Therapeutic Outcomes of Pediatric Acute Myeloblastic Leukemia Patients at a Tertiary Hospital in Bandung, Indonesia

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Abstract

Background: Acute myeloblastic leukemia (AML) is a subtype of leukemia characterized by myeloid infiltration into the bone marrow, blood, and other tissues. AML ranks 5th malignancy in children and the prognosis is poor. After chemotherapy, the outcomes vary. Therefore, this study aimed to provide further insight into the therapeutic outcomes of pediatric AML patients.

Methods: This study was conducted with a cross-sectional descriptive method. The data were obtained from the medical records of children diagnosed with AML at the Department of Child Health of Dr. Hasan Sadikin General Hospital in 2017–2019 with the total sampling method. Data including age at determination, gender, laboratory values including hemoglobin, leukocyte, thrombocyte as well as blast cell count on peripheral blood smear were collected. Also, the bone marrow punctures gathered were clustered based on the French-American-British (FAB) classification. Data were presented in tables.

Results: In total, 46 data of AML patients were retrieved, with the age category at first diagnosis was >5–12 years (48%) and predominantly males (63%), children with moderate anemia (41%), leukocytosis (35%), severe thrombocytopenia (46%), and blast cell count ≥20% (83%). AML-M2 was the most common subtype (30.4%). The majority of patients (91%) underwent chemotherapy and most (45%) patients died during chemotherapy

Conclusion: The outcome of AML therapy among children is mostly poor, and particularly die during chemotherapy. Early detection and follow-up of patients to continue therapy are important aspects to reduce the mortality rate of AML.

Keywords: Acute myeloblastic leukemia, child cancer, outcome of therapy

Introduction

Acute myeloblastic leukemia (AML) is a subtype of leukemia characterized by infiltration into the bone marrow, blood, and other tissues. The infiltration itself is composed of abnormally differentiated, clonal, and proliferative myeloid cells. Acute myeloblastic leukemia accounts for 20% of acute leukemia in children although its prevalence is less common than acute lymphoblastic leukemia.[1]

According to Surveillance, Epidemiology, and End Result (SEER), there were 1,291 pediatric AML patients between 2001–2007 in the United States.[2] Other data recorded in the Pediatric Department of Cipto Mangunkusumo General Hospital, Jakarta[3] showed that between 2007–2010, there were 93 patients with a mortality number of 50 patients. Even though AML is usually found in adults, AML has become the 5th most common malignancy in children and the prognosis is often terrible.[4] The high mortality rate for this leukemia subtype is influenced by many predisposing factors, such as delays in detection and problems with access to healthcare facilities.[5]

The clinical features that appear in AML are various. For the most part, the initial signs and clinical manifestations are regularly vague such as pallor, fever, bruises, and loss of blood. Other patients may also experience headaches,

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bloating, gum hypertrophy, weak extremities, and loss of weight.[4] Laboratory values may reveal low hemoglobin, low thrombocyte, and hyperleukocytosis.[1] However for a proper diagnostic method, a peripheral blood smear and bone marrow puncture should be conducted, which will be further classified under the French-American-British (FAB) classification based on its cytochemical staining of the blasts and morphologies.[6]

The therapy given to AML patients is mostly divided into curative and supportive therapy. Curative therapy aims to diminish the leukemic cells and achieve remission, while supportive therapy aims to prevent and overcome symptoms and side effects of curative therapy. Curative therapy itself is also grouped as induction and consolidation chemotherapy phases.[7] One of the guidelines used in the management of pediatric AML patients in Indonesia is the National Pilot Protocol for AML in Indonesian Children. According to the guidelines, AML therapy in children could last more than 3 months and then be evaluated with laboratory markers to check whether it is remised or not.[8]

Over time, therapies and technology have developed in treating AML patients. According to the SEER from 1975 to 2008 it was revealed that the survival rate increased from less than 20% to more than 60%.[1] Nevertheless, about 20–40% of patients experience a relapse and this becomes another challenge in maintaining patients' survival.[9] Besides, the success of therapy depends on the patient's obedience in following each curing method. Some patients choose to do alternative therapy or discontinue therapy for several reasons.[10]

After going through a series of medications, AML patients showed various outcomes, there were patients who were cured and some have died. The parameters of therapeutic success were assessed by evaluating the patient's bone marrow specimens, both the percentage of blasts that were decreased and those that persisted. Some cured patients may also show re-emerging of leukemic cells or we call it a relapse. The prognosis of AML patients can vary and may be influenced by several risk factors or underlying diseases. Moreover, the prognosis of AML patients is not as great as ALL patients.[11]

Previous research at Dr. Hasan Sadikin General Hospital showed that 38.4% of patients passed away while having AML therapy in 2014–2016.[5] There is still a lack of study covering therapeutic outcomes in childhood AML at Dr. Hasan Sadikin General Hospital.

