Multicenter Randomized Study Comparing Cyclosporine-A Alone and Antithymocyte Globulin With Prednisone for Treatment of Severe Aplastic Anemia

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We report the results of a randomized multicenter study comparing the efficacy of antithymocyte globulin (ATG) with that of cyclosporin A (CsA) as first-line therapy for severe aplastic anemia (SAA). Patients were randomized to receive ATG and prednisone (PDN) or CsA; hematologic response and toxicity were compared. At 3-month evaluation, patients who had no or minimal response received the alternative therapy to assess the value of a sequential immunosuppressive therapy for treatment of severe aplastic anemia. One hundred nineteen patients were randomized; 25 were excluded, of whom 3 were misdiagnosed and 22 did not follow the cross-over protocol. Ninety-four patients were analyzed; 46 received CsA, and 48 received ATG-PDN. The actuarial survival was 66.7%, with a median follow-up time of 19 months. There was no significant difference in survival between the groups with, at 3 months, an actuarial survival of 88% in the CsA group and 75% in the ATG group (NS); at 12 months, it was 70% in the CsA group and 64% in the ATG group (NS). The percentage of complete and partial response was 11.6% and 16%, respectively, at 3 months, and 31.6% and 30%, respectively, at 12 months (NS). The main prognostic factor was the absolute neutrophil count (ANC) at entry: Patients with ANC < 0.2 × 10^9/L had a significantly lower survival as compared with patients with more than 0.2 × 10^9/L ANC (P = .0001). At 12 months, 62 evaluable patients were alive, with a complete or partial response in 36 patients. Patients who had responded to the first treatment had a better recovery of bone marrow failure than those who had sequential immunosuppression. The main complication was infection, which was more often observed and more often lethal during ATG and PDN therapy. In this study, initial treatment of SAA with either CsA or ATG-PDN followed by cross-over therapy for nonresponders produced comparable response and survival rates.

SEVERE APLASTIC ANEMIA (SAA) is a heterogeneous disorder of marrow stem cells and/or of the microenvironment; there are several possible etiologic mechanisms, including an autoimmune process, a preleukemic disorder, or a viral disease. Bone marrow transplantation (BMT) with an HLA-matched sibling donor is the best curative treatment, with 60% to 80% long-term survival mostly in very severe AA in young patients.[1,2] In the absence of a compatible donor, treatment with antithymocyte globulin (ATG) with or without androgens provides 50% to 70% long-term survival.[3-7] The mechanism of action of ATG is unknown: It may reverse abnormal immune-mediated suppression of hematopoiesis or induce growth and differentiation of marrow stem cells through activation or inhibition of growth factors or various cytokines.[8-11]

Previous studies have shown that the hematologic response to ATG is poorer in young patients and in patients with less than 0.2 × 10^9/L granulocytes, who have 20% long-term survival.[4,12,13] Recently, several studies have shown that another immunosuppressive drug, cyclosporine A (CsA), could be effective treatment for SAA.[14-24]

We report the results of a randomized study comparing the efficacy of ATG and prednisone (PDN) with that of CsA as first-line therapy for SAA. The main purposes of the study were comparison of ATG and CsA in terms of the hematologic response and toxicity, the prognostic value of a 3-month assessment for predicting outcome, and the benefit of changing the type of immunosuppression in patients who had not responded at 3 months (cross-over study).

MATERIALS AND METHODS

The multicenter study involved 28 centers in France, eight centers in Belgium, and one center in Switzerland.

Inclusion and exclusion criteria. Patients were included if at least two of the following hematologic values were noted at weekly assessments during the 2 weeks from the time of diagnosis: reticulocytes less than 20 × 10^9/L, granulocytes less than 0.5 × 10^9/L, and platelets less than 20 × 10^9/L, with BM aspiration and biopsy showing greater than 30% reduction in cellularity.

