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Acquired aplastic anemia: treatment in a developing country.

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ACQUIRED APLASTIC ANEMIA: TREATMENT IN A DEVELOPING COUNTRY
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ABSTRACT
Objective: The aim of this study was to evaluate the clinical presentation of aplastic anemia as well as to assess the efficacy of Cyclosporin -A in patients with aplastic anemia.
Methodology: This is a hospital based interventional study. During the three year study period, 44 children were enrolled. Mean age was 9.3 years and there was a male predominance.
Results: Most common clinical presentation was anemia and bleeding. Four children died before therapy was started. Cyclosporin-A was started in 40 patients. Eleven patients died before completion of therapy and three patients were lost to follow-up. Out of 26 patients who completed therapy, 11 were cured and 9 were responders while 6 were non responders according to the selected criteria.
Conclusion: In developing third world countries like Pakistan majority of the patients with aplastic anemia cannot afford BMT. Alternative modalities of treatment must therefore be looked into. Cyclosporin-A seems to be a reasonable therapeutic option in such cases.

KEY WORDS: Aplastic Anemia, Cyclosporin- A, Immunosuppression.

INTRODUCTION
Severe aplastic anemia is a syndrome characterized by bone marrow failure with peripheral cytopenia and a hypocellular bone marrow biopsy, without blasts or myelodysplasia.¹ It primarily affects children, young adults, and those over 60 years of age. The majority of cases are idiopathic; however, idiosyncratic reactions to some drugs, chemicals, and viruses have been implicated in its etiology. Probably an autoimmune T-cell reaction causes the stem cell depletion, but the precise mechanism, as well as the eliciting target antigens, is unknown. Symptoms vary from severe life-threatening cytopenias to moderate or non-severe disease that does not require transfusion support.²

The treatment of first choice for these patients is allogeneic bone marrow transplantation (BMT) from a sibling matched for HLA-A, HLA-B and HLA-DR. BMT is limited by treatment related toxicity and by availability of matched donors. Unfortunately only 30% of patients have an HLA-matched sibling (25% chance per sibling). Immunosuppression is an alternative to BMT i.e. Antithymocyte globulin (ATG) and cyclosporine.¹³ ATG unfortunately is also an expensive option, beyond the reach of many of our local patients. The miseries of these patients and their parents are further increased by difficulty in getting blood and blood products.
However, immunosuppression is only a bridging therapy. About a third of patients fail to respond, and even responders may have chronically low blood cell counts. These problems have resulted in remarks like immunosuppression only “postpones the inevitable.” The present study was conducted to evaluate the clinical presentation of Acquired Aplastic Anemia and to assess the efficacy of cyclosporin-A along with steroids, in patients with aplastic anemia who cannot afford other treatment options of immunosuppressive therapy with antithymocyte globulin.

Since the early 1980s Cyclosporin-A has been used in the management of patients with aplastic anemia who cannot undergo BMT. Cyclosporin A is a potent immunosuppressive agent, cheap, easily available and less toxic. It has marked immunosuppressive effects and lacks myelotoxicity and is therefore used to treat a range of inflammatory and immune mediated diseases. The mechanism of action is complex. It affects the early phase of T cell activation and inhibits lymphokine production. It has little inhibitory effects on B cell function. It can be used alone or in combination with methyl prednisolone or along with antithymocytic globulin.

Although ATG has been used extensively, the exact mechanism of its action is still not well understood. The reported response rate from ATG ranges from 30% to 75%. Combination of ATG and cyclosporin-A along with granulocytes colony stimulating factor (G-CSF) improves the response rate up to 70-80%. ATG is also not free of side effects and is expensive and so Cyclosporin-A alone can also be used as a valuable therapeutic option for the treatment of aplastic anemia.

**PATEIENTS AND METHODS**

The study was conducted from June 2000 to May 2003 at The National Institute of Child Health, Karachi. All children presenting with pallor, petechiae, bruises and mucosal bleeds with clinical suspicion of bone marrow failure were enrolled. Patients with obvious dysmorphic features suggestive of Constitutional Aplastic Anemia, laboratory evidence of leukemia, myelodysplasia and lymphoma were excluded. Hemoglobin, total and differential leucocytes counts, platelets, reticulocyte count, red cell indices and peripheral smear were done in all patients. Confirmation of diagnosis of aplastic anemia was based on bone marrow aspirate and or trephine biopsy. Renal, liver function and screening for hepatitis B & C was undertaken in every patient before starting therapy. Hams test was done to exclude nocturnal hemoglobinuria.

Chromosomal breakage studies were carried out in all those, consistent with Fanconi were excluded from the treatment protocol. The patients were classified according to the severity based on Cammitta classification.

Based on the selected criteria, 44 patients were enrolled during the three year study period.

The children were started on steroids and cyclosporin-A. Intravenous methylprednisolone was given from day 1-5, followed by oral steroid to complete two weeks of steroid therapy. Oral cyclosporin-A was started from the first day and continued for 18-24 months.

**Treatment Protocol:**

* Injection methyl prednisone 2mg/kg/day from day 1 to 5.
* Tablet prednisone 1mg/kg/day from day 6 to 14.
* Tablet cyclosporin-A 10mg/kg/day from day 1 onwards.

