

ALLOGENIC BONE MARROW TRANSPLANTATION IN APLASTIC ANEMIA

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ABSTRACT

Eighteen patients, twelve men and six women, with aplastic anemia underwent allogenic bone marrow transplantation (BMT) from HLA-matched siblings during the period of 1990 to 1996. The conditioning regimen was cyclophosphamide with or without busulfan, depending on the cause of aplasia. Antilymphocyte globulin (ALG) and cyclosporine were used for rejection and acute GVHD prophylaxis, respectively. Eleven patients are alive (61%) and seven (39%) died. Twelve patients developed acute GVHD. We found an inverse relationship between the incidence of acute GVHD and the number of units of transfused packed cells and platelets before BMT ($p < 0.01$). We could not find an association between the incidence of chronic GVHD and age or a positive history of acute GVHD. The time of cellular recovery ($WBC > 1000$, $PLT > 100000$) after BMT was inversely related to the total number of cells transplanted ($p < 0.05$).

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INTRODUCTION

Aplastic anemia is a disease characterized by pancytopenia and a hypocellular bone marrow.¹ It has been associated with infections, drugs and chemicals, and constitutional disorders like Fanconi's anemia, but in the majority of patients no etiologic factor can be found.

Fanconi's anemia is also a separate entity. It is the most common, though not the only, form of constitutional aplasia. Dyskeratosis congenita, a dermatologic disease inherited in X-linked or autosomal recessive pattern, may be complicated by bone marrow hypoplasia.² Patients with the following findings appear to have a particularly unfavorable prognosis: a granulocyte count of less than

$0.5 \times 10^9/L$, platelet count of less than $20 \times 10^9/L$, reticulocyte value of less than 1% in the presence of anemia, and a hypoplastic marrow with less than 30% cellularity. Mortality in such severe cases of aplastic anemia is 80-90%. Most patients die within six months of diagnosis. In 1972, an article described the results of the first 4 transplants of marrow from human leukocyte antigen (HLA)-identical sibling donors.³ The report showed that allogenic BMT could cure the disease. Since then, allogenic bone marrow transplantation from HLA identical siblings has been tried in several centers in the world as a way for curing these high risk patients. The risks of graft rejection and acute graft versus host disease (GVHD) have lessened in recent reports,⁴ whereas the problem of chronic GVHD has persisted.^{5,6} Although a 40-45% survival rate was the rule during the 1970s, survival has markedly improved during recent years due to better prophylaxis and management of acute

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GVHD and rejection (60-90% in recent reports), so under the age of 40, bone marrow transplantation from an HLA identical donor is the best method of treatment for aplastic anemia. Patients over 40 may benefit more from immunosuppressive treatment.⁷

PATIENTS AND METHODS

Eighteen patients, 12 men and 6 women, with aplastic anemia underwent allogeneic bone marrow transplantation from HLA identical siblings during the period of 1990-1996. The mean age of the patients was 16.5 (SD: 7.62) years. The cause of aplasia was Fanconi's anemia in three, dyskeratosis congenita in two, toxin and drugs in two, and idiopathic in the remainder. The cases due to toxins, drugs, and idiopathic ones were eligible for BMT when their CBC had shown a neutrophil count of less than 500/mm³ and platelet count of less than 20000/mm³ and the bone marrow biopsy (BMB) was severely hypocellular (less than 25%). The selection criteria for BMT in patients with Fanconi's anemia and dyskeratosis congenita was a progressive irreversible cytopenia in the CBC and BMB, even before the indices of severe aplastic anemia became evident. All patients were below 40 years old and almost all had a fully

Table I. Pretransplant characteristics.

| | Mean | SD | Minimum | Maximum |
|--------------|-------|-------|---------|---------|
| Age | 16.5 | 7.62 | 4 | 33 |
| WBC | 1900 | 960 | 600 | 3800 |
| PLT | 27888 | 25349 | 6000 | 100000 |
| Hb | 6.4 | 2.5 | 4 | 12 |
| Reticulocyte | 0.5% | 0.54% | 0.1% | 1.8% |
| PPCT* | 6.8 | 7.8 | 0 | 35 |

*Pretransplant packed cell transfusion.

matched HLA identical sibling. Pretransplant treatment including androgens and cyclosporin was generally ineffective in some of these patients who underwent such treatment before BMT. All patients were free of chronic hepatitis and had an adequate ejection fraction and pulmonary function tests in the cardiopulmonary assay