Patients were excluded if they had received previous treatment for SAA, except those who had received less than 1-month treatment with androgens or corticosteroids. Patients with myelofibrosis, myelodysplastic syndrome, malignant infiltration, patients who had received previous chemotherapy or irradiation, and patients with paroxysmal nocturnal hemoglobinuria, Fanconi's anemia, or other hereditary disorders were excluded.

Study design. Patients were randomized to receive either ATG and PDN or CsA. Horse ATG (Institut Mérieux) was administered intravenously (IV) as a 6-hour infusion at a dose of 12 mg/kg for 5 consecutive days. It was administered with methyl-prednisolone 5 mg/kg IV from day 1 to day 4 and 4 mg/kg from day 5 to day 8. On day 9, oral PDN was administered at a dose of 2 mg/kg from day 9 to day 14, 1 mg/kg from day 15 to 21, 0.5 mg/kg from day 22 to 28, and 0.2 mg/kg from day 29 to 60; it was then discontinued.

CsA was administered orally at a dose of 6 mg/kg/day divided in two equal daily portions. The dose was subsequentially modified according to weekly blood or serum levels of CsA measured by

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radioimmunoassay (RIA) with polyclonal antibodies to obtain a level of 100 to 200 ng/mL (serum) or 400 to 800 ng/mL (blood). Urea and creatinine were measured weekly, and the dose was modified according to the results.

Patients were transfused to maintain hemoglobin levels at more than 8 g/dL and platelets at more than 20×10^9/L. Irradiating all blood products at 40 Gy was recommended. Prophylaxis and treatment of infection varied according to the policy of each center.

All surviving patients were evaluated at 3, 6, and 12 months. Complete response (CR) was defined as hemoglobin (Hb) more than 12 g/dL, granulocyte count more than 1.5×10^9/L, and platelet count more than 100×10^9/L, and the absence of transfusion for more than 2 weeks. Partial response (PR) was defined as an increase, for at least 1 month, of a granulocyte count 0.5×10^9/L and a platelet count 30×10^9/L above baseline data, associated with improvement of infections and decreased transfusion requirement. Minimal response (MR) was defined as a reduced need for transfusions, reduced incidence of infections, improvement of blood counts, and failure (F) was defined as unchanged or worsening blood counts without reduction in transfusion requirements. Relapse (R) was defined as deterioration of blood counts after CR or PR.

Patients were evaluated weekly during the first month and then at least twice a month or as indicated by the clinical and hematologic status. Complete blood counts, liver and renal function tests, complications, side effects, number of transfusions, infections, concomitant treatments, CsA levels, and viral serologies were recorded regularly.

At the 3-month evaluation, patients with PR or CR had no further therapy in the ATG-PDN group, whereas in the CsA group the treatment was continued for another 3 months and then stopped if the response was maintained. Patients with MR or F had a cross-over: patients in the CsA group received ATG and PDN, and patients in the ATG-PDN group received CsA.

At 6 months, the patients were evaluated for response and survival; subsequent treatment was given according to the choice of each center. This protocol was approved by our local ethics committee. All patients were informed and gave oral consent. The study was initiated in January 1986 and patient entry was closed in December 1989. All patients had been followed-up for at least 1 year when the analysis was performed.

Statistical analysis was performed on a personal IBM computer with BMDP statistical software. Probability estimates were obtained with the Kaplan-Meier method, and differences between survival patterns were evaluated by log-rank statistics. Multivariate proportional-hazards regression analyses used the Cox method. All covariates that added information to the model at the 0.05 significance level as measured by the maximum likelihood ratio test were included. All significance levels were two-sided.

RESULTS

Patient characteristics before treatment. One hundred nineteen patients were randomized, and, owing to diagnostic errors, three were excluded before receiving treatment. One hundred sixteen patients fulfilled the criteria of inclusion and were analyzed. Sixty received CsA and 56 received ATG-PDN as first-line therapy. The main characteristics of the patients are shown in Table 1; there were no significant differences between the two groups in age, sex, complications, or severity of disease. At 3 months, 22 patients did not follow the cross-over protocol and were analyzed separately.

