A multicentre, retrospective study of epidemiology and outcome of aplastic anaemia among adult population in Sabah and Sarawak from year 2006 to 2017

Grace Wan Chieng Lee, MRCP (UK)[1], Mei Yee Yeap, MRCP (UK)[2] ,Xin Yee Tan, MRCP (UK)[3], Andy Sing Ong Tang, MRCP (UK)[4], Yoke Fun Ho, MRCP (UK)[5], Kian Boon Law, MSc[6], Shalin Wan Fei Lee, MNSc (UM)[7], Lee Ping Chew, MRCP (UK)[1], Lily Lee Lee Wong, MRCP (UK)[2]

[1]Haematology Unit, Department of Medicine, Sarawak General Hospital, Sarawak, Ministry of Health, Malaysia, [2]Haematology Unit, Department of Medicine, Queen Elizabeth Hospital, Sabah, Ministry of Health, Malaysia, [3]Department of Medicine, Sibu Hospital, Sarawak, Ministry of Health, Malaysia, [4]Department of Medicine, Miri Hospital, Sarawak, Ministry of Health, Malaysia, [5]Department of Medicine, Bintulu Hospital, Sarawak, Ministry of Health, Malaysia, [6]Institute for Clinical Research, National Institute of Health, Ministry of Health, Malaysia, [7]Department of Nursing, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Ministry of Higher Education, Malaysia

ABSTRACT

Introduction: Aplastic anaemia (AA) is a rare disorder of bone marrow failure, characterized by bone marrow hypocellularity with pancytopenia. The annual incidence rates of AA in Asia are observed to be two to three times higher than Europe and North America. Since the introduction of immunosuppressive therapy (IST) and of allogenic stem cell transplant (SCT), the outcome of severe AA has significantly improved. We conducted a 12-year multi-centre retrospective study among the adult AA population in Sabah and Sarawak.

Materials and methods: A total of 119 AA patients had been identified from hospital records of the involved sites, namely Queen Elizabeth Hospital in Sabah, Sarawak General Hospital, Sibu Hospital, Miri Hospital and Bintulu Hospital in Sarawak from Jan 2006 to Dec 2017.

Results: The median age at diagnosis was 46 years, and native ethnic group from Sabah, Kadazan-Dusun, recorded the highest percentage of 41.2%, which could be explained by higher frequency of HLA-DRB1*15:01, an alelle linked to increased risk of AA, among this ethnic group. The majority of patients (59.7%) received cyclosporine (CsA) as monotherapy or in combination with other non-IST agents such as danazol, which was instituted in 48.7% of the patients, while a third of them (33.7%) received anti-thymocyte globulin (ATG) therapy with or without CsA, and 12.4% underwent allogenic SCT. The five-year overall survival (OS) for all AA patients was 76.1%. Elderly patients >60 years old and those with severe disease had more inferior 5-year survival.

Conclusion: A prospective study is warranted to determine the true incidence rate, epidemiological distributions, treatment outcome and overall survival of AA patients in Malaysia. Establishment of allogenic SCT in East Malaysia is imperative to make this curative therapy more accessible to patients with severe disease and improve the outcome.

KEYWORDS:
Aplastic anaemia, epidemiology, outcome, Sabah and Sarawak

INTRODUCTION

Aplastic anaemia (AA) is a rare disorder of bone marrow failure, characterized by bone marrow hypocellularity with peripheral blood pancytopenia. The annual incidence rates of AA in Asia, including countries like China, Korea, Japan and Thailand, are observed to be two to three times higher than Europe and North America, where the annual incidence is approximately 2.0 per million population per year.[1] In Malaysia, a retrospective epidemiological study of AA had been conducted in Sabah in the nineties, which revealed significantly higher incidence of AA at 4.8 per million population per year among the South East Asia regions with significant preponderance of the Kadazan-Dusun ethnic group.[2] Although AA has been known to be associated with several aetiologies, including environmental exposure to chemical, medical drugs and viral infections, it has also been linked to genetic susceptibility of certain population to AA.[3] Aplastic anaemia can be life-threatening in its severe form, with early mortality rate at three months as high as 22.6% in the very severe group of a Swedish cohort.[4] However, the outcome has significantly improved with 5-year survival of 70-80% in selected patient cohorts since the introduction of immunosuppresive therapy (IST) and of allogenic stem cell transplant (SCT).[4] In view of the lack of local epidemiological data in AA for the last two decades, this 12-year multi-centre retrospective study was performed to gain a better understanding of the demographic characteristics of AA and to look into real-world treatment outcome among the adult AA population in Sabah and Sarawak.

MATERIALS AND METHODS

A total of 259 adult AA patients had been identified from hospital records and new case registration of the involved sites, including Queen Elizabeth Hospital (QEH) in Sabah, Sarawak General Hospital, Sibu Hospital, Miri Hospital and Bintulu Hospital in Sarawak from January 2006 to December 2017. All AA patients diagnosed in other hospitals in Sabah were referred to QEH for further management as there was only one haematologist in the whole state of Sabah during the study period, hence captured in the AA registration list at QEH. Ethical approval was obtained from Medical Research

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Corresponding Author: Grace Lee Wan Chieng
Email: wanchieng82@gmail.com

and Ethics Committee (MREC), Ministry of Health Malaysia with registered ID NMRR-18-2160-42948 prior to the start of any study-related activities. Informed consent was not applicable as this was a retrospective study involving data collection which did not involve any investigational product or procedure on the subjects.