Therefore, this study aimed to provide more information about the therapeutic outcomes of AML patients in children at Dr. Hasan Sadikin General Hospital. This information could help to evaluate and select further therapy to improve the survival rate.

Methods

This study was conducted with a descriptive method. The data were obtained from the medical records of children diagnosed with AML at the Department of Child Health Dr. Hasan Sadikin General Hospital. Inclusion criteria were children who had been diagnosed with AML from 2017 to 2019 using the total sampling method. Exclusion criteria were incomplete, missing, and inaccessible medical records.

Data including age at determination and gender were collected. Laboratory values were also checked including hemoglobin, leukocyte, thrombocyte as well as blast cell counts on the peripheral blood smears. This study defined Hb <6 g/dl as severe anemia, 6–8.9 g/dl as moderate anemia, 9–11.9 g/dl as mild anemia, and ≥12 g/dl as normal. For leukocytes, <10,000 cells/mm^3 was defined as normal, 10,000–49,999 cells/mm^3 as high normal, 50,000–99,000 cells/mm^3 as hyperleukocytosis, ≥100,000 cells/mm^3 as severe hyperleukocytosis. For thrombocyte, <20,000 cells/mm^3 was defined as severe thrombocytopenia, 20,000–99,999 cells/mm^3 as thrombocytopenia, ≥100,000 cells/mm^3 as normal. For blast counting, <20% was defined as normal and ≥20% as high blast cell count. Also, the bone marrow punctures gathered were clustered based on the FAB classification which depends on the cytoplasm, chromatin, nucleolus, cell size morphologies. M0 was an acute myeloblastic leukemia, minimally differentiated. M1 was an acute myeloblastic leukemia without maturation. M2 was an acute myeloblastic leukemia with maturation. M3 was acute promyelocytic leukemia, hypergranular. M4 was acute myelomonocytic leukemia. M5 was acute monoblastic leukemia, poorly differentiated. M6 was erythroleukemia. M7 was acute megakaryoblastic leukemia. This study also included the "no classification" criteria because the results of bone marrow puncture were ambiguous. In addition, chemotherapy status was also obtained whether the patients did therapy or not. Finally, the outcome of therapy was also evaluated, whether complete remission, relapsed and death, died during

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Table 1 Characteristics of Acute Myeloblastic Leukemia in Children Registered at Dr. Hasan Sadikin General Hospital in 2017–2019 (n=46)

Characteristics		Total	
		n	%
Age (years old)	1–5	16	35
	>5–12	22	48
	>12–18	8	17
Gender	Male	29	63
	Female	17	37

chemotherapy, loss to follow up, or even refused chemotherapy.

This study has been approved by the Research Ethics Committee of Universitas Padjadjaran with the number of ethical clearance 634/UN6.KEP/EC/2020 and research permit issued by the Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung No. LB.02.01/X.2.2.1/19546/2020. The data were processed and presented in frequency in the form of tables.

Results

From 81 medical records, 46 subjects met the inclusion criteria during 2017–2019. Most of the exclusion was based on the incompleteness of the data. This may also be due to the uncertain diagnosis of AML as determined by the description of the bone marrow puncture. Most of the AML patients were diagnosed for the first time in the age category >5–12 years (47.8%) and were predominantly male (63%)