Survival. The overall survival was 55% for all randomized patients. Ninety-four patients who completed the protocol were analyzed for survival and responses; 46 were in the CsA group, and 48 were in the ATG group. The 2-year actuarial survival was 66.7% with a median follow-up time of 19 months. There was no relevant difference in survival according to first treatment with CsA or ATG-PDN (Fig 1).

Table 1. Pretreatment Characteristics of Patients

Treatment Group	CsA	ATG
No. of patients	60	56
Median age (yr) (range)	27 (2-83)	17 (5-72)
Sex, M/F	33/27	39/17
Median interval from diagnosis to treatment (days)	25	23
No. with infection	18	13
No. with hemorrhages	21	17
No. of RBC transfusions (mean units) (range)	10 (0-30)	9 (1-25)
Platelet transfusions (mean units) (range)	14 (5-30)	16 (5-50)
Median Hb (g/dL) (range)	9 (4-13)	9 (4-12)
Median reticulocytes 10^9/L (range)	10 (0-76)	10 (0-72)
Median leukocytes 10^9/L (range)	1.9 (0.4-5)	2 (0.1-6)
Median granulocytes 10^9/L (range)	0.3 (0-1.5)	0.3 (0-0.9)
Median platelets 10^9/L	16 (2-64)	15 (4-69)

Abbreviations: CsA, cyclosporine A; ATG, antithymocyte globulin; Hb, hemoglobin.

Age was not a significant prognostic factor, with a 2-year actuarial survival of 64% in patients aged more than 18 years, 60% in patients aged between 10 and 18 years, and 72% in patients aged less than 10 years. The interval between diagnosis and treatment did not influence the 2-year actuarial survival, which was 67% in patients treated

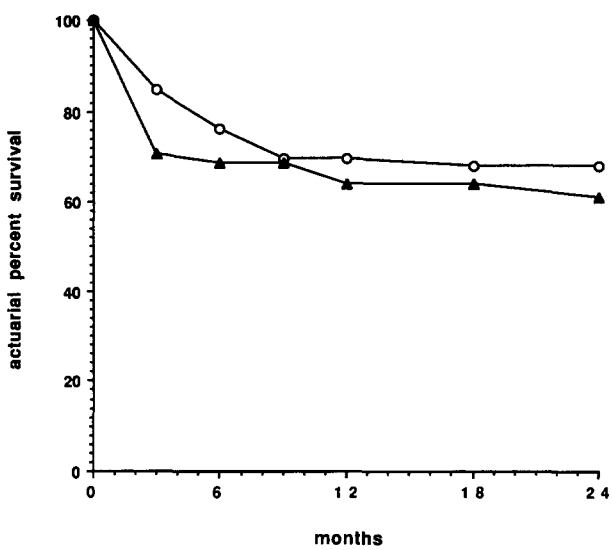

Fig 1. Survival according to first treatment. Patients who did not follow the cross-over protocol at 3 months were excluded. (○) CsA (n = 46); (▲) ATG (n = 48).

at more than 25 days after diagnosis and 61% in patients treated at less than 25 days after diagnosis.

The most important prognostic factor was the absolute number of nucleated cells (ANC): Patients with less than 0.2×10^9/L ANC had an actuarial survival of 41.3%, and patients with more than 0.2×10^9/L ANC had an actuarial survival of 65.5% ($P = .0001$). There was no difference in survival in the groups treated with ATG-PDN or CsA according to the initial ANC values (Fig 2).

Clinical evolution. The clinical outcome of the patients is summarized in Table 2. At 3 months, 101 patients were alive: 58 in the CsA group and 43 in the ATG-PDN group. The difference is related to the higher number of infectious deaths in the ATG-PDN group (13 infectious deaths in the ATG-PDN group and two in the CsA group). CR or PR was observed in seven patients in the CsA group (11.6%) and in nine in the ATG-PDN group (16%).

