The Treatment of Severe Aplastic Anemia: Outcomes of Bone Marrow Transplantation and Immunosuppressive Therapy in a Single Institution of Korea

The present study represents an analysis of 96 patients with severe aplastic anemia (SAA) treated in Seoul National University Hospital, Seoul, Korea between 1990 and 1999. Twenty-two patients were treated by allogeneic bone marrow transplantation (BMT) from HLA identical sibling donors and 74 by immunosuppressive therapy (IS) with antithymocyte globulin (ATG) or antilymphocyte globulin (ALG). There was no statistical difference between the two treatment groups in age, sex, disease duration, and previous transfusion amount. In the BMT group, grade II-IV acute graft versus host disease (GVHD) developed in 10% and chronic GVHD occurred in 33% of patient. Only one patient died from complication of transplantation (veno-occlusive disease). Of 74 patients who received IS treatment, 45% achieved a complete or partial response. Twenty patients died among IS treatment group. Major causes of death were hemorrhage (40%) and infection (55%). In the BMT group, the 5-yr overall survival (OS) was 95% after a median follow-up of 42 months. In the IS group, the 5-yr OS was 70% after a median follow-up of 49 months (p=0.04). In conclusion, the long-term survival rates of SAA in Koreans receiving BMT or IS were excellent compared with the Western data. Further evaluation on the prognosis of aplastic anemia in Asians should be done.

Key Words : *Anemia, Aplastic; Bone Marrow Transplantation; Immunosuppression; Korea*

Inho Kim[*,†], Sung Soo Yoon[*],
Seonyang Park[*], Byoung Kook Kim[*],
Noe Kyeong Kim[*]

Department of Internal Medicine, Seoul National University, College of Medicine[*], Seoul; Department of Internal Medicine, Inha University, College of Medicine[†], Incheon, Korea

Address for correspondence
Seonyang Park, M.D.
Department of Internal Medicine, Seoul National University, College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea
Tel : +82.2-760-3347, Fax : 82.2-762-9662
E-mail : seonpark@plaza.snu.ac.kr

INTRODUCTION

Bone marrow transplantation (BMT) is a well established treatment modality in severe aplastic anemia (SAA). In patients with SAA who have HLA-identical, related donors, BMT is usually considered the treatment of choice. The use of antithymocyte globulin (ATG) or antilymphocyte globulin (ALG), given alone (1) or together with high-dose prednisolone (2) or androgens (3), is accepted as an effective form of treatment for SAA patients who do not have a compatible donor. The aim of the present study was to compare the treatment outcomes of BMT and immunosuppressive therapy (IS) in patients with SAA at a single institution between 1990 and 1999. We speculated that the analysis of cases where modern supportive care has been given would be more likely to yield reliable data as a comparison of two treatment modalities. Since 1985, the authors' group, the hemato-oncology team in Seoul National University Hospital, Seoul, Korea, has treated patient with SAA via either immunosuppressive treatment or BMT on the basis of the availability of a eligible bone marrow donor. Because morbidity and mortality from BMT increase with the patient's age, BMT is not usually recommended for pati-

ents older than 50 yr of age. Thus, for older patients and for patients who do not have a matched, related donor, immunosuppressive therapy is usually recommended as primary therapy.

MATERIALS AND METHODS

Patients

Patients eligible for this study were 96 patients diagnosed as having SAA according to the International Aplastic Anemia Study Group diagnostic criteria (4). These criteria include the presence of at least two of the following three peripheral blood findings: 1) a neutrophil count of less than 0.5×10^9/L, 2) a corrected reticulocyte count of less than 1%, and 3) a platelet count of less than 20×10^9/L. And the marrow cellularity less than 25% was added to the criteria. Among SAA, a neutrophil count of less than 0.2×10^9/L has been recognized as a bad prognosis factor (5). So, such patients were further classified as very severe aplastic anemia (VSAA) group. Before therapy, diagnoses were confirmed by aspirates and biopsies

of bone marrow and by cytogenetic studies of bone marrow cells. They were treated between January 1990 and December 1999. During the study period, we offered BMT to patients with SAA who were younger than 50 yr of age and had HLA matched related donors. Patients without such donors received IS therapy with an antithymocyte globulin-based or antilymphocyte globulin-based regimen. Twenty-two patients were given an HLA identical sibling transplant and 74 patients were given IS. Patient characteristics by treatment group are shown in Table 1. The groups were comparable in age, sex, disease duration, previous red cell transfusion, absolute neutrophil count, and disease severity.

