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ORIGINAL ARTICLE

FREQUENCY OF CURE WITH CYCLOSPORIN THERAPY IN PATIENTS WITH APLASTIC ANEMIA

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ABSTRACT

Aplastic Anemia (AA) is rare haemopoietic stem cell disorder characterized by pancytopenia in peripheral blood and hypocellular marrow in which normal haemopoietic marrow is replaced by fat cells.

Objective: The objective of this study was to determine the frequency of cure with cyclosporin therapy in patients with aplastic anemia.

Materials and Methods: It was a descriptive case series study carried in the Department of Haematology, Shaikh Zayed Hospital, Lahore. The study was completed in six months from January 2010 to July 2010. It was a hospital based case series of 45 patients suffering from aplastic anemia who fulfilled the inclusion criteria. The patients were given cyclosporin for six months and cure was assessed after 3 and 6 months by haematological parameters. Standard procedures were followed for all laboratory tests. Data was analyzed by SPSS version 10.

Results: After six months of cyclosporin therapy, 6 (21.4%) patients were cured .Seven (25%) were partial responders and 15(54%) were non responders.

Conclusion: In developing countries like Pakistan majority of patients cannot afford bone marrow transplant and antithymocyte globulin (as these are expensive options) hence cyclosporin which is a relatively inexpensive drug is a valuable therapeutic option.

Key Words: Aplastic anemia, pancytopenia, Cyclosporin.

INTRODUCTION

Aplastic anemia is defined as presence of pancytopenia in peripheral blood and hypocellular marrow in which normal haemopoietic marrow is replaced by fat cells[1].

The incidence of aplastic anemia is 2 – 3 cases per million per year in Europe, it is two to three times higher in Southeast Asia.[2]

In Pakistan, aplastic anemia is found to occur mostly in young males. The common type is idiopathic severe aplastic anemia.[3] The treatment of choice for aplastic Anemia is allogenic bone marrow transplantation (BMT) from an HLA-identical sibling donor. Unfortunately only 30% of patients have an HLA – matched sibling. Immunosuppression is an alternative to bone marrow transplantation i.e. antithymocyte globulin (ATG) and cyclosporin (CSA).[4- 6]

Since the early 1980's cyclosporin has been used in the management of Patients with aplastic anemia who cannot afford BMT. Cyclosporin is a potent immunosuppressive agent, cheap, easily available and less toxic. It affects the early phase of T-cell activation and inhibits lymphokine production. It can be used alone or in combination with methyl prednisolone or along with antithymocyte globulin. According to one study, cyclosporin has a cure rate of 42.3%.[5]

In developing countries like Pakistan, majority of patients cannot afford BMT, and antithymocyte globulin is also an expensive option, and is beyond the affordable range of many patients, so cyclosporin alone can be used as a valuable therapeutic option for treatment of aplastic anemia.

The purpose of this study was to determine the frequency of cure with cyclosporin in patients with aplastic anemia.

METHODOLOGY

This descriptive, case series was carried out in the Department of Haematology, Sheikh Zayed Medical complex, Lahore, from January, 2010 to July, 2010. Forty five diagnosed patients of aplastic anemia (on bone marrow aspiration and trephine biopsy) were included in the study during a period of six months. Sampling was non probability purposive in type. Adult patients (> 15 years) of both genders were included. Aplastic anemia with paroxysmal nocturnal haemoglobinuria (diagnosed on flow cytometry), chemotherapy induced aplastic anemia (diagnosed on history) and inherited aplastic anemia (diagnosed on cytogenetics)