The main prognostic factor for survival was the ANC at 3 months: 14 patients with less than 0.2×10^9/L ANC had an actuarial survival of 41.3%, and patients with more than 0.2×10^9/L ANC had an actuarial survival of 65.5% ($P = .0001$). There was no difference in survival in the groups treated with ATG-PDN or CsA according to the initial values (Fig 2).

For subsequent analysis, the patients who did not follow the cross-over protocol were excluded and were analyzed separately. At 6 months, 78 patients were alive. During the 3- to 6-month follow-up period, 10 patients died in the group that received ATG after failure of 3-month CsA, whereas only one patient died in the group that received CsA 3 months after failure of ATG. At 6 months, 4 of 39 patients had responded to ATG after failure of CsA and 8 of 26 patients had responded to CsA after failure of ATG. No patient in the group that responded to the first treatment relapsed.

At 12 months, 67 patients were evaluable. During the 6- to 12-month follow-up, five patients died, one after relapse after ATG and four in the combination group. One patient only relapsed in the group of patients who responded with ATG-PDN alone. In the group of patients who were not

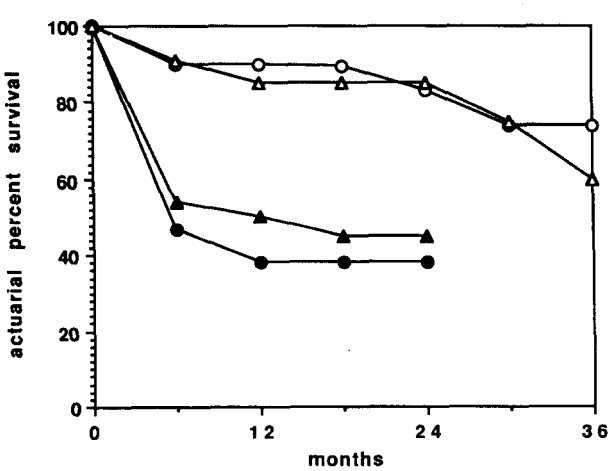

Fig 2. Survival according to treatment and initial absolute neutrophil counts before treatment.

Table 2. Clinical Outcome of Patients

No. of patients randomized				119
No. of patients excluded at entry				3
First treatment			CsA 60	ATG-PDN 56
Three-month evaluation				
CR + RP			7	9
MR + F			51	34
Death 0-3 mo			2	13
Excluded			14	8
Treatment at 3 mo				
	CsA	Csa + ATG	ATG	ATG + CsA
No. treated	5	39	8	26
Evaluation of 3- to 6-mo period				
			Alive at 6 mo	
	5	29	8	25
CR + PR	5	4	8	8
MR + F	0	25	0	7
Death	0	10	0	1
			Alive at 12 mo	
	5	27	7	23
CR + PR	5	14	6	11
MR + F	0	13	0	12
Relapse	0	0	1	0
Lost to follow-up	0	0	1	0
Death	0	2	1	2

Abbreviations: CR, complete response; PR, partial response; MR, minimal response; F, failure.

responders at 3 months and received a second course of immunosuppression, at 1 year 14 of 27 patients (51.8%) alive were in CR or PR in the CsA followed by the ATG-PDN group (14 of 29 allocated to this group: 48%). In the group that received ATG-PDN followed by CsA, 11 of 23 patients (47.8%) alive at 1 year were complete or partial responders (11 of 25 patients treated: 44%). The difference in response between these groups was not significant.

Twenty-two patients did not cross over because of protocol misinterpretation, 12 patients with failure in CsA treatment did not receive ATG-PDN; at 1 year, six were in CR, three were in MR, and three died, and two patients had a course of ATG despite a good response to CsA; at 1 year, one was in CR, one relapsed and died, and seven patients had no response to ATG and did not receive CsA; at 1 year, two were in CR, two failed to respond, two died, one was lost to follow-up, and one patient had responded to ATG and had received CsA and was in CR at 1 year.