Table 2 Laboratory Examination

Laboratory Examination		Total (n=46)	
		n	%
Hemoglobin	<6 g/dl (severe anemia)	7	15
	6–8.9 g/dl (moderate anemia)	19	41
	9–11.9 g/dl (mild anemia)	17	37
	≥12 g/dl (normal)	3	7
Leukocyte	<10,000 cells/mm^3 (normal)	11	24
	10,000–49,999 cells/mm^3 (high normal)	16	35
	50,000–99,000 cells/mm^3 (hyperleukocytosis)	11	24
	≥100,000 cells/mm^3 (severe hyperleukocytosis)	8	17
Thrombocyte	<20,000 cells/mm^3 (severe thrombocytopenia)	21	46
	20,000–99,999 cells/mm^3 (thrombocytopenia)	17	37
	≥100,000 cells/mm^3 (normal)	8	17
Blast cell count	<20% (normal)	8	17
	≥20% (high)	38	83
Bone marrow puncture*	M0 (acute myeloblastic leukemia, minimally differentiated)	1	2
	M1 (acute myeloblastic leukemia without maturation)	7	15
	M2 (acute myeloblastic leukemia with maturation)	14	30
	M3 (acute promyelocytic leukemia, hypergranular)	5	11
	M4 (acute myelomonocytic leukemia)	3	7
	M5 (acute monoblastic leukemia, poorly differentiated)	3	7
	M6 (erythroleukemia)	1	2
	M7 (acute megakaryoblastic leukemia)	0	0
	No classification	12	26

Note: *=classified under the French-American-British (FAB) classification

Table 3 Chemotherapy Status and Therapeutic Outcomes

		Total (n=46)	
		n	%
Chemotherapy status	Undergo chemotherapy	42	91
	No chemotherapy	4	9
Therapeutic outcome (n=42)	Complete remission	3	7
	Relapse and died	5	12
	Died during chemotherapy	19	45
	Loss to follow up	15	36

(Table 1).

Laboratory examination data were recorded when the patient was first diagnosed with AML. From the measurement of hemoglobin levels, most of the patients showed moderate anemia (n=19; 41%), leukocytosis was high normal (n=16; 35%) and severe thrombocytopenia (n=21; 46%). A peripheral blood smear was also done and the blast cell count was evaluated. Majority of patients (n=38; 83%) showed high blast cells (Table 2).

In addition, the core diagnosis of AML, bone marrow puncture should be conducted. There were 12 of 46 subjects whose FAB classification results were not listed in the medical records. Besides, the M2 classification was more common in AML patients (n=14; 30%), whereas M1 and M3 classifications were presented in 7(15%) and 5(11%) patients consecutively (Table 2).

The chemotherapy given to the patients was depicted in Table 3. This variable was evaluated after the patients were diagnosed with AML, either the patient decided to accept some kind of chemotherapy regimen or the patient decided to refuse chemotherapy. The results showed that 42 patients underwent chemotherapy (91%) while the rest did not undergo chemotherapy (Table 3).

This study also evaluated the response to chemotherapy among patients who received treatment. The majority of patients (n=19; 45%) passed away while bearing chemotherapy. A total of 15 patients (36%) dropped out or lost to follow-up while undergoing chemotherapy cycles. There were 5 patients (12%) who finished their treatment cycle but relapsed and died. In addition, there were 3 patients (7%) who completed their treatment cycle and achieved complete remission (Table 3).

Discussion

The results of this study indicate that most of the AML in children is diagnosed at the age of >5–12 years while different studies conducted in the United States demonstrate that the age of diagnosis mostly occurs at the age of less than 1 year and diagnosed at the age of 1–4 years in another study.[2,12] Boys were predominantly found in this study and consistent with the previous studies.[12]

Acute myeloblastic leukemia shows some abnormal laboratory values like other types of leukemia. On the patient's blood test, hemoglobin level and thrombocyte were low but usually, the leukocyte count was increased. Low levels of hemoglobin and thrombocyte could be reflected by several clinical features that existed in the patients, such as pallor, easy bleeding, and bruising.[1] In this study it was found that more than 90% of patients were anemic (<12g/dl) and more than 80% of patients had thrombocytopenia (<100,000 cells/mm^3). These findings are supported by similar studies showing that AML patients have anemia and thrombocytopenia on laboratory findings.[13] There were 35 patients (76%) with leukocytosis ≥10,000 cells/mm^3, even 8 of them had severe hyperleukocytosis (≥100,000 cells/mm^3). Likewise, an increase in white blood cells was found in a previous study. All these values may be due to the accumulation of leukemic cells in the bone marrow and interfering with normal blood cell production resulting in anemia, thrombocytopenia, and hyperleukocytosis in AML patients.[14]