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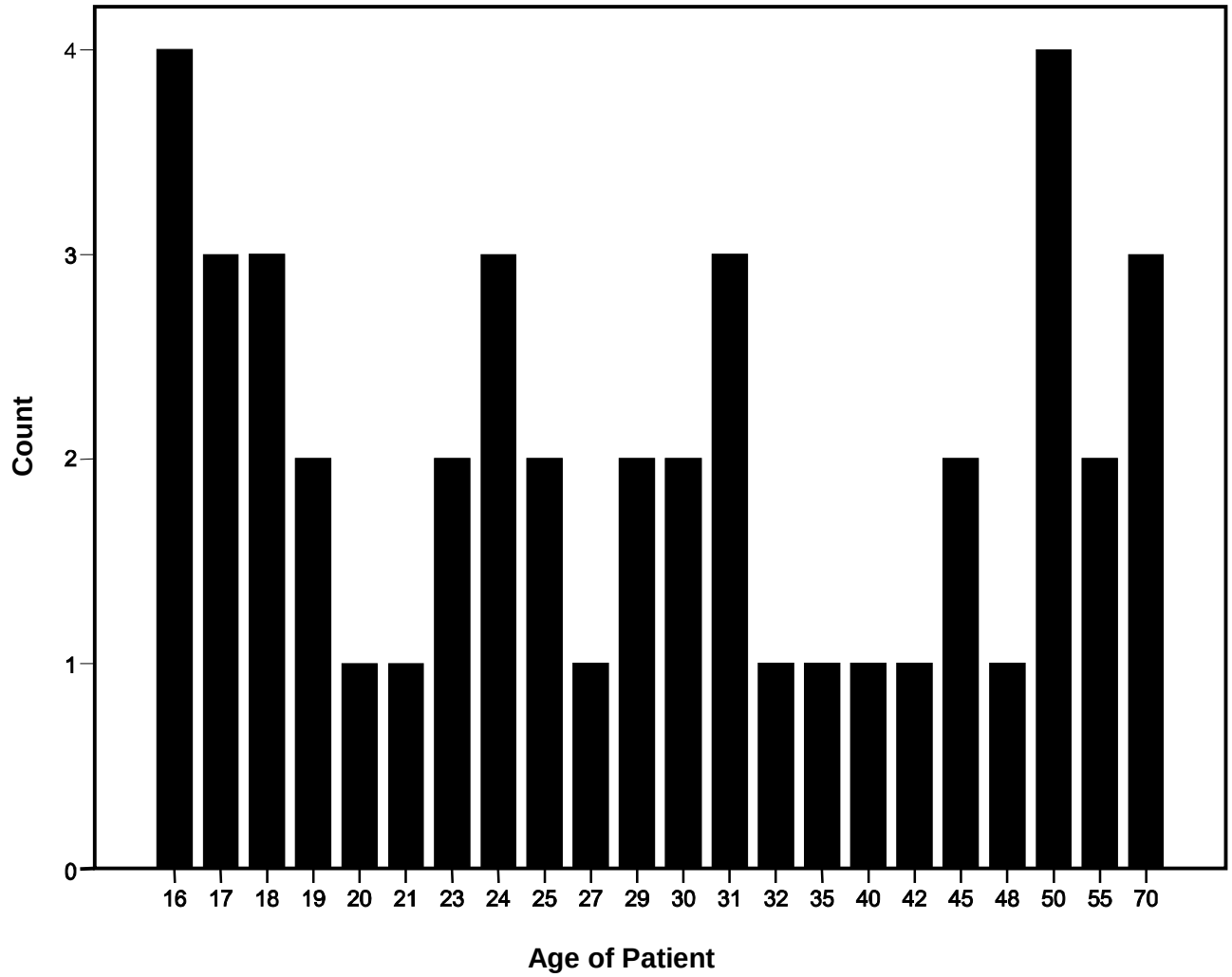

Figure 2: *Age Distribution of aplastic anemia patients in present Study.*

were excluded from the study.

Aplastic anemia was defined as hemoglobin (Hb) concentration less than 10g/dl, platelet count (PLT) less than 150×10^9/l, absolute neutrophil count (ANC) less than 1.5×10^9/l. Cure was defined as achievement of normal haematological parameters i.e Hb more than 12 g/dl, platelet count more than 150×10^9/l and absolute neutrophil count more than 2×10^9/l.

Informed consent was taken and socio-demographic data like name, age and address was collected. Patients were given cyclosporin (5 mg/ kg/ day) for 6 months. Hemoglobin, platelet count and absolute neutrophil count were noted on day 1, after 3 months and after 6 months of treatment.

These tests were performed on haematology analyzer Sysmex XT1800i. Other variables like partial response (counts below normal but above these values i.e. hemoglobin > 10 g/dl, platelet count > 100×10^9/l and absolute neutrophil count > 1.5×10^9/l and no response (no improvement in counts or counts below responders) were also noted. All this information was entered a specially designed performa. All collected information was entered into SPSS version 10.0 and was analyzed through its statistical package. Age was presented in terms of mean and standard deviation, sex in terms of frequency and percentages. Hemoglobin, platelet count and absolute neutrophil count were analyzed and expressed as frequency and percentages. Overall cure was presented as percentage.

