THE RESULTS OF INTENSIVE IMMUNOSUPPRESSION WITH ANTITHYMOCYTE GLOBULIN AND CYCLOSPORINE A IN SEVERE APLASTIC ANEMIA

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ABSTRACT

Objective: It was reported that intensive immunosuppressive therapy is the current treatment of choice for patients with aplastic anemia who do not have histocompatible siblings or who are otherwise ineligible for alogenic bone marrow transplantation. We therefore designed a clinical study to establish the efficacy of intensive immunosuppressive therapy in these patients.

Methods: Ten patients with severe aplastic anemia were treated with Antithymocyte globulin (ATG) 15 mg/kg/d for 10 days in 4 hours infusion, Cyclosporine A (CsA) 10 mg/kg/d p.o initially and regulated according to the serum CsA level for 3-6 months and methylprednisolone 1 mg/kg/d as a short infusion for 2 weeks.

Results: The hematologic response was achieved in 7 of the 10 patients, in a mean duration of 102.3 (30-168) days. All of the responders are in continuing remission for a median of 25.2 (7-60) months. Three of the non-responders died of intercurrent infection.

Conclusion: In this study we achieved a high hematologic response with intensive immunosuppressive therapy as reported in the literature.

Key Words: Severe aplastic anemia, Antithymocyte globulin, Cyclosporine A.

INTRODUCTION

Aplastic anemia is characterized by a failure of blood cell production resulting in varying degrees of pancytopenia with a markedly hypocellular bone marrow. Although blood product support and antibiotics are effective therapies, aplastic anemia could still be described as a fatal disease. By the end of the 1960's, bone marrow transplantation (BMT) was shown to be curative in studies performed by Thomas et al. in Seattle and in several European centers (1,2). In the 1970's the observation of autologous marrow recovery after treatment with antilymphocyte sera suggested that nonreplacement therapy could restore marrow function. Later it was shown that intensified immunosuppressive therapy, improved transfusion support and modern antimicrobial therapy have produced hematologic improvement, and long-term survival rates (3). Antithymocyte globulin (ATG) is the current treatment of choice for patients who do not have histocompatible sibling donors or who are otherwise ineligible for allogeneic BMT. About 50% of patients respond to an initial course of ATG, and many nonresponders can be salvaged by subsequent treatment with Cyclosporine A (CsA) (3). After observation of efficiency of either ATG or CsA, both agents were used together in the treatment of severe aplastic anemia (SAA) (4).

MATERIALS AND METHODS

The outcomes of 10 adult severe aplastic anemia patients who were treated at Gülhane Military Medical Academy, Haydarpaşa Training Hospital, Department of Hematology from 1991-1995 were evaluated. All patients had severe aplastic anemia according to The International Aplastic Anemia Study Group's classification (granulocyte <500/mm3, PLT<20000/mm3, corrected reticulocyte<1%), and one patient had very severe aplastic anemia (granulocyte<200/mm3, PLT<20000/mm3, corrected

reticulocyte<1%) (5). All the patients were male and the mean age was 40.4 (from 20 to 80) years. The mean follow-up was 25.2 (8-60) months. No obvious reason was found for aplasia. Ten patients who were eligible for the immunosuppressive protocol received ATG 15 mg/kg/d for 10 days in 4 hours infusion, CsA 10 mg/kg/d po initially and regulated according to the serum CsA level for 3-6 months, and methylprednisolone 1 mg/kg/d as a short infusion for 2 weeks. Hematologic Response: The presence of at least two of the following criteria was accepted as response, granulocytes increasing more than 500/mm3 from the initial value or platelet (PLT) increasing more than 30000/mm3 from the initial value and the decreasing transfusion requirement.

