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Aplastic Anemia: Clinicohaematological Features, Treatment and Outcome Analysis

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CLINICAL PRACTICE ARTICLE

Aplastic Anemia: Clinicohaematological Features, Treatment and Outcome Analysis

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ABSTRACT

Objective: To determine the clinicohaematological features, treatment and outcome of children diagnosed with aplastic anemia at a single institution.

Study Design: Observational study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from January 1999 till December 2008.

Methodology: Medical records of children aged less than 15 years of age diagnosed with aplastic anemia were reviewed. Clinicohaematological features, treatment and its response to therapy and outcome were recorded. Results were described in percentages.

Results: Ninety patients were diagnosed to have aplastic anemia (AA); 65 were male during the study period. Age ranged from 1 to 15 years. Fever in 65 patients (72.2%), pallor in 53 (58.8%), skin bleeding in 49 (54.4%) and epistaxis in 31(34.4%) were the most common and frequent presenting features. Congenital (Fanconi's) anemia was found in 15 (16.6%) and acquired idiopathic in 75 (83.4%) of patients. Very severe aplastic anemia (VSAA) was seen in 29 (32.2%), 26 (28.9%) had severe AA and 17 (18.9%) had moderate AA. Eight patients (8.9%) underwent haematopoietic stem cell transplantation (HSCT), 12 (13.3%) received immunosuppressive therapy (IST) and 70 patients (77.7%) received other and supportive therapy. Five (62.5%) patients showed complete response to HSCT and 3 (37.5%) failed to engraft. IST showed complete response in 3 (25%), partial response in 5 (41.6%) and no response in 4 (33.3%). Twenty two patients (24.4%) expired either due to infection in 16 (72.7%, fungal in 6, bacterial in 10) and intracranial haemorrhage in 6 (27.3%) cases.

Conclusion: Majority of cases with AA were acquired and idiopathic in etiology. VSAA and SAA were frequent. Response to HSCT and IST was sub-optimal.

Key words: *Aplastic anemia. Treatment. Outcome. Idiopathic. Haematopoietic stem cell transplantation. Immunosuppressive therapy.*

INTRODUCTION

Aplastic anemia (AA) is a term describing pancytopenia with hypo-plastic marrow. AA is linked to exposure to benzene, pesticides and other chemicals. Marrow failure is a severe idiosyncratic complication due to the use of certain medical drugs. It can follow specific viral infections, as in postseronegative hepatitis.[1]

The incidence of this disease has been found to be low in prospective studies from the United Kingdom, France, Brazil, and in the International Agranulocytosis and Aplastic Anemia Study (IAAAS) conducted in several European countries as well as in Israel.[2]

In addition, the incidence of aplastic anemia shows geographical variability. It seems to be lower in Europe, North America and Brazil, and higher in Asia. Based on the two epidemiological studies carried out in Europe and Asia that used the same methodology, the incidence of the disease is two to three fold higher in Asia than in the West. This variability in incidence rates may reflect differences in exposure to environmental factors including viruses, drugs and chemicals, genetic background, diagnostic criteria, and study designs.[3]

Severe aplastic anemia (SAA) can occur at any age. In children it is either acquired, idiopathic or is a consequence of a range of genetic disorders.[4] Outcome of patients with SAA has considerably improved over the last couple of decades with the better supportive care and advances in treatment modalities. The preferred treatment for children with AA is haematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA) - identical sibling. This results in approximately 90% cure rates.[4] The alternative treatment for patients without a HLA identical donor is an immunosuppressive therapy (IST). This has shown 75% cure rates.[5] A lot of Western data is available on aplastic anemia, but very few studies are found from the Indian sub-continent.

The aim of this study was to present the data regarding the clinicohaematological features, the important treatment modalities being given and their outcomes.