The duration of cyclosporin-A therapy was determined by the time required to achieve transfusion independence. Therapy was given for 18 months to those patients who achieved transfusion independence within one year of starting therapy. Treatment was given for 24 months to patients who achieved transfusion independence after 12 months of starting cyclosporin therapy. Patients were followed at monthly intervals in the outpatient clinic. Assessment of response to therapy was made by regular measurements of hemoglobin, total leucocytes, neutrophils and platelets counts. Record of blood and blood product transfusion,
infective and hemorrhagic complications was maintained. Patients were also monitored for side-effects of cyclosporin therapy.

Measurement of outcome:

Cured: Achievement of transfusion independence and maintains of hematological response at the completion of cyclosporin therapy.

Responders: Transfusion independence while on cyclosporin therapy and an absolute neutrophil count of > 1500 mm$^3$ platelet count >150000/ml and hemoglobin > 11gm%.

Non- Responders: No hematological response after 6 months of commencement of cyclosporin therapy.

Relapse: A drop in platelet count to < 20000/ml, hemoglobin <8gm% and absolute neutrophil count < 1000 mm$^3$ after an initial response of at least 2 months.

RESULTS

During the three year study period, 44 children were enrolled in the study. The age of the patients ranged from 2.5 to 13 years. The male to female ratio was 3.4:1. The age range and clinical signs at admission are shown in Figure-1, Table-I.

According to Cammitta classification 4 patients had very severe aplastic anemia (VSAA), 12 patients had severe aplastic anemia (SAA) and 28 patients were diagnosed as having non severe aplastic anemia (NSAA). Four patients died before the treatment was started. Two died of severe neutropenia and sepsis and the other two died of intracranial bleeding. Forty patients were started on cyclosporin therapy, out of which 11 expired during the course of the treatment 6(54%) due to intracranial hemorrhage, 4(36.6%) died because of septicemia and 1(9%) was unluckily expired because of renal failure. Three patients lost the follow up. The fate of patients on treatment is described in Table-II

Cyclosporine therapy was continued in the 26 surviving patients. Majority of these had NSAA. The transfusion of blood and blood products decreased in patients on therapy Figure-2. Out of the 26 patients, 11 (42.3%) were completely cured and 9 (34.6%) were still on treatment at the end of the study and showed significant improvement in the counts of all three cell lines while 6 (23.0%) were non responders.

DISCUSSION

In the past 30 years morbidity and mortality from aplastic anemia has decreased dramati-
clinically, primarily because of effective treatment modalities like BMT, stem cell transplantation and immunosuppression with ATG. Five years survival rates are now 70% to 90%. Patients not fulfilling the criteria for BMT or those unable to afford treatment with one of the more expensive immunosuppressant need an alternative option. Multiple immunosuppressive regimens have been tried in this regard with variable success rates. Cyclosporin-A is an easily available and cheap immunosuppressing agent that can be used in an out patient setting, further cutting down the cost of hospital stay.

In the present study cyclosporin-A along with steroids was used in the treatment of acquired aplastic anemia. Majority of the patients in the current study were male. Most studies conducted in the past have reported a similar pattern. Some have documented female preponderance. Age range of the patients in the present study was 2.5 to 13 years with a mean of 9.3 years, which is similar to that reported in the other studies.

Majority of the children in the current study presented with anemia and hemorrhages, mostly in the form of skin bleeds. This mode of presentation of the disease is the same as compared to other studies. Out of 26 patients who completed therapy, 42.3% were cured and 34.6% were responders and 23% were non-responder according to the selected criteria. Similar cure rates have been documented by Rai, in a study conducted at Banaras. In the past cyclosporin monotherapy has been used with variable success rates of between 16%-85%, depending upon the severity of the disease, with a better response observed in patients with NSAA. A recent study done by Agha has shown significant response rates in patients of acquired aplastic anemia treated with cyclosporin-A and steroids. Another large French multicenter trial attempted a direct comparison of cyclosporin versus ATG as initial treatment for aplastic anemia and found no difference in the outcome. Some of the more recent studies have used a more intensive regimen of Cyclosporin- A along with steroids and G-CSF with a response rate of between 45-70%. In the present study cyclosporin-A was used in a dose of 10mg/kg/day, which is the recommended protocol in many studies.

Transfusion requirement of patients on cyclosporin-A therapy decreased markedly. Eleven patients died in the first 6 months of starting therapy mostly due to infection and hemorrhages. One patient died as a side effect of therapy. Response could not be evaluated in these patients. The most common side effect of cyclosporin-A noted in patients was hirsutism, which was observed in 29 patients. One patient developed renal failure and expired during the course of the therapy. Three had deranged LFTs and recovered within two weeks, on decreasing the dose of cyclosporin. Nephrotoxicity was the most common side effect observed in a large trial of 66 children treated with cyclosporin-A. Others have found liver toxicity to be the most common. But in general cyclosporin-A is a well-tolerated immunosuppressive agent for the treatment of aplastic anemia. Compared to ATG it is safer as it is less toxic and less immunosuppressive and thus carries a lesser chance of early death due to infection.

Untreated Aplastic anemia has a very high mortality rate, and cyclosporin-A appears to be a reasonable therapeutic option for patients.
who cannot undergo BMT due to non-identical donor or cost constraints. It can help in achieving remission in 40% of patients, while in the remaining patients it can slow down the stormy course of the disease, maintain the peripheral blood counts and reduce the transfusion requirements.

CONCLUSION

The decision of management of aplastic anemia in a developing country like ours is largely limited by the availability of resources. Although allogenic BMT from a HLA matched sibling is the treatment of choice but cyclosporin-A along with steroids is a reasonable alternative.

REFERENCES