RESULTS

The remission of disease was achieved in 7 of 10 cases (70%) in a mean of 102.3 (30-168) days. All of the responders were in continuing remission for a median of 25.2 (7-60) months.The characteristics of patients were shown in Table-I. Three non-responding patients died of infection on 35th, 45th, and 120th days respectively after the therapy. Only one patient developed serum sickness on the 35th day of ATG therapy. Tremor was observed in 3 patients and mild hypertension and BUN retention were seen in one patient. The decrease in transfusion requirement was achieved in all the responding patients.

DISCUSSION

The pathophysiology of the disease suggests two approaches to the therapy: replacement of deficient stem cells by BMT or supression of a destructive immunologic process. Unfortunately, neither measures of stem cell number nor immune system dysfunction are clinically useful guides to treatment selection in individual patients.

Antilymphocyte globulin is cytolytic of T cells and both ALG and CsA inhibit T cell function, especially the production of suppressive lymphokines. Different ALG preparations in-vitro stimulate T cell proliferation and promote secretion of some growth factors (6,7). The review of results with immunosuppression in the early 1980's suggested that about 45% of patients with severe disease responded to ALG, including randomized controlled, and large multicenter trials of ATG in the United States (8-10).

In more systematic studies, CsA produced about a 50% response rate in patients who were refractory to ATG or ALG treatment (11). Most hematologic improvement occurred within a few months after starting the therapy and was usually sustained after CsA was discontinued; however recovery was sometimes dependent on continued CsA administration. A French multicenter trial attempted a direct comparison of CsA to ALG as initial treatment for aplastic anemia and found no difference in outcome, but the response rates to either agent were poor, probably because of the low doses of CsA and ALG used (12). Although in some studies lower doses have been effective, best results have been achieved with high doses of CsA (12 mg/kg/d for adults and 15 mg/kg/d for children) (3,12).

Clinical trials, that combined CsA and ATG followed from the observation of clinical efficiency in aplastic anemia of each agent alone. Joining their different mechanisms of action, lymphocytoxicity provided by ATG or ALG and functional block of lymphocyte activation and activity by CsA, would produce more

Table I. The Characteristics of Patients

No	Age	Sex	ATG	CsA	Cort.	Continuing Hematologic Remission
1 NA	54	M	+	+	+	Death (35th day)
2 IS	75	M	+	+	+	8th month
3 RÇ	80	M	+	+	+	Death (45th day)
4 SA	20	M	+	+	+	7th month
5 EK	21	M	+	+	+	19th month
6 NK	48	M	+	+	+	Death (4th month)
7 AY	20	M	+	+	+	60th month
8 MZ	22	M	+	+	+	59th month
9 AÜ	21	M	+	+	+	57th month
10 FZ	43	M	+	+	+	36th month

intensive immunosuppression. Recent trials have indicated that intensive immunosuppression is superior to ALG or ATG alone in SAA. In a study at the National Institutes of Health Clinical Center of Untreated SAA, CsA plus ATG produced hematologic remissions in almost 80% of patients, more than twice the remission rate for matched historical controls (4).

Methylprednisolone in modest doses, usually 1 mg/kg/d, is administred during ALG and ATG therapy to ameliorate serum sickness. Extremely high does of methylprednisolone (20 to 50 mg/kg/d) can induce hematologic responses in aplastic anemia but are not preferable to either ALG or CsA (13).

In this study we confirmed that combined intensive immunosuppression with ALG or ATG plus CsA induces high hematologic response at 70 per cent. All the remissions are durable (median 25.2 months) and no relapse has occurred so far. Side effects are tolerable and severe serum sickness is manageable by iv methylprednisolone (only one serum sickness out of 10). Although the major curative approach is allogeneic BMT, only one-fourth of all patients have compatible donor. As a result, BMT cures aplastic anemia but with a risk of morbidity and mortality secondary to treatment. Prompt combined immunosuppression with CsA and ATG is indicated for most patients with SAA. These encouraging results with immunosuppressive therapy are in some instances equal to or perhaps greater than long-term results after marrow transplantation. However long-term sequel of intensive immunosuppression must be closely monitorized.

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