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METHODOLOGY

The charts of children less than 15 years of age from the year 1999 till 2008 were studied at the Aga Khan University Hospital, Karachi. The selection of patients was based on the diagnosis of aplastic anemia confirmed by bone marrow trephine biopsy. The data collected by chart review included age, gender, date of diagnosis, prior treatment, clinical features, family history, complete blood count, bone marrow aspirate and trephine biopsy features, chromosomal breakage studies, hepatitis B and C serology, treatment options, complications, response and outcome.

Patients were classified according to proposed criteria for the disease severity. Aplastic anaemia was considered severe (SAA) if the marrow cellularity was < 25%, with at least 2 of either neutrophil count < 0.5 x 10^9/L or platelet count < 20 x 10^9/L or reticulocyte count < 20 x 10^9/L.

AA was considered very severe (VSAA) if the above criteria for SAA were fulfilled, and the neutrophil count was < 0.2 x 10^9/L.

Moderate AA was defined as a hypo-cellular bone marrow with at least two of the following haematological values: neutrophil count < 1 x 10^9/L, platelet count < 50 x 10^9/L or reticulocyte count of < 60 x 10^9/L.[6] Patients not meeting the above criteria were labelled to have mild AA.[6]

Patients were treated with HSCT and immuno-suppressive therapy (IST) which included ATG, steroids, and cyclosporine; those who received only cyclosporine and steroids were excluded from the IST regimen. Some patients got supportive therapy due to financial constraints. Fanconi's anemia patients who could not undergo HSCT were given androgens.

Criteria for response after immunosuppressive therapy (IST) were divided into complete, partial and no response. Complete response (CR) was defined as achieving normal levels of haemoglobin according to age, platelet count > 100 x 10^9/L and neutrophil count > 1.5 x 10^9/L. Partial response (PR) was defined as transfusion independence, platelet count > 30 x 10^9/L, and neutrophil count > 0.5 x 10^9/L above baseline. No response meant neutrophil count < 0.5 x 10^9/L, platelets count < 20 x 10^9/L and transfusions dependence (meet SAA criteria).[6]

For HSCT complete response (CR) was increased in the white cell and platelet count and no response (engraftment failure) was defined by the return of peripheral blood cell count to levels meeting the definition of severe or moderate AA and the requirement for blood transfusion.[7]

The mortality and cause of death was noted. Descriptive statistical analysis was carried out using the SPSS version 16.0 software.

RESULTS

Over a period of 9 years, 90 children with AA were diagnosed. Children up to 15 years of age were included. The clinicohaematological features are given in Table I. More than one clinical manifestation was observed in patients.

Viral serology was done in 56 patients; 2 were positive for hepatitis B surface antigen and 4 had antibodies positive to hepatitis C virus.

Congenital Fanconi's anemia was seen in 15 (16.6%) patients and rests were acquired, idiopathic aplastic anemia in 75 (83.4%) patients.

Severity of disease is given in Table I. Eight patients (8.9%) underwent HSCT and 12 (13.3%) received IST. Patients with mild AA were not given any specific treatment and were observed with weekly blood counts which normalized within 2-4 weeks (Table II).

Complete response (CR) was seen in 5 and engraftment failure in 3 patients with HSCT. Among those who received IST therapy, complete response was seen in 3 (25%), partial response in 5 (41.6%) and no response in 4 (33.3%). Outcome of patients with HSCT and IST is shown in Table III.

Table I: Showing the clinicohaematological features in aplastic anemia.

Patients' characteristics	Number of patients (n=90)
Male / Female	65/25 (72.2%/27.8%)
Median age at diagnosis (years)	8
Presentation	
Fever	65 (72.2%)
Pallor	53 (58.8%)
Skin bleed	49 (54.4%)
Epistaxis	31 (34.4%)
Causes of aplastic anemia	
Fanconi's anemia	15 (16.6%)
Idiopathic	75 (83.4%)
Severity of disease	
Very severe	29 (32.2)
Severe	26 (28.8%)
Moderate	17 (18.8%)
Mild	18 (20%)

Table II: Shows the different treatment and outcome in all patients with AA.