Treatment Regimens

Among 22 patients who received a bone marrow transplant, 17 were conditioned with cyclophosphamide and total lymphoid irradiation (CY/TLI). In CY/TLI regimen, patients received CY 50 mg/kg, i.v. on each of four consecutive days (total 200 mg/kg), followed by single-fraction 500 cGy TLI. In two patients, besides cyclophosphamide (200 mg/kg), unirradiated viable donor buffy coat cells after the bone marrow infusion (CY/buffy) were used in an attempt to enhance engraftment. Two patients received horse antihuman thymocyte globulin (30 mg/kg × 3 days), in addition to cyclophosphamide (CY/ATG). In one patient whose preceding disease was paroxysmal nocturnal hemoglobinuria, busulfan and cyclophosphamide (BU/CY) were used as a conditioning regimen. Busulfan (1 mg/kg according to the actual body weight) was

administered four times per day for four consecutive days from day -7 to day -4. Cyclophosphamide (60 mg/kg according to the ideal body weight) was administered on days -3 and -2. Table 2 shows the conditioning regimens and engraftment data of BMT recipients. In all patients, cyclosporin A (CSA) and methotrexate (MTX) were used for prevention fo graft-versus-host disease (GVHD). It consisted of a short course of MTX, 15 mg/m² intravenously on day 1 and 10 mg/m² on days 3, 6, and 11, plus cyclosporine (3 mg/ kg/d), continuous infusion since day 1. Conversion to oral CSA was done

Table 2. Preparative regimens and engraftment data of bone marrow transplant recipients (n=22)

Preparative regimen and engraftment	Value
Conditioning regimen, n (%)	
Cyclophosphamide plus total lymphoid irradiation	17 (77)
Cyclophosphamide plus ATG*	2 (9)
Cyclophosphamide plus unirradiated buffy-coat	2 (9)
Busulfan plus cyclophosphamide	1 (5)
Median bone marrow cell dose (range)	
×10⁸ total nucleated cells/kg of body weight	4.5 (2.0-5.9)
Median time to absolute neutrophil count of	
500/μL (range), days	17 (12-27)
Median time to absolute neutrophil count of	
1,000/μL (range), days	19 (13-42)
Median time to platelet count of	
20×10³/μL (range), days	21 (13-67)
Median time to platelet count of	
50×10³/μL (range), days	25 (13-74)

*ATG: antithymocyte globulin.

Table 1. Patient characteristics

Characteristics	Bone marrow transplantation group (n=22)	Immunosuppressive therapy group (n=74)	*p* value
Median patient age (range), yr	22 (14-43)	34 (15-75)	
Age, yr: 14-20	8	11	0.06
>20	14	63	
Median donor age (range), yr	32 (12-56)	NA	
Sex of patient/donor, number (%)			
Male/male	5 (23)	37/NA (50)	
Male/female	11 (50)		0.1*
Female/male	1 (4)	37/NA (50)	
Female/female	5 (23)		
Median disease duration† (range) months	10 (1-118)	5 (1-364)	0.95
Cause of aplasia, n (%)			
Idiopathic	19 (86)	71 (96)	
Chemical	2 (9)	0	
Pregnancy	0	2 (3)	
Hepatitis	0	1 (1)	
Paroxysmal nocturnal hemoglobinuria	1 (5)	0	
Number of previous RBC transfusion (%)			
≤5U	6 (27)	39 (53)	0.06
>5U	16 (73)	35 (47)	
Median absolute neutrophil count at admission (range, /μL)	399 (24-1280)	510 (64-1500)	0.44
Number of patients with VSAA‡ (%)	3 (14)	12 (16)	0.77

*Comparison by patients' sex; †duration between diagnosis and treatment; ‡very severe aplastic anemia, defined by absolute neutrophil count less than 200/μL.

