Treatment of Aplastic Anemia

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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.

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 50 mg/kg i.v. on four successive days. In recent studies, cyclophosphamide has been combined with antilymphocyte globulin...
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ACTUARIAL SURVIVAL

In an experimental model of AA in rabbits, we docu-
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with SAA. Later we documented that ALG was the active principle [13]. The marrow infusion is not necessary in
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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 hemoglobin-
uria (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 seri-
ous is the evolution into myelodysplasia (MDS) and
leukemia. In a European study, the cumulative ten-year inci-
dence 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,
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and Alloimmune Rejection

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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 par-
ial hemopoietic recovery after immunosuppressive ther-
apy 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 improve-
ment 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

immunosuppressive therapy 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 contin-
uous 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 concentra-
tion 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 sur-
vivors. 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
allogeneic 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 mor-
tality. Besides age, multiple transfusions, serious infections
before grafting, and a prolonged interval between diagnosis
and transplant are risk factors for treatment failure [9].

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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 hematopoietic 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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