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Aplastic Anaemia – A South African Public Sector Perspective

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ABSTRACT

Background: Aplastic anaemia (AA) is a rare condition that is characterised by a pancytopenia in the peripheral blood in association with a hypocallular/acellular bone marrow. **Objectives:** To document the demographic profile, clinical features, treatment modalities and outcome of patients diagnosed with AA at Chris Hani Baragwanath Academic Hospital (CHBAH). **Patients and Methods:** This is a retrospective study of patients with AA, seen at the Clinical Haematology Unit, Department of Medicine, CHBAH, during the period 01/01/1995 to 31/12/2012 (17 years). **Results:** A total of 100 patients were seen during this period. The median age at presentation was 24.5 years (range 14-78 years), with a male to female ratio of 1.7:1. The majority of patients had acquired, idiopathic AA (82%). Severe AA was noted in 69.9% of the patients. Human immunodeficiency virus (HIV) was the most frequently detected secondary cause of hypoplastic/aplastic anaemia (whether coincidental or causal), accounting for 12% of patients. In addition to supportive care, immunosuppressive therapy with Antithymocyte Globulin as the backbone constituted the mainstay of specific treatment. Two patients underwent an allogeneic stem cell transplant. The 5-year survival probability for all the patients was 69.2%. The leading cause of mortality was sepsis. HIV seropositive patients had a statistically significantly inferior 5 year survival probability compared to HIV seronegative patients. Three per cent of patients (3%) transformed to acute myeloid leukaemia (AML) and 5% developed Paroxysmal Nocturnal Haemoglobinuria (PNH). **Conclusions:** Aplastic Anaemia is typically a disease of young adults. Severe, acquired, idiopathic AA is encountered in the majority of patients. The clinical presentation and outcome is similar to that described in the literature.

INTRODUCTION

Aplastic anaemia (AA) refers to a peripheral pancytopenia in the presence of a hypocellular or acellular bone marrow, without marrow fibrosis or an abnormal infiltrate in the bone marrow. The incidence of AA is 2-3/ million population per year in Europe but is higher in East Asia. The exact incidence in South Africa is unknown. There is a biphasic distribution with the first peak at 10-25 years and the second over 60 years. There is no significant gender difference between males and females.[1,2] Aplastic anaemia is classified as i) primary-congenital (inherited) and acquired. The acquired variety may be i) idiopathic (where the cause is unknown) and ii) secondary (to a number of known causes). Most of the data on this disease are from North America, Europe and Asia. The aim of this retrospective study was to define the epidemiological, clinical and laboratory features, as well as the treatment modalities and outcomes of patients with Aplastic anaemia at Chris Hani Baragwanath Academic Hospital (a large, tertiary, public sector hospital affiliated with the University of the Witwatersrand), in Johannesburg, South Africa.

PATIENTS AND METHODS

The population studied consisted of all patients older than 14 years of age who were diagnosed with aplastic/hypoplastic anaemia who presented to the Clinical Haematology Unit, Department of Medicine at Chris Hani Baragwanath Academic Hospital (CHBAH) during the period 1 January 1995 to 31 December 2012. The data collection was performed retrospectively from the patient files/records. Demographic data, clinical features, laboratory test results, management and outcome were recorded. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand.

The assessment of the severity of AA was done according to the Camitta criteria.[3] A ‘complete response’ was defined as a haemoglobin of >10g/dl, a neutrophil count of > $1x10^9$/l and a platelet count of >$100x10^9$/l. A ‘partial response’ was defined as a patient who was transfusion independent and did not meet the criteria for severe AA. A ‘less than partial response/ no response’ was designated to patients who did not meet the criteria for a complete or partial response.

Statistical analysis

The Redcap programme was used to facilitate electronic data capture and data analysis. The data was subsequently exported from to Microsoft Excel where further statistical analysis

was performed. Results were presented using descriptive statistics, including the median and range for continuous variables and the percentage for categorical variables. Overall survival data were compared using the Kaplan-Meier Survival Curve and log-rank test. Graph Pad Prism version 6 was also used for some of the data analysis.

RESULTS

One hundred patient files were analysed. There were 64 males and 36 females with a male to female ratio of 1.77:1. The median age was 24.5 years (range 14-78 years). The median age for males was 23.5 years (range of 14-78 years) and for females 26.5 years (range of 14-63 years). The peak frequency was in the second (28%) and third decade (42%). The ethnicity profile of the patients was 92% black, 3% mixed race, 2% white and 2% Asian. The dominant clinical signs were pallor (anaemia) and bleeding manifestations. Secondary causes for AA included: Hepatitis B (2%), EBV (1%) and HIV (12%). Two patients had genotypic evidence of Fanconi Anaemia (2%). Four patients (4%) were diagnosed with AA during pregnancy.

The majority of patients (69.9%) presented with severe and very severe aplastic anaemia. Two patients underwent a matched sibling allogeneic stem cell transplant (SCT). The remainder of the patients had immunosuppressive therapy (IST) consisting of various combinations of Antithymocyte Globulin (ATG), cyclosporin and corticosteroids. The overall response rate was 60.6%. Twenty one (21%) patients relapsed. Three patients (3%) transformed to AML and 5 (5%) patients had associated haemolytic PNH. The response rates in patients who had severe AA (SAA), very severe AA (VSAA) and non severe AA according to the Camitta criteria [3] was 68%, 28.5% and 75% respectively. With regard to HIV status, in the HIV positive population, 6 (54.5%) patients had no response and in the HIV negative population, 29 (38.2%) patients had no response (p-value: 0.33).

