Hematotoxicity in Acute Lymphoblastic Leukemia Children Who Received 6-Mercaptopurine During Maintenance Therapy in Indonesia

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Abstract

This study aimed to determine factors affecting the occurrence of hematotoxicity in acute lymphoblastic leukemia (ALL) patients during maintenance phase therapy.

This retrospective, observational study was conducted by analyzing the medical records of ALL patients undergoing 6-mercaptopurine (6MP)-based treatment (6MP, methotrexate, vincristine, and dexamethasone) during the maintenance phase at the Cipto Mangunkusumo Hospital, Indonesia, from January 2014 to December 2016. Ninety (89.1%) of ALL patients analyzed experienced hematotoxicity occurrence during the maintenance phase (anemia, 77.2%; neutropenia, 35.6%; and thrombocytopenia,26.7%). Most of the anemia and thrombocytopenia cases were grades 1−2, while the neutropenia cases were mostly grade 3−4.

Bivariate analysis revealed no statistically significant differences in disease stratification, gender, body mass index, and serum albumin levels between patients with and without grade 3−4 neutropenia or between those with and without thrombocytopenia. Conversely, age, gender, and disease stratification were significantly different between those with and without anemia. In conclusions, ALL patients often experience hematotoxicity during maintenance phase therapy, especially those with grade 3−4 neutropenia. Anemia was more prevalent in males, in the younger age group, and in patients with standard risk stratification.

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Introduction

Leukemia is the most common malignancy in children, accounting for 30% of all cancers diagnosed in children under 15 years of age in developed countries.[1,2] Acute lymphoblastic leukemia (ALL) accounts for 80% of all child leukemia cases and is the leading cause of death in children with cancer.[1] While 90% of ALL patients reach remission, 30%–40% of them relapse during the maintenance phase.[3] The relapse rate in developed countries over the last few years has been 11%.[4] Meanwhile, the relapse rate at the Cipto Mangunkusumo Hospital, in Jakarta, Indonesia, remains at 28.7%.[5]

ALL patients are treated based on disease stratification, i.e., standard-risk and high-risk. Standard-risk ALL patients receive some phases of therapy, such as induction, consolidation, and maintenance, whereas high-risk patients receive additional phases, such as re-induction or intensification, before entering the maintenance phase. To maintain long-term remission, ALL patients require maintenance phase therapy for up to 2 years with mercaptopurine (daily), low-dose methotrexate (once a week), vincristine, and corticosteroids (each monthly). Chemotherapy is provided during this phase is to suppress blast growth. Nevertheless, it can lead to hematotoxicity due to bone marrow suppression, especially during the maintenance phase of chemotherapy, and includes anemia, leukopenia or neutropenia, and thrombocytopenia.[6]

Hematologic toxicity is one of the major dose-limiting toxicities of chemotherapy.[7] ALL patients with severe neutropenia or severe thrombocytopenia may require lower doses or even discontinuation of mercaptopurine. Thrombocytopenia may render the patient

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susceptible to bleeding. In severe neutropenia, the body is predisposed to infections and sepsis, leading to mortality.[7–9] A previous study conducted at the Cipto Mangunkusumo Hospital revealed sepsis as the main cause of mortality in ALL patients (66.7%).[10]

Drug toxicity during the maintenance phase is an important issue to consider; it is the major cause of drug discontinuation, leading to relapse. Furthermore, hematotoxicity is life threatening,[11,12] so determining what factors affect hematologic toxicity is essential.