At 1 year after randomization, only one patient in the CsA-alone group continued to require transfusion; none in the ATG-PDN group required transfusion. In the group that had received ATG-PDN followed by CsA, 5 of 24 (25%) were receiving transfusions; in the group that received CsA followed by ATG-PDN, 5 of 28 (21.4%) were transfused. The median ANC was 2.4×10^9/L (range, 1.3 to 3.2) in the CsA group, 1.6 (0.5 to 4.9) in the ATG-PDN group, 1.5 (0.3 to 5.6) in the CsA-ATG group, and 0.9 (0.1 to 4.2) in the ATG-CsA group (Fig 3). Despite the relatively good survival of this group of patients at 1 year, 30 patients were still classified as nonresponders or minimal responders, six in the group of patients who received one treatment and 24 in the group who received a second

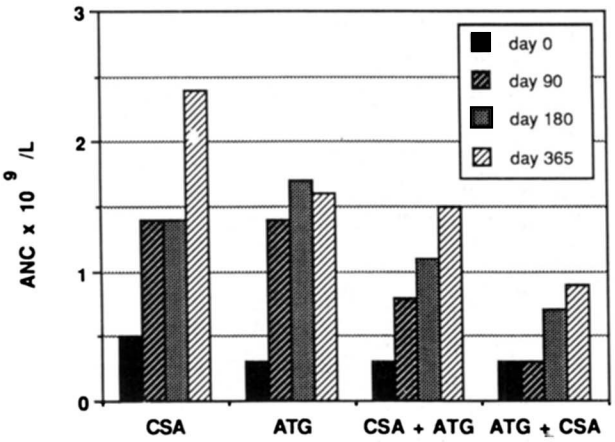

Fig 3. Evolution of the median neutrophil counts according to treatment. CsA + ATG, CsA followed at 3 months by ATG in nonresponders; ATG + CsA, ATG followed at 3 months by CsA in nonresponders. (●) ATG <0.2 ANC; (▲) CsA <0.2 ANC; (○) ATG >0.2 ANC; (△) CsA >0.2 ANC.

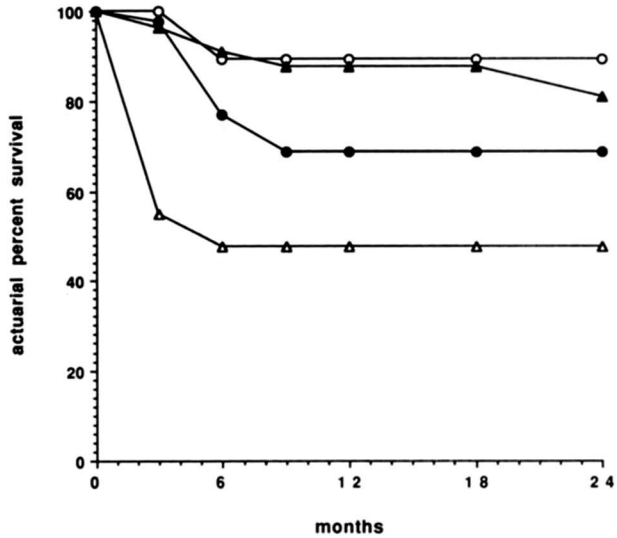

Fig 4. Survival according to overall treatment. (○) CsA and (△) ATG groups were initially randomized to receive this treatment and were responders to the treatment at 3 months. (●) CsA + ATG, patients who were randomized to receive CsA; at 3 months, they were nonresponders and received a course of ATG. (▲) ATG + CsA, patients who were randomized to receive ATG; at 3 months, they were nonresponders and received CsA. Patients who did not follow the cross-over protocol were excluded.

treatment. A longer follow-up is needed to assess possible further improvement of this group and the incidence of late complications.

