) and leukemia. In a European study, the cumulative ten-year incidence was 9.6% for MDS and 6.6% for acute leukemia [20, 21]. Besides clonal marrow disorders, patients with AA after immunosuppression and BMT (particularly if radiation is used in a conditioning regimen) have an increased incidence of malignant tumors—2%-3% after 10 years [22].

Patients >30-40 years old have better survival after immunosuppressive therapy than after BMT. On the other hand, children, in particular girls, respond relatively poorly to ALG.

Androgens

It is quite clear that androgens alone are not effective in the severe form of AA. In some cases, however, particularly women, they can accelerate autologous bone marrow recovery after treatment with ALG [23]. A very small fraction of patients become androgen dependent. Considering the side effects of androgens, long-term maintenance therapy is usually not indicated.

Splenectomy

Splenectomy is not indicated as a primary treatment of SAA. In our experience, some patients who have only partial hemopoietic recovery after immunosuppressive therapy can benefit from splenectomy because platelet counts rapidly increase to levels which are more compatible with life, and transfusion requirements decrease [24]. In a large percentage of patients, progressive hemopoietic improvement follows splenectomy, indicating that the spleen plays a pathophysiological role in AA. In patients with serious platelet support problems after immunosuppression, splenectomy is indicated. It has to be borne in mind that a large European study showed an increased incidence of MDS leukemia after this procedure [22]. In our own study, splenectomy did not increase the incidence of late clonal complications but worsened their course [24].

Hematopoietic Growth Factors

Results of present studies are rather disappointing. G-CSF, GM-GSF and interleukin 3 can lead to an increased number of granulocytes in patients who still
have sufficient committed precursor cells. In patients with total aplasia, there is usually no improvement. The prognosis of SAA is not influenced by such therapy [25]. The first available data with stem cell factor also look rather disappointing. An initial treatment with haemopoietic growth factors alone is not indicated. Perhaps G-CSF and GM-CSF have a certain place as short-course therapy in patients with severe infection after immunosuppressive therapy or BMT. Current studies examining the role of combined growth-factor therapy in AA are under way.

**BMT FROM UNRELATED DONORS**

If donor and recipient are phenotypically matched for HLA-A, -B, and -DR, they still have major and minor histocompatibility antigen differences. This results in a higher rejection rate and more severe GVHD. T cell depletion further increases the risk of graft failure. A recent European study compared 913 HLA-identical sibling transplants with 143 alternative BMTs [26]. Actuarial survival at five years was 30% for the alternative BMT and 65% for sibling BMT ($p \leq 0.0001$). An important factor was the time elapsed between diagnosis and BMT. If a BMT was performed in the first year, 35% of the patients survived compared with only 22% for those transplanted later ($p = 0.04$). Inclusion of CsA in the postgraft immunosuppressive protocol was associated with improved probability of five-year survival, 45% compared with 20% for patients not receiving CsA ($p = 0.04$). It is concluded that alternative BMT for SAA and Fanconi anemia remained inferior to sibling BMT. Because of improved results of immunosuppressive treatment, alternative donor BMT should not be considered as the first-line therapy for AA. Unrelated transplants remain a high-risk procedure, which should be performed only by experienced teams contributing to the progress in the treatment of this disorder. A most recent communication on unrelated BMT showed more promising results by using early transplantation and improved histocompatibility matching in leukemia [27]. This could also be relevant for SAA.

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