Materials and methods

This was a retrospective, observational study. Data were obtained from ALL patients' medical records at the Cipto Mangunkusumo Hospital in Indonesia, from January 2014 to December 2016. The inclusion criteria were ALL patients aged ≤18 years who underwent 6-mercaptopurine (6MP)-based treatment during maintenance phase therapy according to the Indonesian protocol ALL 2013.[13]

The treatment regimen was based on patient stratification (high or standard risk). Patients were considered high risk if they presented with any of the following at the time of diagnosis: age >10 years; hyperleukocytosis (white blood count [WBC] >50.000/μL); mediastinal mass; and central nervous system infiltration.[10]

During the maintenance phase, both groups of patients received the same treatment regimen as follows: oral dose (50 mg/m^2/day) of 6MP daily with per-oral dose (20 mg/m^2/week) of methotrexate (MTX) weekly for 5 weeks; 1.5 mg/m^2 of Vincristine (VCR; intravenous) every 6 weeks; and daily per-oral dose of dexamethasone in addition to VCR. Standard-risk patients received a 4 mg dose of dexamethasone; high-risk patients received 6 mg. During the first year of maintenance therapy, all patients received intratechal MTX every 7weeks. The doses of oral 6MP and MTX were targeted at a WBC of >2000–4000 cells/μL.[13]

The data collected from medical records included age at diagnosis, gender, disease stratification, nutritional status (weight, height), serum albumin level, and hematology data.

Hematotological data were collected at the end of each 6MP treatment cycle. Patients often experienced more than 1 hematoxicity condition (anemia, neutropenia or thrombocytopenia), but only 1 event was recorded. At the time of each event, data regarding body weight, height, and serum albumin level were recorded. Hematologic toxicity data were categorized according to The Eastern Cooperative Oncology Group (ECOG) Common Toxicity Criteria (CTC), 2007.[14] Nutritional status was categorized according to WHO.[15]

Statistical analysis was conducted using SPSS 20 software (New York, U.S). The normality of distribution was evaluated using the Kolmogorov-Smirnov test. Patients were grouped based on the type of hematotoxicity exhibited. Unpaired t-test, Mann–Whitney's Wilcoxon test, Chi square test or Fisher's exact test were used as appropriate. A *P*-value <.05 was considered statistically significant. For neutropenia toxicity, the data were analyzed, and patients were graded as 3–4 neutropenia, which was defined as an ANC of <1000/μL; dose reduction or temporary discontinuation of chemotherapy was required for patients in this condition.

This study was approved by The Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital (No. 836/UN2.F1/ETIK/2017). The committee waived the need for written informed consent since the data was collected retrospectively and was analyzed anonymously.

Results

Among the 141 medical records collected from the ALL patients who underwent 6MP-based therapy at the hospital, 101 were included for the data analysis. The remaining 40 were excluded because of missing the maintenance phase data.

ALL was more commonly found in males (58.4%) than females (41.6%), and there were more standard-risk (53.5%) than high-risk (46.5%) patients. Ninety (89.1%) out of 101 patients had at least 1 hematotoxicity event during the maintenance phase. Anemia occurred in 78 (77.2%) patients, neutropenia in 57 (56.4%), and thrombocytopenia in 27 (26.7%) patients. The most prevalent grades of anemia, neutropenia and thrombocytopenia observed were 1-2 (95%), 3-4 (65%) and 1-2 (66.8%), respectively.

Table 1 presents patient characteristics based on hematotoxicity grading. Differences in the characteristics of patients with anemia (grades 1–4) and without anemia are presented in Table 2. Statistically significant differences in gender, age, and disease stratification were observed between the 2 groups. The occurrence of anemia was greater in males (67.9%), in the younger age groups, and in those with standard-risk stratification (59%). No statistically significant differences in body mass index (BMI) and serum albumin levels were noted between the groups.

