Cyclosporine monotherapy for severe aplastic anemia: a developing country experience

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BACKGROUND: Immunosuppression is the most effective treatment for aplastic anemia after hematopoietic stem cell transplantation. Although the combination of cyclosporine and antithymocyte globulin (ATG) is superior to either agent alone, cyclosporine monotherapy is an easily available, safe and cheap immunosuppressive therapy (IST) option. These advantages are particularly valuable in developing countries where ATG is frequently not available.

PATIENTS AND METHODS: In the referral hematology center in Yemen, 20 patients (16 males and 4 females) with severe aplastic anemia (SAA) were prospectively identified and managed with cyclosporine monotherapy during the period between April 2001 and November 2004.

RESULTS: Data from 14 patients who received cyclosporine for at least 3 months were analyzed. At 6 months, 2 (14.3%) patients achieved complete remission (CR) and 5 (35.7%) patients achieved partial remission (PR) and at 1 year, 4 (28.6%) patients achieved CR and 3 (21.4%) patients remained in PR. The overall response rate was 50% and the cumulative survival rate at 1 year was 78.6%. The median time to remission was 120 days (range, 46 to 131 days). Side effects were modest and easily monitored.

CONCLUSION: Our results support findings that cyclosporine monotherapy is an effective and safe immunosuppressive therapy for SAA, and that it could be a reasonable IST option for patients in developing countries.

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Aplastic anemia is thought to be an immune-mediated bone marrow disease.[1] It is characterized by pancytopenia and an empty bone marrow. Although not a common disease, it has a social impact disproportionate to its incidence. Epidemiologically, aplastic anemia has a pattern of geographic variation opposite to the leukemias, with a higher frequency in the developing world than in the industrialized west.[2] Aplastic anemia was associated with benzene exposure and chloramphenicol use and has been linked to many classes of pharmaceuticals widely used in medical practice.[2]

Most cases of aplastic anemia can be pathophysiologically characterized by T-cell mediated organ-specific destruction of the bone marrow hematopoietic cells.[1,3] The disease is believed to be induced by an inciting event (e.g., viral infection, drug or chemical exposure) followed by an aberrant immune response that leads to destruction of hematopoietic stem cells and progenitor cells.[1,3] Most patients can be successfully treated with either hematopoietic stem cell transplantation (HSCT) or immunosuppressive therapy (IST).[3,4] In developed countries, most patients do not have donors for standard-risk allogeneic transplantation

and rely on IST as the first line treatment.[3] On the other hand, allogeneic transplantation is usually not feasible in most developing countries.

IST is based on the premise of suppressing the immune dysregulation observed in aplastic anemia evidenced by the finding of activated cytotoxic lymphocytes producing the inhibitory lymphokines interferon gamma and TNF.[5] In contrast to the biologic agents antithymocyte globulin (ATG) and antilymphocyte globulin (ALG), cyclosporine is not cytotoxic but does inhibit several lymphocyte functions including the production of lymphokines and the proliferation of T-cells.[5]

In a randomized trial, cyclosporine was as effective as ATG in patients with severe aplastic anemia (SAA).[6] In other randomized trials, the combination of ATG and cyclosporine showed a better response than either agent alone.[7,8] Compared to ATG, cyclosporine is less expensive, can be administered on an outpatient basis, is more readily available and is less toxic.[6] These advantages make it suitable for use as initial treatment for patients in developing countries, particularly since most patients cannot afford the cost of ATG.[22]

We report the experience of the referral hematology center in Sana'a, Yemen, a developing country, in the treatment of patients with severe acquired aplastic anemia bearing in mind that in Yemen, cyclosporine is the only immunosuppressive therapeutic option available. The government provided it originally for post renal-transplant patients so we used the opportunity of its availability to provide it free for our patients with aplastic anemia.

Patients and Methods

All patients evaluated and treated after March 2001 at the Hematology Unit, Al-Jomhori Educational Hospital in Sana'a, Yemen were prospectively identified and entered in the study. The Hematology Unit is the main hematology center in Yemen and receives patients from all over the country. All patients were required to have a bone marrow cellularity less than 25% as well as two of the following three criteria: an absolute neutrophil count $<0.5\times10^9$/L, a platelet count of less than 20×10^9/L and a corrected reticulocyte count of less than 0.6%.[2] The patients provided informed consent to treatment.