RESULTS

The study was carried out over a period of six months. Forty five patients were included from outpatient department of Sheikh Zayed Hospital Lahore. Patients were diagnosed as having aplastic anemia according to criteria (Hb < 10 g/l, Platelet count < 150×10^9/l, absolute neutrophil count < 1.5×10^9/l and a hypocellular marrow).

There were 32 (71%) males and 13 (29%) females in the cohort. Mean age of the patients was 32 years (SD ± 15.7). Mean age in male patients was 30 years (SD ± 14) and in female patients was 37 years (SD ± 19). Most of the patients in the present study presented in second decade.

Forty five patients started cyclosporine (CSA) at day 1 at a dose of 5 mg/kg/day. Complete blood counts were performed on day 1, at 3 months and at 6 months. Mean Hb at day 1, 3 months and 6 months is shown in (table 1). Mean absolute neutrophil count (ANC) at day 1, 3 months and 6 months showed increasing pattern (table 2). Mean platelet count (PLT) at day 1, 3 months and 6 months shown in (table 3).

Cyclosporin (CSA) therapy was started in forty five patients at a dose of 5 mg/kg. After 3 months, 43 patients remained, one patient expired due to severe infection and one did not come for follow up. Four of 43 patients (9.3%) were completely cured, 7 (16.3%) were partial responders and 32 (74%) were non responders.

After 6 months, 28 patients remained on follow up. In these subsequent 3 months a further 2 out of 43 (4.65%) patients expired, one due to intracranial bleed and the other due to severe infection and 13 (30.2%) were lost from follow up. Two more patients were completely cured thus total number of cured patients after six months were 6 (21.4%). Seven (25%) were partial responders and 15 (54%) were non responders.

DISCUSSION

In our study, 71% patients were male and 29% were female. Mean age was 32 years (range 16-70 years). Majority of our patients were in second decade (Fig. 2). Male to female ratio was 2.4**:**1. According to

Table 1: *Hemoglobin (Hb) (g/dl) at day1, at 3months and 6 months in aplastic anemia patients in present study.*

Patients	*Hb Mean ± SD (Day 1)*	*Hb Mean ± SD (3 Months)*	*Hb Mean ± SD (6 Months)*
Female	5.66 ± 1.50	9.13 ± 2.37	9.21 ± 2.95
Male	6.05 ± 2.21	9.33 ± 2.75	11.06 ± 2.52
Total	5.94 ± 2.02	9.27 ± 2.61	10.33 ± 2.80

Table 2: *Absolute Neutrophil count (ANC) (n × 10^9/l) at day 1, at 3 months and 6 months in aplastic anemia patients in present study.*

Patients	*ANC mean ± SD (Day 1)*	*ANC Mean ± SD (3 Months)*	*ANC Mean ± SD (6 Months)*
Female	1.08 ± 0.78	1.78 ± 1.53	1.45 ± 1.08
Male	0.85 ± 1.32	1.49 ± 1.53	2.21 ± 1.77
Total	0.92 ± 1.19	1.57 ± 1.52	1.91 ± 1.56

Table 3: *Platelet count (PLT) (n × 10^9/l) at day 1, at 3 months and 6 months in aplastic anemia patients in present study.*

Patients	*PLT Mean ± SD (Day 1)*	*PLT Mean ± SD (3 Months)*	*PLT Mean ± SD (6 Months)*
Female	40.23 ± 35.70	53.85 ± 51.58	47.82 ± 55.99
Male	15.66 ± 18.43	79.33 ± 94.54	115.76 ± 71.05
Total	22.75 ± 26.72	71.63 ± 84.09	89.07 ± 72.76

Table 4: *Comparison of cure rate in aplastic anemia patients after cyclosporin therapy in different studies.*