Variables	Anemia				
	Grade 0 (n=23)	Grade 1 (n=55)	Grade 2 (n=18)	Grade 3 (n=2)	Grade 4 (n=3)
Gender [n, (%)]					
- Males	6 (26.1)	37 (67.3)	11 (61)	2(100)	3 (100)
- Females	17(73.9)	18 (32.7)	7 (39)	-	-
Age (years)					
- Mean (±SD)	8.6 (±4.3)	6.4 (±2.9)	5.5 (±4.4)	4.8 (±1.4)	6.0 (±3.0)
- Median	7.9	5.9	3.6	4.8	6.0
Range	6–15.8	1.4–15.8	1.8–16.5	3.8–5.8	3.9–8.2
Nutritional Status [n, (%)]					
- Normal-overweight	23 (100)	54 (98)	18 (100)	2 (100)	3 (100)
- Underweight	-	1 (2)	-	-	-
BMI (kg/m^2)					
- Median	17.5	16.1	15.8	16.4	16.2
- Range	13.5–31.8	12.2–26.6	13.7–26.5	15.3–17.4	13.5–17.1
Hb (g/dL)					
- Mean (SD)	13.0 (±1.2)	11.2 (±0.74)	9.28 (±0.54)	7.5 (±0.49)	5.65 (±0.77)
- Median	13.2	11.3	9.35	7.5	5.65
- Range	11.5–15.9	10–12.7	8.2–9.9	7.2–7.9	5.1–6.2
Albumin (g/dL) (n = 70)					
- Mean (SD)	4.6 (±0.27)	4.52 (±0.39)	4.06 (±0.38)	5.15 (±0.35)	4.5 (±0.42)
- Median	4.6	4.5	4.35	5.15	4.5
- Range	4.1–5.3	3.3–5.3	3.7–4.9	4.9–5.4	4.2–4.8
Stratification [n, (%)]					
- HR	15 (65.2)	18 (33)	11 (61)	1 (50)	2 (67)
- SR	8 (34.8)	37 (67)	7 (39)	1 (50)	1 (33)

Hb= Hemoglobin, SD=Standard Deviation, HR=High Risk, SR=Standard Risk, BMI=Body Mass Index

Table 1. Characteristics of Patients Based on The Grade of Anemia.

Variables	Anemia		*p*
	Grades 1-4 (n=78)	Grade 0 (n=23)	
Gender [n, (%)]			
- Males	53 (67.9)	6 (26.1)	*.001†
- Females	25 (32.1)	17 (73.9)	
Age (years)			
- Mean (SD)	5.5 (±3.4)	8.6 (±4.3)	
- Median	4.0	7.9	*.005‡
- Range	0.3–16.5	6–15.8	
BMI (kg/m^2)			
- Median	16.1	17.5	.052‡
- Range	12.2–26.6	13.5–31.8	
Hb (g/dL) mean (SD)	10.4 (±1.54)	12.9 (±1.15)	*<.001§
Albumin (g/dL)$^{\#}$ (n = 70)	(n=53)	(n=17)	
- Mean (SD)	4.5 (±0.41)	4.6 (±0.27)	.405§
Stratification [n, (%)]			
- HR	32 (41.0)	15 (65.2)	
- SR	46 (59.0)	8 (34.8)	*.041†

Hb= Hemoglobin, SD= Standard Deviation, HR= High Risk, SR=Standard Risk, BMI=Body Mass Index
# Not all patients had data of serum albumin levels
* p<.05
†Chi square test
‡Mann–Whitney test
§Unpaired T-test

Table 2. Characteristics of Patients With or Without Anemia.

Patient characteristics based on neutropenia grading are presented in Table 3, while Table 4 illustrates the differences in the characteristics of patients with and without grade 3-4 neutropenia (ANC <1000). No statistically significant differences in gender, age, BMI, serum albumin levels, and disease stratification were found betweenthe2groups of patients. Similarly, Table 5 provides patient characteristics based on thrombocytopenia grading, while a comparison of characteristics of patients with and without thrombocytopenia are presented in Table 6. No statistically significant differences in gender, BMI, serum albumin levels, and disease risk stratification were noted between groups. The age of the patients with thrombocytopenia was lower than those without thrombocytopenia.