Cyclosporine was administered orally at a dose of 6 mg/kg/day divided in two equal portions. We intended to modify the dose according to the cyclosporine level measured by the cyclosporine monoclonal whole blood assay, which utilizes fluorescence polarization immunoassay (FPIA) technology. However, this was not available most of the time because of shortage of the reagents. Therefore, adjustment was dependent mainly on serum creatinine levels. Serum creatinine was measured at least weekly for the first month and then every 2 weeks for the next 2 months and later every month if there was no significant elevation of serum creatinine. The dose of cyclosporine remained the same if the serum creatinine was normal and was lowered when serum creatinine rose above normal. At 6 months, cyclosporine was stopped for non-responders and continued for all responders at the therapeutic doses until the blood cell count plateaued. Treatment was then stopped or tapered with reinstitution if relapse occured.

Patients were evaluated every other day during the first 2 weeks and then weekly during the next month and then at least once a month or as indicated by the hematological or clinical status. The complete blood count, liver function tests, renal function tests, complications, side effects, number of transfusions, infections, and concomitant treatment were recorded regularly. Hematological response was evaluated at 6 months and 1 year. Complete remission was defined as entirely normal or near normal blood counts (hemoglobin >12 g/dL, a neutrophil count $>1.5\times10^9$/L and a platelet count $>100\times10^9$/L). A partial response was defined as a neutrophil count $>1\times10^9$/L, a platelet count $>30\times10^9$/L, and transfusion independence. Patients who remained transfusion dependant were classified as non-responders regardless of the neutrophil and platelet counts. All remission had to be confirmed by at least two blood counts at least 4 weeks apart. Time to remission was defined as the time from first day of treatment until the day a patient achieves partial remission.

Results

Twenty patients (16 males and 4 females) with acquired SSA were studied in the 44-month period (between April 2001 and November 2004) (Table 1). Six patients were followed for less than 3 months and in consequence were excluded from the analysis, which includes 14 patients (Table 2). Of those patients who were followed for less than 3 months, two died, one on day 25 and one on day 30, two were lost to follow up, and two had disease progression and could afford the cost of allogeneic bone marrow transplantation, which was successfully performed abroad.

At the 6-month evaluation 2 (14.3%) patients had a CR and 5 (35.7%) patients had a PR. One patient

Table 1. Characteristics of 20 patients (16 males, 4 females) with severe aplastic anemia.

Characteristic	Median (range)
Age (years)	22 (10-48)
Hemoglobin (g/dL)	5.3 (2.9-8.5)
Neutrophil count (×10^9/L	0.400 (0.200-0.840)
Platelet count (×10^9/L)	10 (3-23)
Follow-up period (days)	430 (15-1339)

Table 2. Outcome of cyclosporine monotherapy in 14 patients with severe aplastic anemia.

	At 6 months	At 1 year*
No. of evaluable patients	14	14
Complete response	2 (14.3%)	4 (28.6%)
Partial response	5 (35.7%)	3 (21.4%)
Overall response	7 (50%)	7 (50%)
Death	1 (7.1%)	2 (14.3%)
Lost to follow up	0	1 (7.1%)
No response	6 (42.9%)	4 (28.6%)
Overall survival	93%	78.6%
Hematological values of responding patients		
Median hemoglobin (range) (g/dL)	12.5 (8.9-13.4)	12.9 (10-13.5)
Median neutrophil count (range) (x10^9/L)	1.840 (1.020-3.510)	1.890 (1.020-7.500)
Median platelet count (range) (x10^9/L)	67 (44-120)	113 (48-151)

* Number of patients and percentage at 1 year are cumulative

died at day 122 and 6 patients had no response. The overall response rate was 50% and the overall survival rate was 93%. The median time to remission was 120 days with a range of 46 to 131 days.

At the 1-year evaluation, 2 of those in PR achieved CR and 3 (21.4%) remained in PR. As a result the total number of CR cases reached 4 (28.6%) patients at 1 year. Of the responders, 2 still needed cyclosporine and show a progressive response, 2 showed a decrease in cell counts when cyclosporine was stopped and responded when cyclosporine was readministered with a return to previous cell counts. In one patient the cyclosporine dose was tapered without affecting response whereas 2 were free of cyclosporine at 1 year. Of the 6 patients who had no response at 6 months, one patient died at day 240, one patient was lost to follow up after 328 days and the other 4 patients showed no response and remained on supportive therapy at 1 year. So the overall response rate at 1 year remained 50%, the same as at 6 months and the cumulative survival rate was 78.6%.