Table 3. Outcomes of bone marrow transplant recipients (n=22)

Preparative regimen and outcomes	Value
Acute graft-versus-host disease, n (%)	5 (23)
(>grade II), n (%)	2 (9)
Grade I	3
Grade II	1
Grade III	1
Grade IV	0
Chronic graft-versus-host disease, n (%)	7 (33)
Limited	4
Extensive	3
Hepatic veno-occlusive disease, n (%)	2 (9)
Median hospital days after start of conditioning therapy	
(range), days	40 (27-70)
Death, n (%)	2 (9)
Cause of death, n	
Hepatic veno-occlusive disease	1
Traffic accident	1
TRM*, n (%)	2 (8)
Median Karnofsky score of surviving patients	
(n=21) (range)	100 (80-100)

*TRM: treatment-related mortality (death by causes other than relapse).

Table 4. Treatment regimens and responses to therapy in patients receiving immunosuppressive therapy (n=74)

Treatment regimen and response to therapy	Value
Treatment regimen, n (%)	
Horse antithymocyte globulin only	38 (51)
Horse antithymocyte globulin plus	
cyclosporine	17 (23)
Horse antilymphocyte globulin only	19 (26)
Clinical response, n (%)	
Complete	16 (22)
Partial	17 (23)
None	41 (55)
Cause of death (n=20), n (%)	
Hemorrhage	8 (40)
Infection	11 (55)
Secondary malignant condition	1 (5)
Late complications	
Recurrent aplasia	4
Acute myelogenous leukemia	1
Myelodysplastic syndrome	1
Paroxysmal nocturnal hemoglobinuria	2
Median Karnofsky score of surviving patients	
(n=54) (range)	80 (50-100)

when signs of gastrointestinal toxicity subsided, and the dose was accommodated according to the CSA blood levels. CSA was discontinued at 6 months after BMT unless the evidence of GVHD was present. Acute GVHD was graded from 0 to IV according to the Thomas'criteria (6), and chronic GVHD was defined and classified by the Sullivan's criteria (7). Veno-occlusive disease of the liver (VOD) was defined as an increase in bilirubin level greater than 2 mg/dL with at least two of three of the followings: hepatomegaly, ascites, and greater than 5% body weight gain (8).

Among 74 patients who received IS therapy, 38 (51%) patients received ATG 20 mg/kg/day by intravenous infusion for eight consecutive days (ATG regimen); 17 (23%) patients, ATG 40 mg/kg/day for four consecutive days combined with cyclosporine from day 14 (5 mg/kg) (ATG/CSP regimen); 19 (26%) patients, ALG 10 mg/kg/day for five days (ALG regimen) (Table 4). Patients were premedicated with acetaminophen 600 mg and diphenhydramine 50 mg and hydrocortisone 50 mg before ATG or ALG infusion. All patients received corticosteroids during ATG or ALG therapy to reduce side effects.

Criteria for response to immunosuppressive therapy

We defined nonresponders as patients whose peripheral blood counts did not improve until day 180 and patients who died before day 180. For responders, the degree of response was assessed when the maximum improvement in peripheral blood counts occurred. The following definitions of response were used: 1) complete responders attained a hematocrit of 35% or greater, an absolute neutrophil count of 1.0×10^9/L or greater, and a platelet count of 100×10^9/L without transfusion; 2) partial responders achieved a sustained improvement

in any of the following measurements: neutrophil count increment by $\geq 0.5 \times 10^9$/L above the baseline, platelet count increment by $\geq 30 \times 10^9$/L above the baseline, or no need for red blood cell transfusions. Documentation of an improvement in hematologic parameters required three or more values obtained more than 1 week apart.