The 5-year survival probability was 69.2%. The 5-year survival probability was 37.5% for the HIV positive patients and 78.5% in the HIV negative patients (p-value: 0.01). In patients who responded to treatment, the 5-year survival probability was 88.9% and in those who did not respond to treatment, it was 17.3% (p-value: 0.0001). The most common cause of death was infection accounting for 61.5% of all deaths.

DISCUSSION

One hundred patients were reviewed over a period of seventeen years. The average number of patients seen per year was 5.8. The majority of patients were of black ethnicity (92.9%). Aplastic anaemia is typically a disease of young individuals with the peak frequency occurring in the second and third decades. A second peak at 65 years is described in the literature.[1,2] The median age at diagnosis in this study was 24.5 years and there was no clear second peak. There was a male predominance in this cohort of patients with a ratio of 1.7:1 which is similar to a previous study done on aplastic anaemia at this centre which reported a male-to-female ratio of 2.15:1.[4] Anaemia was the dominant clinical feature occurring in 92.9% of patients, followed by signs of mucocutaneous bleeding.

Clinical features suggestive of a possible inherited bone marrow failure syndrome (IBMFS) were present in 7 patients of which skin pigmentation and short stature were the most common manifestations. Results of genetic studies which were available for 2 patients confirmed Fanconi Anaemia. Secondary causes of AA included: 12 patients with HIV, 2 with Hepatitis B, 1 with EBV and an association with pregnancy in 4 patients.

Human immunodeficiency virus (HIV) infection was the dominant secondary cause. HIV infection, whether coincidental or causal, is rarely associated with hypoplastic/aplastic anaemia.[5-7] All patients with HIV seropositivity were treated with antiretroviral therapy. However, there was no association between the severity of the aplastic anaemia and the CD_4 count. The median CD_4 count was $274.5x10^6$/l with a range of $4\text{-}840x10^6$/l. The response to therapy appeared to be less favourable in HIV seropositive patients compared to seronegative patients with a complete response achieved in 27.3% versus 35.5% and a partial response of 18.2% versus 26.3%, respectively. 54.5% of HIV positive patients and 38.2% of HIV negative patients had less than a partial response. The survival also appeared statistically significantly poorer in the HIV positive subset (p-value: 0.01). Sepsis was the cause of death in all the patients with HIV, who died.

The majority of patients in this study had VSAA and SAA which is similar to international data. In a study done in 2007 where 2479 consecutive patients with AA were analysed using data from 257 centres reporting to the European group for Blood and Marrow Transplantation by the Severe Aplastic Anaemia Working Party between 1991-2002, 1421 patients had data on severity. There were 40.8% who had VSAA, 24.4% with SAA and 34.6% with moderately severe AA.[8] Two patients in our study underwent an HLA

compatible sibling SCT. Both achieved a complete response. However, SCT is rarely performed in our setting, due to lack of HLA compatibility. Matched unrelated donor transplantation is not done at our public sector hospital, primarily because of financial constraints.

Immunosuppressive therapy in various combinations with ATG as the backbone was used in 97 patients. In the literature, studies using immunosuppression with ATG, cyclosporine, ± corticosteroids as the standard of care, have resulted in a generally favourable outcome. The 10-year actuarial survival in patients receiving first line immunosuppressive therapy is 80% in children and 70% in adults.[8] The overall response rate in our study was 60.6%. A second course of ATG was given to 11 patients: 7 of whom relapsed and 4 who did not respond to the first course of ATG. Of the non-responders, only 1 patient had a partial response. Of those who relapsed, 4 (57%) of the patients responded. The response rate to a second course of immunosuppressive therapy is between 30-60% with the response being better in previous responders compared to non-responders. All 4 of the patients who responded previously attained a complete response. Thus, the overall response rate of 60.6% is comparable to the international literature on AA. [8]

Responders (complete and partial response) had a better survival when compared to non-responders with a cumulative survival probability at 5 years of 88.9% and 17.3% respectively (p: 0.0001). There were 16 out of 26 (61.5%) deaths that occurred in the non-responders. In the HIV positive patients, the response was less favourable than the HIV negative patients with 54.5% not achieving a response compared to 38.2% (p-value: 0.33). There were 21 patients out of 60 patients who responded initially and subsequently relapsed (35%). Three patients transformed to acute myeloid leukaemia (AML) and all 3 demised subsequently. The frequency of transformation to AML is less than that reported in the literature.[1,9] The overall 5-year survival in this study was 69.2%.

CONCLUSION

The clinical presentation AA in our South African cohort is similar to that of other studies reported in the literature with features of anaemia and bleeding manifestations predominating. The severity of AA was also similar with most of the patients classified as having severe and very severe aplastic anaemia. Acquired idiopathic aplastic anaemia was most commonly encountered. However, the most frequent secondary cause of aplastic/hypoplastic anaemia was HIV. This is not unusual, given the high prevalence of HIV

in our background population.[10] Other secondary causes included EBV, Hepatitis B and pregnancy. A genotypically confirmed diagnosis of Fanconi Anaemia was made in 2 patients (2%). Immunosuppressive therapy was the mainstay of treatment in the vast majority of patients. Haematopoietic stem cell transplantation with an HLA matched sibling donor was performed in 2 patients (2%).

The response rate, relapse rate and overall survival are similar to that reported in the published literature from studies done internationally. The rate of transformation was less in this study relative to that reported in the literature. The most common cause of mortality was infection. HIV positivity and non-response to therapy were associated with inferior survival.

These limitations of the study included the retrospective nature of the study, missing data in some patients, non-compliance/lost to follow–up and the study being conducted at a single institution.

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