Attempts had been made to trace the case notes and clinic folders from Haematology clinic and medical record unit of respective hospitals, and only 119 case notes were retrievable. There were 140 patients (diagnosed in earlier years) from the AA registry of QEH whose case notes were not traceable since QEH was not equipped with central computerised system for clinical notes documentation, hence they were not included in the study. The retrieved case notes were reviewed, and all the relevant information, including patient's demographic details, environmental and occupational exposure to chemicals and toxin, full blood count on presentation, diagnostic bone marrow results, treatment details and outcome, were tabulated into a predesigned case report form. Assessment of exposure to chemicals and toxins, such as solvents and pesticides, was done by history taking from patients or family members. Diagnostic bone marrow aspirate and trephine biopsy reports were traced from the central pathology laboratory of Queen Elizabeth Hospital and Sarawak General Hospital, which handle all the bone marrow trephine specimens from the whole state of Sabah and Sarawak respectively, and reviewed to confirm the diagnosis of AA. Aplastic anaemia is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis with at least two of the following: haemoglobin concentration (Hb) <10 g/dL, platelet count <50 x $10^3/\mu$L, neutrophil count <1.5 x 10/μL. Disease severity was classified according to modified Camitta criteria as followed:[5]

1. Severe AA (SAA): Marrow cellularity <25% (or 25-30% with <30% residual haematopoietic cells), plus at least two of: (i) neutrophils <0.5 x$10^3/\mu$L, (ii) platelets <20 x$10^3/\mu$L (iii) reticulocyte count <20 x$10^3/\mu$L (<60 x$10^3/\mu$L for automated reticulocyte counting)
2. Very severe AA (VSAA): As for SAA but neutrophils <0.2 x$10^3/\mu$L
3. Non-severe (NSAA): AA not fulfilling the criteria for SAA or VSAA

Outcome assessment was done at one year, three years and five years from the date of diagnosis, which was based on response criteria from 'Guidelines for the diagnosis and management of adult aplastic anaemia' of British Society for Haematology 2016:[5]

(a) Response criteria in severe/very severe AA

- None (NR)
  Still fulfil severe disease criteria
- Partial (PR)
  Transfusion independent
  No longer meet criteria for severe disease
- Complete (CR)
  Haemoglobin concentration normal for age and gender
  Neutrophil count >1.5 x$10^3/\mu$L
  Platelet count >150 x$10^3/\mu$L

(b) Response criteria for non-severe AA

- None (NR)
  Blood counts are worse, or do not meet criteria below
- Partial (PR)
  Transfusion independence (if previously dependent) or doubling or normalization of at least one cell line or increase of baseline:
  - Haemoglobin concentration of >3 g/dL (if initially <6)
  - Neutrophils of >0.5 x$10^3/\mu$L (if initially <0.5)
  - Platelets of >20 x$10^3/\mu$L (if initially <20)
- Complete (CR)
  Same criteria as for severe disease

Patients with congenital or secondary bone marrow failure due to chemotherapy or radiotherapy, hypoplastic MDS and patients of age 12 years and below at the time of data collection were excluded from the study.

Demographic characteristics of patients were summarised using descriptive statistics, such as median for numerical variables, frequency and proportion for categorical variables, which were presented in tables. Association of different treatment modalities to disease outcomes was assessed using Pearson's Chi-square test at 0.05 significance level. Overall survival (OS) was defined as the time taken from confirmation of diagnosis to death from any cause or last follow-up. Mortality was confirmed through hospital certification of death or National Registration Department (JPN). Patients who were alive or lost to follow-up were censored. The OS rates were calculated using Kaplan-Meier (KM) method for three months, one year, three years and five years. Differences in OS between groups were compared and tested using the Log-rank test at 0.05 significance level.

RESULTS

Epidemiological characteristics

A total of 119 adult patients with confirmed diagnosis of AA had been identified over the 12-year study period, with 82 patients from Sabah and the remaining 37 from Sarawak. The number of AA cases retrieved in each year from 2006 to 2017 for Sabah and Sarawak is represented in Figure 1. Female preponderance was observed among the AA patients in this cohort, with a male-to-female ratio of 1:1.64. The median age at diagnosis was 46 years, and the majority of patients were from the late middle age group 40-59 years (37.8%, n=45), followed by young adult group 19-39 years (31.9%, n=38) (Table I). Native ethnic group from Sabah, Kadazan-Dusun, recorded the highest percentage 41.2% (n=49), followed by Malay and Bajau, who both recorded 10.9% (n=13) respectively, while Iban had the highest percentage 7.6% (n=9) among the other Sarawak indigenous groups.

Clinical characteristics

Analysis of the clinical characteristics of AA patients revealed that the lowest median pre-transfusion haemoglobin upon presentation was 5.95 g/dL, white blood count (WBC) 2.3x10^3/uL, absolute neutrophil count (ANC) 0.6x10^3/uL and platelet 7x10^3/uL for all severity groups. About half of the patients (n=61) were classified as having severe AA upon presentation, while 23.5% (n=28) had very severe AA. In the