Stastical analysis

Overall survival curves were obtained using Kaplan-Meier product-limit estimates, and comparisons between curves were based on the log-rank statistic. All p values were two-sided. Means were compared using Student t-test. Categoric variables were compared using chi-square test. The analysis was performed on an IBM personal computer with SAS statistical software.

RESULTS

Bone marrow transplantation

Engraftment was defined as an absolute neutrophil count (ANC) >500/μL for three consecutive days, and independency of transfusion. All patients attained successful engraftment. The median time to recovery of ANC to 500/μL was 17 days after transplantation (range, 12-27 days), and platelet counts to 20,000/μL and transfusion independency occurred 21 days after transplantation (range 13-67 days). Only one patient experienced marrow graft rejection at 75 days after transplantation. She received a second transplantation from the same
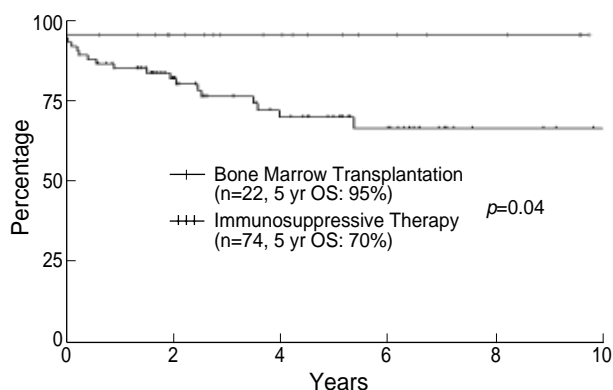
Fig. 1. Overall survival after therapy for severe aplastic anemia. Tick marks denote censoring times of surviving patients. The difference in overall survival between patients who received transplantation and those who received immunosuppressive therapy was statistically significant (p=0.04; log-rank test).

Fig. 2. Overall survival according to the response to immunosuppressive therapy for severe aplastic anemia.

donor and achieved sustained engraftment and has been alive in a cured state.

Acute GVHD occurred in five patients (23%), but grade II to IV acute GVHD has been seen in only two patients (10%, II:1, III:1). Treatment of acute GVHD consisted of corticosteroid and cyclosporine, alone or in combination, but grade I acute GVHD of skin was usually observed without treatment. The resolution of GVHD was the rule in all cases. Chronic GVHD, on the other hand, was observed in 7 out of 21 patients who survived more than 100 days posttransplant (33%, limited in 4 and extensive in 3). Hepatic veno-occlusive disease (VOD) occurred in 2 out of 22 patients (9%). It was the cause of death in one. Myelodysplastic syndrome or other hematologic malignancies were not developed in transplant recipients. Other complications such as interstitial pneumonitis (IP) were not noted. Table 3 shows the outcome of BMT.

Immunosuppressive therapy

The clinical response to IS therapy is shown in Table 4. Responses were observed in 33 (45%) of 74 adult patients treated with IS therapy including 16 (22%) with complete and 17 (23%) with partial responses. No response was seen in 41 patients (55%). Among 12 VSAA patients, 4 (33%) were responders. Among the other SAA 62 patients, 29 (47%) were responders. There was a tendency of a lower response rate in VSAA, but it was not statistically significant. IS regimen did not influence the response rate, either. The response rates were 53% in ATG/CSP regimen, 44% in ATG regimen, and 37% in ALG regimen. Response to IS did not correlate with the disease duration, previous RBC transfusion, patient age, or sex.

Long-term complications of IS therapy included recurrent aplasia in 4 patients among 33 responding patients (12%), evolution to a myelodysplastic syndrome or acute leukemia in 2 (3%) patients, and appearance of paroxysmal
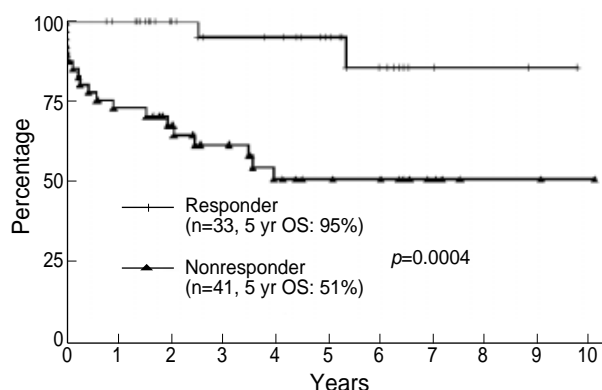
nocturnal hemoglobinuria in 2 (3%) patients (Table 4). The probability of developing a clonal stem cell disorder after IS therapy (4 of 74 patients) or BMT (0 of 22 patients) was different, but did not reach statistical significance.