After 6 months of treatment, several patients received additional therapy because of treatment failure: 20 received androgens; six responded. One patient was transplanted with an HLA-identical sibling and survived; of three patients transplanted with an HLA-matched unrelated donor, one is currently alive; and of six patients who received a haplomismatched BMT from a family member, none survived.

Relapse was very rare; it was observed in two patients at 10 and 11 months, after randomization, after a PR in patients treated with ATG alone. This number is relatively low because a 1-year follow-up is not sufficient to observe late relapses.

Cause of death and complications. The main cause of death was infection, reported in 26 patients; it occurred frequently (20 patients) during the course of ATG as first or second treatment. Other causes of death are shown in Table 3. This observation explains why the survival curve of patients who received only ATG-PDN was significantly inferior to that of the other treatment groups (Fig 4) ($P = .0001$). The multivariate analysis showed the relative causes of death to be ANC ($P = .0001$) and use of ATG-PDN alone ($P = .0002$) (Table 4).

Four patients developed a new disorder: One patient who had responded to ATG and CsA developed breast cancer 18 months after treatment; she was treated successfully with local irradiation and chemotherapy, which was well tolerated hematologically. After a response to ATG, one patient developed Philadelphia chromosome-positive chronic granulocytic leukemia; she is currently in chronic phase treated with hydroxyurea. One patient had transient idiopathic thrombocytopenic purpura, and one developed a myelodysplastic syndrome more than 1 year after treatment. Longer follow-up is necessary to assess the incidence of secondary disorders after these treatments.

The toxicity of the treatment was tolerable. Eighty-seven patients received CsA as primary or secondary treatment; 28 had no modification of renal function, defined as an increase of creatinine of 30% above baseline. Forty-nine patients had an increase in creatinine, and CsA dose was diminished in 23 patients, with an improvement of renal function; the others, despite continuation of CsA at the same dose, had no aggravation of renal function. CsA was discontinued in eight patients because of renal toxicity, which was reversible after withdrawal, and in five patients because of liver toxicity. The outcome of these patients did not appear to be different from that of the other patients. Other side effects of CsA were an increase in liver alkaline phosphatase in 17 patients, arterial hypertension in 15, gum

Table 3. Cause of Death

Treatment Group	CsA	CsA + ATG	ATG	ATG CsA
Infection	3	9	11	3
BMT	2	1	2	
Hemorrhage	1	3		
Liver failure			1	
Pulmonary emboli	1			
Total	5	13	16	3

Table 4. Relative Risk of Death (Cox Analysis)

Covariate	Favorable	Unfavorable	RR	CI	*P* Value
ANC 10^9/L	>0.2	<0.2	5.07	2.5-10	.0001
Treatment	CsA alone or combination	ATG alone	4	1.3-6	.0002

Abbreviations: CI, confidence interval; ANC, absolute neutrophil counts.

hypertrophy in eight, and a neuropsychiatric syndrome in 14 cases. In the ATG-PDN group, serum sickness was observed in 11 patients, an increase in liver alkaline phosphatase in 18 patients, diabetes in 10 (probably related to concomitant corticosteroid treatment), arterial hypertension in six, a neuropsychiatric syndrome in four, and cardiac arythmia in six.