Variables	Neutropenia				
	Grade 0 (n=45)	Grade 1 (n=13)	Grade 2 (n=7)	Grade 3 (n=18)	Grade 4 (n=18)
Gender [n, (%)]					
- Males	24 (53.3)	8 (61.5)	5 (71.4)	9 (50)	13 (72.2)
- Females	21 (46.7)	5 (38.5)	2 (28.6)	9 (50)	5 (27.8)
Age (years)					
- Mean (±SD)	6.9 (±4.3)	5.3 (±3.1)	4.0 (±1.4)	6.7 (±3.7)	5.3 (±3.8)
- Median	6	4.3	3.9	6.1	3.8
- Range	1.5–15.8	0.3–11	2.2–6.0	2.0–12.7	1.8–16.5
Nutritional Status[#] [n, (%)]					
- Normal-overweight	44 (97.8)	13 (100)	7 (100)	18 (100)	18 (100)
- Underweight	1 (2.2)	-	-	-	-
BMI (kg/m^2)					
- Median	17.8	15.4	16.3	16.1	15.9
- Range	12.2–27.2	14.2–26.5	15.1–21.2	14.7–20.1	13.4–31.8
ANC (Neutrophils/µL)					
- Median	3041	1737	1242	745.5	274.5
- Range	2000–10697	1548–1935	1010–1359	500–990	0–480
Albumin (g/dL)(n = 69)					
- Mean (SD)	4.5 (±0.3)	4.4 (±0.1)	4.8 (±0.4)	4.5 (±0.1)	4.5 (±0.4)
- Median	4.6	4.4	4.7	4.6	4.4
- Range	3.7–5.3	4.2–4.5	4.4–5.3	3.8–5.1	4.0–5.4
Stratification [n, (%)]					
- HR	24 (53.3)	3 (23.1)	2 (28.6)	10 (55.6)	8 (44.4)
- SR	21 (46.7)	10 (76.9)	5 (71.4)	8 (44.4)	10 (55.6)

SD= Standard Deviation, HR= High Risk, SR=Standard Risk, BMI=Body Mass Index, ANC=Absolute Neutrophil Count.

Table 3. Characteristics of Patients Based on Neutropenia Grading.

Variables	Neutropenia grade 3-4		*P*
	Yes (n=36)	No (n=65)	
Gender [n, (%)]			.683[†]
- Males	22 (61.1)	37 (56.9)	
- Females	14 (38.9)	28 (43.1)	
Age (years)			.742[‡]
- Median	4.2	5.1	
- Range	1.8–16.5	0.3–15.8	
BMI (kg/m^2)			.077[‡]
- Median	15.9	16.5	
- Range	13.4–31.8	12.2–27.2	
ANC (Neutrophils/µL)			*<.001[‡]
- Mean (SD)	500.1 (±287.70)	2955.9 (±1769.28)	
- Median	490.0	2438.5	
- Range	0.0–990.0	1010.0–10697.0	
Albumin (g/dL)[#] (n=69)	(n=24)	(n=45)	.594[‡]
- Mean (SD)	4.5 (0.40)	4.5 (0.37)	
- Median	4.5	4.5	
- Range	3.8–5.4	3.7–5.3	
Stratification [n, (%)]			.603[†]
- HR	18 (50.0)	29 (44.6)	
- SR	18 (50.0)	36 (55.4)	

SD= Standard Deviation, HR= High Risk, SR=Standard Risk, BMI=Body Mass Index,
ANC=Absolute Neutrophil Count; # Not all patients had data of serum albumin levels; * *P*<.05; [†] Chi square test; [‡] Mann–Whitney test.

Table 4. Characteristics of Patients With or Without Neutropenia (grade 3-4).