Survival analysis

Fig. 1 illustrates the overall 5-yr survival of 96 patients according to treatment: 95% for BMT and 70% for IS. The difference was statistically significant (p=0.04). In the IS treatment group, the survival correlated with response: at 5 yr, the survival rates for responders and nonresponders were 95% and 51%, respectively (Fig. 2, p=0.0004). The response to IS was the only factor associated with improved survival. In patients receiving BMT, no factor was significantly associated with improved survival. Disease severity and age did not influence the survival rate in either groups. Two patients died in the BMT group. Severe VOD was the cause of death in one and the other died from traffic accident in a cured state. For patients receiving IS treatment, infection and hemorrhage were major causes of death (55% and 40% of deaths, respectively). Causes of death for all patients are listed in Tables 3 and 4. Besides survival rate, the quality of life of the two groups was different. The surviving patients receiving BMT had a median Karnofsky score of 100%. By contrast, the median Karnofsky score of the patients receiving IS was 80%.

DISCUSSION

During the study period, we offered BMT to patients with SAA who were younger than 50 yr of age and had HLA matched related donors. Patients without such donors received IS therapy with an antithymocyte globulin-based or antilymphocyte globulin-based regimen. The range of age differed between groups because there was no upper age restriction for patients receiving IS therapy, however the difference was not statistically significant. In the previous study, a high-

er absolute neutrophil count has been correlated with both an increased rate of response to IS therapy and an increased survival rate (9). For patients receiving IS therapy, a higher absolute neutrophil count may indicate that the bone marrow has a reversible stem-cell injury and thus is capable of autologous recovery. The association between a higher absolute neutrophil count before treatment and improved survival of the patients who received IS therapy was reported (SAA vs. VSAA; 47% vs. 27% in 15-yr OS, p=0.002) (10). However this was not observed in our series (SAA vs. VSAA; 71% vs. 67% in 5-yr OS).

Experimental studies in animals and analysis of human transplantation data suggest that transfusion-induced sensitization to minor histocompatibility antigens is the principal pathogenic mechanism of marrow graft failure/rejection (11, 12). The importance of restricting transfusion whenever possible and of performing marrow transplantation as soon as possible has been regarded as essential if a suitable donor is available. But the majority of patients require blood transfusion in the pretransplant period and such support should not be withheld on the basis that future graft rejection risks may be increased. In fact, small amounts of transfusion did not influence the engraftment after BMT in several reports (13, 14). In our series, all patients receiving BMT except one patient had received multiple transfusions, however the rejection occurred in only one patient. In addition, there was no difference in the survival rate according to the transfusion amount. Thus, on the basis of our result, previous multiple transfusions should not be regarded as a contraindication of BMT. The transfusion amount did not influence the survival rate in the IS group, either, as in our series.

Most studies have indicated that long-term survival of BMT recipients is significantly lower for patients older than 20 yr than for those who are younger (15). As explanations, in younger patients, GVHD incidence and severity are reduced and graft rejection is rare. There are a couple of surprising points in our results as far as age is concerned. Statistically there was no survival difference according to age. Therefore, based on the encouraging results of the present study, more liberal entry into a marrow transplantation program may be acceptable if age is the only unfavorable factor. Age, also, did not influence the survival rate of IS group in our series.