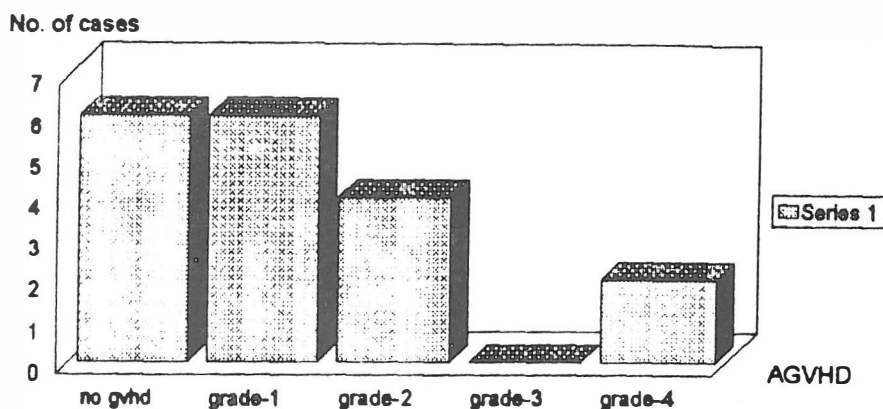


Fig. 1. Acute GVHD incidence.

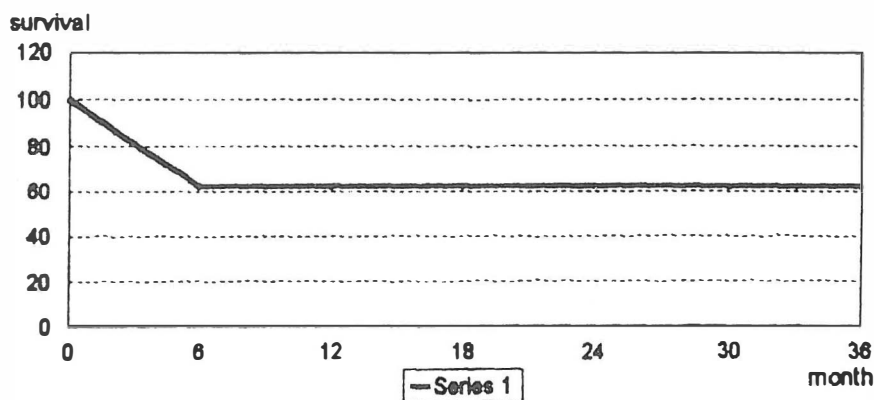


Fig. 2. Survival after transplantation.

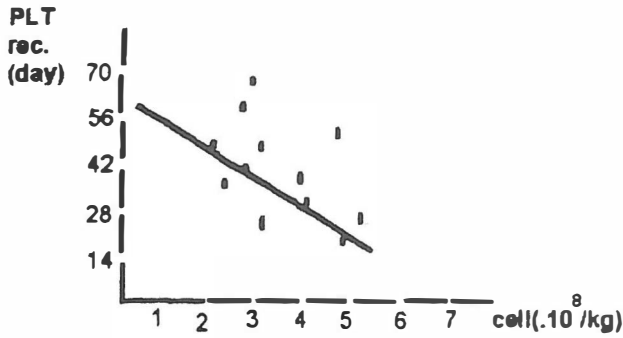


Fig. 3. Inverse relationship between PLT recovery and number of cells transplanted.

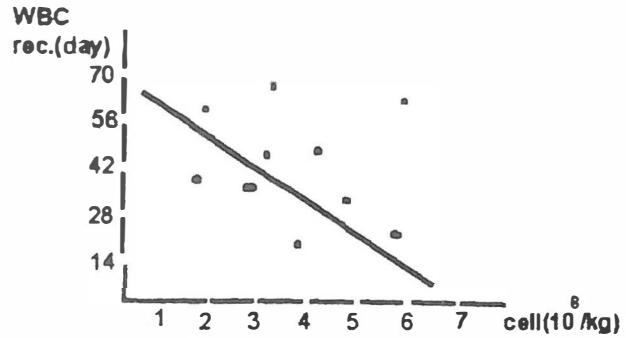


Fig. 4. Inverse relationship between WBC recovery and number of cells transplanted.