Peripheral blood smears are also conducted in blood tests. According to Ciesla's[15] theory, AML patients as well as other acute leukemia patients often show high levels in immature blood cells or blasts. This theory correlates with the result of this study that most AML patients showed high levels of blast cell (≥20%). The main diagnostic method for AML patients is bone marrow puncture where it can evaluate myeloblasts infiltration in the bone marrow,[15] then classified using FAB classification. This study showed that 14 patients (30.4%) had

M2 classification along with M1 and M3 in second and third places. None of the patients showed the M7 subtype in this study. Mukda et al.[16] collected data on pediatric AML in one hospital in Thailand showing that M2 was the most common subtype followed by M1. For comparison, we found a study in European countries containing AML patients with FAB-classification. It was stated that the most common subtype was M2.[17] This FAB-based classification demonstrates quite various results in each study. From the information listed above, it can be assumed that the most common FAB subtypes in children are M1, M2, and M3.

After the patients are confirmed by bone marrow puncture, the patients should undergo chemotherapy to reduce the leukemic cells. On the other hand, some patients refuse to do therapy for some reason. Of the 46 subjects in this study, there were 4 subjects (9%) who refused to undergo chemotherapy. The main reason patients refuse chemotherapy is because they doubt the effectiveness of chemotherapy or prefer alternative medicine. A study in China[18] was also conducted on the childhood AML therapy. The study revealed that sixty patients (32%) refused chemotherapy. The reason for therapy refusal may be related to poor economic status and low knowledge about leukemia.[18] However, most of the subjects (91%) in this study decided to undergo chemotherapy.

Chemotherapy is divided into two-phases, namely the induction phase and the consolidation phase. The induction phase is directed to achieve remission (blast cells <20%) and controlled leukemic process which will be evaluated by re-performing a bone marrow puncture, whereas the consolidation phase is a more intensive therapy to remove the remaining leukemic cells.[19] Although chemotherapy is still ongoing, some patients could not survive. A local study at Cipto Mangunkusumo General Hospital Jakarta[3] showed that death in the induction and consolidation phases was the highest contributor, 38% and 34%, respectively. This study results are also similar to a previous study conducted at the Cipto Mangunkusumo General Hospital Jakarta. There were 19 patients (45.2%) died during the process of chemotherapy. Moreover, 5 patients (12%) were found to have relapsed and passed away in this study. A similar previous study on the outcome of AML therapy also demonstrated 20.3% of patients were found to have relapsed and died.[18] High mortality rates are still a major problem in lower-middle income countries. The high mortality rate can be caused by many factors such as the clinical condition of patients, punctual schedule of chemotherapy, and the availability of bone marrow transplantation methods.[3]

Therapy abandonment also plays a big challenge in curing AML patients. Many patients drop out during chemotherapy. This study showed that 15 patients (36%) abandoned therapy. This occurs when they are already on a chemotherapy regimen or starting their first cycle of chemotherapy. Patients need to come to the hospital every 1–3 weeks to continue the chemotherapy cycle. This variable was determined by assessing the data written in the medical record of the last chemotherapy conducted and there was no further information whether the patient passed away or survived. Previous study on cancer management in children at Dr. Hasan Sadikin General Hospital Bandung revealed that 51% of AML patients abandoned therapy.[5] Therapy abandonment in lower-middle income countries such as Indonesia, could be related to financial problems, doubts about possible cures and alternative medicine.[5,18] Despite the poor outcome in AML patients, this study found that 3 patients (7%) achieved complete remission. When compared with western countries where the survival rate for pediatric AML is more than 50%, improvement and evaluations in therapeutic methods are still needed.[1] In comparison, a previous study in the US showed that 74% of pediatric AML patients had a good response to the chemotherapy.[20]

The limitations of this study are incomplete medical records and samples taken from one center only. In addition, chemotherapy in the medical record was not classified into the induction or consolidation phase. Hence, adequate information and a larger sample size are needed to generalize the study. It is recommended for further studies to identify risk factors for pediatric AML mortality.

In conclusion, AML predominantly occurs in the age group of >5–12 years and males. The most common laboratory findings in children with AML are moderate anemia, leukocytosis, severe thrombocytopenia, and high blast cell count. The most common FAB subtype is AML-M2. Majority of patients undergo therapy and most patients die during chemotherapy.

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