Variables	*Present study*	*Al-Ghazaly J*[9]	*Marsh et al*[10]	*Hanif S et al*[5]	*Gluckman et al*[11]
Age	> 15 y	10 – 48 y	17 – 84 y	2.5 – 13 y	2 – 83 y
Cured	9.3% (3 m)			42.3%	11.6% (3 m)
	21.4% (6 m)	14.3% (6 m)	23% (6 m)		
		28.6% (1 y)			
Partial responder	16.2% (3 m)			34.6%	
	25% (6 m)	35.7% (6 m)	23% (6 m)		
		21.4% (1 y)			
Non responder	74% (3 m)			23%	31.6% (1 y)
	53.5% (6 m)	42.9% (6 m)	54% (6 m)		
		28.6% (1 y)			

Hassan et al, males were more commonly affected with a male to female ratio of 3.3**:**1.[7] Adil et al reported in their study that most of patients were below 30 years of age and 74% were males and 26% were females.[3] Hanif et al reported male to female ratio of 3.4**:**1 in a study in paediatric age group[5].A recent Indian study done by Gupta V et al concluded that males outnumbered females by 5**:**1.[8]

Analysis of laboratory data in forty five patients of aplastic anemia revealed that mean hemoglobin at day 1 (D1) was 5.94 g/dl (SD ± 2.02), after three months 9.27 g/dl (SD ± 2.6) and after six months 10.33 g/dl (SD ± 2.8) where as in a study from Yemen by Al Ghazaly J et al the mean Hb after six months was 12.5 g/dl and after one year was 12.9 g/dl.[9]

Mean ANC at day1 (D1) was 0.9×10^9/l (SD ± 1.2), after three months it was 1.57×10^9/l (SD ± 1.52) and after six months it was 1.91×10^9/l (SD ± 1.56) where as in study by Al-Ghazaly J et al the mean ANC after six month was 1.8×10^9/l and after one year 1.9×10^9/l.[9]

Mean platelet count at day1 (D1) was 23×10^9/l (SD ± 26.7), after three months it was 72×10^9/l (SD ± 84) and after six months it was 89×10^9/l (SD ± 73),where as Al-Ghazaly J et al reported the mean platelet count after six months was 67×10^9/l and after one year it was 113×10^9/l.

In our study 3 of 45 patients (6.6%) expired. One after three months and 2 after six months. Fourteen were lost from follow up (1 after three month and 13 after six months). Remaining 28 patients completed the therapy. Six of these 28 (21.4%) were cured, 4 patients (14.3%) after three months and 2 more patients (7.1%) after six months. Overall cure rate at 6 months was 21.4%. A multicenter study done in Europe by Marsh et al has shown results close to our results i.e the cure rate of 23% at 6 months.[10] In a study, Al-Ghazaly J reported the cure rate of 14.3% at 6 months and 28.6% after 1year.[9] In a French multicenter study by Gluckman et al the response rate (which included both complete remission and partial response) was 11.6% after 3 months and 31.6% after 1 year[11]. In a Pakistani study by Hanif S et al the cure rate was 42.3% after 3 years of treatment by cyclosporine in a cohort of paediatric patients.[5]

In our study 7 of 43 patients (16%) were partial responders after 3 months and they remained partial responders even after 6 months therapy but the number of patients were reduced to 28 (2 expired and 13 were lost to follow-up). Seven of 28 patients (25%) were partial responders after 6 months. Al Ghazaly J et al reported that 35.7% were partial responders in their study at 6 months and 21.4% at 1 year.[9] Marsh et al reported 23% partial responders in their study at 6 months.[10] These figures from studies from middle-east and Europe are concordant with our results. Hanif S et al reported that 34.6% were partial responders after 3 years in paediatric patients in Karachi.[5]

In our study 32 of 43 (74.4%) patients were non responders after 3 months and 15 of 28 (53.5%) were non responders after 6 months. Al Ghazaly J et al reported 42.9% non responders at 6 months and 28.6% at 1 year.[9] Marsh reported 54% non responders at 6 months.[11] These figures are similar to our results. Hanif S et al reported 23% non responders after 3 years in paediatric patients.[5]

It is ***concluded*** that Cyclosporin monotherapy is given to patients with aplastic anemia who cannot afford ATG and BMT. In our study the cure rate was 21.4% after 6 months, 25% were partial responders and 53.5% were non-responders. Our figures are close to results from different studies done in France, Europe and Yemen in term of cure and non-responders. In developing countries like Pakistan majority of patients cannot afford BMT and ATG (as these are expensive options) cyclosporine which is a cheap drug is a valuable therapeutic option.

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