Above-mentioned observations (pretreatment neutrophil count, pretreatment transfusion amount, and patient age were not correlated with survival rates in our series) have not been documented in other reports, published in Western countries. This might be due to the small sample size, but there is a some possibility that the prognosis of aplastic anemia in Asians, at least in Koreans, is very good. In fact the 5-yr OS rates for patients receiving BMT and IS were 95% and 70%, respectively, in our series. In other published papers about Korean patients with SAA (16, 17), similar good results were reported. In these papers, the overall survivals were 80% (patients receiving BMT), 97% (patients responding to IS therapy), and

45% (patients not responding to IS therapy). By contrast, actuarial survival rates in the European Bone Marrow Transplantation Registry for patients receiving BMT and IS were inferior to our results (63% and 61%, respectively, at 6 yr) (5). In another Western report (18), similar results (72% for BMT and 45% for IS) was observed. There have been a few reports suggesting that the race of the recipients is a factor of prognostic relevance especially in transplantation (19-21). According to the Klingemann's report, Black patients transplanted for aplastic anemia had a significantly lower incidence of sustained engraftment and inferior survival when compared with Caucasians and Asians. And Asian patients with SAA who received BMT had a tendency of higher survival rate compared with Caucasians and Blacks. There was a tendency of a lower incidence of graft failure in Asians compared to Caucasians (12.5% vs. 19%), but the difference did not reach a statistical significance. Another explanation for a superior result of BMT recipients in our series compared with Western BMT recipients is that the incidence of acute GVHD was very low. The low incidence of early death of BMT recipients (1/22, 5%) in this series might be due to the low incidence (2/22, 9%) of acute GVHD. Thus, it might have contributed to the long-term survival of BMT recipients.

Immunosuppressive therapy with antithymocyte globulin or antilymphocyte globulin is used as an alternative to BMT. Long-term follow-up reports from the European SAA Working Party, however, showed no survival plateau has yet been achieved (22). Development of a clonal malignant disease was even noted in 14% of patients who survived longer than 2 yr. Compared to BMT, uncertain curability and probability of secondary hematologic malignancies are known as unfavorable factors of IS therapy.

Thirty-three out of 74 patients (45%) treated at our institution responded to IS therapy. This figure is quite similar to that in a previous report (22). Several early attempts to improve the outcome of ATG-treated patients were not successful. Repeated administration of ATG did not improve response or survival rates (23). A randomized placebo-controlled trial at UCLA showed no difference in response or survival rates between patients treated with ATG and androgens compared with those receiving ATG alone (24). The combined use of cyclosporine and ATG resulted in significantly improved response rates compared with ATG administration alone in a randomized study by the German Aplastic Anemia Group, but differences in survival were not observed between the treatment groups (25). In our study, we used three regimens of IS, i.e., ATG alone, ALG alone, and ATG combined with cyclosporine. There were no differences in response and survival rate.

Crump et al. (26) recently conducted a trial in which all adult SAA patients were initially treated with immunosuppressive therapy and only those who did not respond were considered for BMT. This strategy resulted in an 80% 5-yr actuarial survival rate for 31 aplastic anemia patients. In our

series, the OS of responders to IS therapy was 95%, and it was comparable to the BMT group. So, the authors think that IS therapy as a primary treatment is a plausible option, especially in high-risk patients. The BMT salvage approach may be appropriate for patients with moderate aplastic anemia or for a subset of SAA patients who are at increased risk for BMT-related complications. Further study should be done on this point.

As previously mentioned, the long-term survival rate in the IS group (70%) in our series is superior to the Western results. The authors think that two factors have contributed to this. One is that the incidence of recurrent aplasia in our series (4/33, 12%) was lower than those of the Western reports (32% and 36%, respectively) (10, 27). The other is that the incidence of clonal evolution such as acute myelogenous leukemia or myelodysplastic syndrome (3%) was very low compared with those of the Western reports (13% and 9%, respectively) (10, 18). These low incidences of late complications might result in excellent long-term survival rate in patients receiving IS. Further studies on the characteristics of aplastic anemia in Asians should be done.

The use of immunosuppressive therapy and BMT has dramatically improved the survival of aplastic anemia patients. Refinements in the use of these treatment modalities and supportive care will further enhance the long-term outlook for aplastic anemia patients.

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