Of the two patients who had allogeneic BMT, one (a 19-year-old male patient) was followed for 2 years and 9 months after BMT. He showed successful engraftment with normal CBC. Cyclosporine treatment was continued for 2 years after BMT and was discontinued without relapse. The other patient (a 22-year-old female) was followed for 18 months. She received cyclosporine for only 9 months after BMT, according to the transplantation center. At the time of last follow-up, she had a normal CBC but she developed graft-versus-host disease, for which she was treated.

The side effects of treatment were tolerable. Four patients had alteration of renal function that was reversible with modification of the cyclosporine dose. Cyclosporine was not discontinued in any patient because of renal toxicity. One patient had transient alterations of liver function. Three patients had arterial hypertension that responded to treatment with amlodipine. Two patients had gum hypertrophy and two patients had hirsutism.

Two patients who died during the first month of treatment had intracranial hemorrhage. One of the other two patients died because of septicemia and the second patient died because of internal hemorrhage and septicemia.

Discussion

ATG has been shown previously to improve hematopoiesis in patients with SAA, with hematologic improvement in 40% to 60% of patients.[9,10,11] Other

treatments, including androgens[12] and high-dose corticosteroids,[13,21] have not proven been beneficial in SAA. Several studies have shown that cyclosporine could be effective in the treatment of SAA.[14-18] In other systemic studies cyclosporine produced about a 50% response rate in patients who were refractory to ATG or ALG treatment.[19,20] In a randomized multicenter study, Glukman et al showed that initial treatment of SAA with either cyclosporine or ATG produced comparable response and survival rates, but cyclosporine induced fewer infections, death and toxicity than ATG.[6] Results of the German multicenter trial demonstrated that the response to IST can be significantly improved by the addition of cyclosporine to ATG with a 70% response rate.[7]

Published studies concerning the treatment of SAA in developing countries are scarce. A study in Pakistan compared cyclosporine with high-dose corticosteroid in the treatment of aplastic anemia. The result was 45% response rate in the cyclosporine group compared with 8% in the corticosteroid group.[21] In Mexico, only few patients can afford adequate treatment for SAA, and in a single institution study, some patients could not be given IST because of economic constraints, and received only androgens while some others received only cyclosporine.[22]

In our study, all patients diagnosed as SAA received cyclosporine only because this is the only option available. The response rate was 50% in patients who received at least 3 months of cyclosporine and the cumulative survival rate at 1 year was 78.6%. The cyclosporine-associated toxicity was modest, tolerable and easily monitored and none of the patients had to discontinue cyclosporine because of toxicity. A similar profile of toxicity was observed by Frickhofen et al in a study in which patients received cyclosporine for a median of 1.1 year (range, 7 day to 12 years).[26] Others reported a similar safety profile with cyclosporine.[6,22] Although two of our patients relapsed after discontinuation of cyclosporine, they did respond well to reinstitution of cyclosporine and none of the patients relapsed while on cyclosporine. Such findings are seen in other studies.[22,26] In our study, adjustment of cyclosporine dose was dependent mainly on serum creatinine levels because cyclosporine levels were not feasible most of the time due to the shortage of reagents. However, it seems that this did not have a negative impact on the response or toxicity of treatment, probably because the cyclosporin dose was modest and did not exceed 6 mg/kg/day.

It is widely agreed that the combination of ATG and cyclosporine shows a better response than either agent alone in patients with SAA.[7,23,24,25] However, in developing countries where facilities are modest and most patients cannot afford adequate treatment of SAA, cyclosporine provides an easily available, cheap, safe and readily monitored immunosuppressive therapy option for patients with severe aplastic anemia.

Our study reflects certain facts about the treatment of SAA in our country and probably in other developing countries where economic aspects cannot be overlooked in taking therapeutic decisions. Indirectly, it also points to the difficulties that might be faced in managing hematologic diseases, which need expensive facilities.[27,28]

The Yemeni Ministry of Health provided the cyclosporine originally for post renal-transplant patients and we obtained the agreement to provide it free for our patients with aplastic anemia. The authors did not receive any form of support, financial or whatsoever from any organization or company. The patients had to pay the costs of investigations and all treatments other than cyclosporine.

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