carried out before transplantation. The method of isolation was reverse isolation. The conditioning regimen was either cyclophosphamide, 50 mg/kg for 4 days or cyclophosphamide and busulfan (5-20 mg/kg and 0.2 mg/kg for 4 days, respectively). The lower doses of cyclophosphamide and busulfan were used in patients with Fanconi's anemia due to the susceptibility of these patients to the toxic effects of higher doses.² All patients with a history of transfusions in excess of 5 units of packed cells received ALG as part of their conditioning regimen. The mean number of cells transplanted was $3.9 \times 10^8/\text{kg}$ (SD=0.967) with a maximum of $6.3 \times 10^8/\text{kg}$ and a minimum of $2.2 \times 10^8/\text{kg}$. Supportive care, including daily CBC, blood chemistry, and appropriate management of any electrolyte imbalance and infection, was provided after transplantation. Engraftment was documented by cell recovery and cytogenetic studies. Cyclosporin was used for acute GVHD prophylaxis in all patients.

Statistical methods

We used the correlation regression test, comparing means with t-tests and chi-square tests, and the Fisher exact test subsequently when necessary for data analysis in this study.

RESULTS

Pretransplant data of our patients are shown in Table I. Duration of disease (from diagnosis to transplantation) varied between 1.5 to 180 months with a mean value of 23 months (SD= 40.36). The rate of acute GVHD among these patients was 66% (12 patients) which was classified as grade one in 6, grade two in 4 and grade four in 2 patients (Fig. 1). Four patients rejected their grafts after bone marrow transplantation. All rejections were early rejections and it was thus impossible to differentiate them from nonengraftment cases.

Eleven patients (61%) were alive and seven (39%) died during 1-5 years of follow up. Figure 2 shows that the

survival curve levels off after 6 months at the 61% level.

We found an inverse relationship between WBC and PLT recovery, and the number of cells transplanted ($p < 0.05$, $r = -0.6$) (Fig. 3).

Transplantation of more than 4.5×10^8 cells/kg decreased the post-transplantation recovery time of WBC and platelet counts.

The mean value of previous packed cell transfusions before transplantation was 11.5 units (SD: 15.76) in the four patients with rejection and this value was 5.3 (SD= 3.3) in nonrejected patients. Although this difference is not statistically significant in our study, it has been documented that increased pretransplant transfusion predisposes to a higher rejection probability.⁸

We did not find any relationship between age and BMT outcome as found in previous reports. This may be because of the special distribution of our patients' age which form 16.5 ± 7.6 , or the small number of cases in this study. There was no relationship between the incidence of acute GVHD and the number of transplanted bone marrow cells; however, the number of cells was inversely correlated with the time of onset of acute GVHD ($r = 0.42$, $p = 0.08$).

Regarding the high mortality rate of patients with severe aplastic anemia (80-90%), BMT offers the best opportunity for cure to these patients; especially when they are under 40 years old. Alternatives to bone marrow grafting were described in 1970 when Mathe in Paris used ATG for treating patients with aplastic anemia. Although there is a significant advantage in overall survival for patients undergoing BMT, this advantage appeared to be restricted mainly to pediatric and young patients, whereas in older patients, survival after ATG and marrow grafting is identical. Nevertheless, the survival curves of ATG-treated patients continually change because of the development of complications and the recurrence of aplastic anemia, whereas survival curves are more stable for patients treated with BMT. Although 40-45% survival was the rule during the 1970s, survival has markedly improved during the 1990s to 60-90%, depending on reports from different centers.^{9,10}

The survival rate of our patients was 61% which is comparable with the survival rates reported by other centers. An important limiting factor in this study was the small number of cases. Taking into account this limiting factor, we found some correlations in our patients which require documentation by studying larger series of patients. These correlations and our conclusions are:

1) We found a more rapid cellular recovery whenever more cells were transplanted. A larger number of transplanted cells is not accompanied by an increased incidence of severe GVHD; so if this fact is documented in studies with larger numbers of patients, we recommend more than 4.5×10^8 cells/kg for transplantation in aplastic anemia. This value does not increase the incidence of chronic GVHD, while it decreases hospital stay and blood product requirements after transplantation.

2) We found an inverse relationship between the incidence of acute GVHD and the number of units of transfused packed cells and platelets before BMT ($p < 0.01$). As rejection and acute GVHD have an inverse correlation following allogenic BMT and more pretransplant blood product transfusion predisposes patients to an increased risk of rejection, the above mentioned correlation appears logical.

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