DISCUSSION

ATG was shown previously to improve hematopoiesis in patients with SAA, with hematologic improvement in 40% to 60% of patients treated.[3-7,25] These results support the concept that SAA may be related to a dysfunction of immune regulation of hematopoiesis, either by a direct lymphocytotoxic mechanism or by release of lymphokines toxic to hematopoietic progenitor stem cells.[11] In the absence of in vitro tests to predict the response to ATG, several factors have been shown to influence treatment results. The most important factor is the severity of the disease. Patients with less than 0.2×10^9/L ANC are more likely to have a poor outcome.[13] Other factors include age, interval between diagnosis and treatment, sex, and treatment response at 3 months. For patients who do not respond, a second course of ATG may improve survival.[4,26] Other treatments, including androgens[27-29] or high-dose corticosteroids,[31] have not been proven beneficial in SAA. Recently, reports showed that CsA may improve hematopoiesis in patients with SAA refractory to ATG.[12,23] Frickhofen et al[30] conducted a randomized study in 84 patients comparing treatment with ATG and methylprednisolone alone or in association with cyclosporine. This study shows that addition of CsA to ATG-PDN significantly improves long-term survival. The superior results of the regimen including CsA were more evident in patients with SAA or very severe AA. Only one study compared CsA with ATG.[32] In our study design, we compared ATG-PDN with CsA as primary treatment of SAA in newly diagnosed patients; our second purpose was to assess the prognostic value of an evaluation performed at 3 months and the efficacy of the alternative immunosuppressive treatment for nonresponders. Our results confirm the poor outcome of patients with very severe AA, with 41.3% actuarial survival in patients with less than 0.2×10^9/L as ANC compared with 65.5% in patients with more than 0.2×10^9/L ANC at the time of diagnosis. We noted no correlation between survival and age, sex, and interval between diagnosis and treatment. There was no difference in survival between the groups randomized to receive ATG or CsA as primary treatment for SAA, showing that CsA is as effective as ATG in terms of long-term survival; patients treated with ATG, at diagnosis or after failure of CsA, had a higher incidence of infectious deaths early in the course of the treatment, mostly in the group of patients with very low granulocyte counts. This explains why the group of patients who received ATG alone had significantly poorer survival, with some patients dying too early to receive the alternative treatment. These results suggest that CsA is safer than ATG for primary treatment of SAA because it may be less immunosuppressive; however, the corticosteroids used in the ATG protocol (to prevent serum sickness) may have been an important contributory factor to the increased severity of infections in this group. This finding demonstrates the importance of supportive care in management of patients with SAA, including isolation, prophylactic antibiotics, and careful management of infectious complications. Indeed, the response rate with ATG may have been better if early deaths had been prevented by better supportive care.

The 3-month evaluation showed that a few patients were classified as complete or partial responders (16%); the speed of recovery was identical in both groups. Patients who still had less than 0.2×10^9/L ANC at 3 months had a poor outcome. This confirms the prognostic value of the 3-month assessment, especially if a BMT with a matched unrelated donor is considered as alternative therapy. At the 1-year evaluation, 11 of 13 patients who received one course of treatment were in CR or PR (84.6%). After cross-over therapy, 25 of 50 patients surviving 1 year had a CR or PR (50%); there was no difference in response or time of recovery according to the sequence of immunosuppressive treatment. This appears to demonstrate the benefit of a second treatment after failure of the first treatment, but spontaneous improvement could be observed in patients who did not respond at 3 months and did not receive further therapy. A prospective randomized study comparing CsA alone with the association of CsA and ATG is needed to demonstrate the value of the association. A longer follow-up is necessary to evaluate the incidence of further improvement or late complications.[32-35] BMT with a partially mismatched related donor failed, and only one of three matched unrelated donor transplants were successful. This result is similar to results of other reported studies,[36,37] probably because of the long delay between diagnosis and BMT and the selection of very-poor-risk patients. Apparently, if a matched unrelated donor is found, transplantation should be performed as second-line therapy only in patients who have less than 0.2×10^9/L ANC, are not infected, and have not responded to 3-month immunosuppressive treatment. Our results show that survival with immunosuppression is inferior to survival with HLA-identical sibling BMT in patients aged less than 40 years. In this study, initial treatment of SAA with either CsA or ATG PDN (followed by cross-over therapy for nonresponders) produced comparable response and survival rates, but CsA induced less infections, death, and toxicity than ATG-PDN. Another advantage is the possibility of using CsA on an outpatient basis, reducing the duration of hospitalization required. The recent availability of various growth factors such as G-CSF, GM-CSF, or IL-3 must be investigated in this context.[38-41]

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