Treatment	n=90
HSCT	8 (8.8%)
IST	
Cyclosporine / ATG/steroids	12 (13.3%)
Cyclosporine / steroids	13 (14.4%)
Androgens	9 (10%)
Supportive	48 (53.3%)
Outcome	n=90
Expired	22 (24.4%)
Off treatment	10 (11.1%)
On treatment	3 (3.3%)
Referred out	10 (11.1%)
Lost to follow-up	45 (50%)

Table III: Showing outcome of patients treated with HSCT and IST.

Treatment	HSCT	IST	Total (n=20)
Outcome			
Expired	1 (25%)	3 (25%)	4
Alive	6 (75%)	3 (25%)	9
Referred out	-	1 (8.3%)	1
Lost to follow-up	1 (25%)	5 (41.6%)	6
Total	8	12	20

Twenty two patients (24.4%) expired; out of whom 16 (72.7%) had infection (fungal in 6, bacterial in 10) and intracranial bleed in 6 (27.3%). One patient receiving HSCT and 3 patients receiving IST died due to infection.

DISCUSSION

In this study, children upto the age of 15 years were included. The median age of 8 years is consistent with other studies done from different regions.[6,8,9] Male predominance probably reflects gender bias in the developing world.

The major presenting feature was fever in 71.4%, pallor in 58.9%, and skin bleed in 54.4% of cases in the current study which is similar to other studies.[8,10]

The frequency of Fanconi's anemia in these patients was 16.6%, higher than reported in Western literature but similar to the studies from India.[11-13] The increased incidence of Fanconi's anemia in this population may be because of increased consanguinity seen in our country.

Hepatitis associated AA was seen in 21% of cases.[6] Post-hepatitis AA accounts for about 10% of marrow failure in Western case series.[14] In this study as only 56 patients were checked for hepatitis serology, therefore, it was not possible to determine an overall frequency of post-hepatitis AA.

The current study showed about approximately two thirds of patients having SAA and VSAA in 61% and moderate AA in 18.9% of cases which is similar to reported elsewhere.[6,9] However, Goswami reported severe and moderate AA in 33.33% and 57.14% of cases respectively.[10]

As the expenses of HSCT and IST are high, different treatment options were discussed with the family. According to their financial resources, some opted for transplantation, IST and others remained on supportive therapy.

CR was seen in 25% and PR in 41.6% in patients who received IST in the present study. This response does not match with studies done elsewhere. Pongtanakul *et al.* found 62% complete response and 19% partial response to IST with ATG, CS and steroids for children with AA.[6] A Japanese pediatric series demonstrated an overall response rate of 65% and complete response rate of 40% among 60 patients.[15] Indeed results have improved dramatically in children with VSAA from 37% in the 1980s to 83% in the 1990s.[16]

HSCT has been shown to have 90% cure rate.[17] Matched sibling donor HSCT routinely provide long-term survival in range of 90%, and 75% of patients respond to IST.[18] In the current study 62.5% of patients who got HSCT showed complete (CR). Shamsi reported 78% long-term survival in AA.[19] The differences in treatment given to these patients according to financial resources may also be a factor for the differences in obtained results.

The overall mortality was (24.4%), out of which infection was the predominant cause being found in 72.7% of patients (45.5% had bacterial and in 27.3% had fungal). Intracranial bleed was observed in 27.3% of patients. A German group reported that 11 (13%) patients died within the 4 months and cause of death was cerebral haemorrhage in 6 (54.5%) patients and bacterial infection in 5 (45.5%) patients.[20] Infections rate was high in this study and the deaths occurred within a year of diagnosis.

The limitations of study is that data was collected retrospectively for a period of time, and that the medical record was the source of information. As a result some information was missing from the charts.

CONCLUSION

The study shows that the majority of cases with AA are acquired idiopathic AA and in inherited AA, Fanconi's anemia is seen more commonly. VSAA and SAA are most frequently seen. The response to IST is poor in this setup in comparison to international data. The outcome of HSCT in this study was 62.5% which is also low as compared to international data.

We recommend that further local studies need to be done in order to obtain better information with regard to treatment selection and outcome.

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