Variables	Thrombocytopenia				
	Grade 0 (n =75)	Grade 1 (n=11)	Grade 2 (n=6)	Grade 3 (n=5)	Grade 4 (n=4)
Gender [n, (%)]					
- Males	43 (57.3)	5 (45.5)	4 (66.7)	4 (80)	3 (75)
- Females	32 (42.7)	6 (54.5)	2 (33.3)	1 (20)	1 (25)
Age (years)					
- Mean (±SD)	6.6 (±3.8)	4.1 (±2.8)	4.0 (±3.8)	5.7 (±2.6)	6.6 (±6.6)
- Median	6	3.3	2.4	6.2	3.8
- Range	0.3–15.8	2.1–11.8	1.8–11.7	2.9–8.3	2.3–16.5
Nutritional Status [n, (%)]	74 (98.7)	11 (100)	6 (100)	5 (100)	4 (100)
- Normal-overweight	1 (1.3)	-	-	-	-
- Underweight					
BMI (kg/m^2)					
- Median	16.4	15.7	16.1	17.1	14.2
- Range	12.2–27.2	14.2–22.3	14.7–19.6	15.3–31.8	13.5–20.2
Thrombocytes (10^3/µL)					
- Mean (±SD)	325.2 (±106.1)	121.7(±19.4)	55.8 (±.8.1)	40.6 (±4.6)	16.8 (±5.6)
Albumin (g/dL) (n = 69)					
- Mean (SD)	4.5 (±0.5)	4.5 (±0.2)	4.7 (±0.2)	4.6 (±0.3)	4.2 (±0.3)
- Median	4.5	4.6	4.7	4.6	4.2
- Range	3.7–5.4	4.2–4.9	4.6–4.9	4.2–4.8	4.0–4.5
Stratification [n, (%)]					
- HR	35 (46.7)	5 (45.5)	3 (50)	3 (60)	1 (25)
- SR	40 (53.3)	6 (54.5)	3 (50)	2 (40)	3 (75)

SD= Standard Deviation, HR= High Risk, SR=Standard Risk, BMI=Body Mass Index.

Table 5. Characteristics of Patients Based on Thrombocytopenia Grading.

Variables	Thrombocytopenia		*P*
	Grade 1–4 (n=26)	Grade 0 (n=75)	
Gender [n, (%)]			.575†
- Males	16 (61.5)	43 (57.3)	
- Females	10 (38.5)	32 (42.7)	
Age (years)			*.003‡
- Mean (SD)	4.7 (±3.6)	6.7 (±3.8)	
- Median	3.3	6.0	
- Range	1.8–16.5	0.3–15.8	
BMI (kg/m^2)			.128‡
- Mean (SD)	16.9 (±3.7)	17.6 (±3.4)	
- Median	15.9	16.5	
- Range	13.5–31.8	12.2–27.2	
Thrombocytes (10^3/µL)			*<.001§
- Mean (SD)	76.8 (±45.2)	327.8 (±104.3)	
- Median	58.0	319.0	
- Range	11.0–14.6	156.0–620.0	
Albumin (g/dL)# (n = 67)	(n=15)	(n=52)	.809‡
- Mean (SD)	4.5 (±0.28)	4.5 (±0.37)	
- Median	4.6	4.5	
- Range	4.0–4.9	3.7–5.4	
Stratification [n, (%)]			.799†
- HR	12 (44.4)	35 (47.3)	
- SR	15 (55.6)	39 (52.7)	

SD= standard deviation, HR= High Risk, SR=Standard Risk, BMI=Body Mass Index
# Not all patients had data of serum albumin levels
* *P*<.05
† Chi square test
‡ Mann–Whitney test
§ Unpaired T-test.

Table 6. Characteristics of Patients With or Without Thrombocytopenia.

Discussion

A prolonged maintenance phase therapy is required to maintain remission and prevent relapse in ALL patients. One major obstacle during this phase was the incidence of dose-limiting hematotoxicity. In some instances, chemotherapy had to be discontinued as a result,

increasing the risk of relapse.[11,12] In this study, hematological toxicity was experienced by most ALL patients during the maintenance phase. The incidences of anemia, neutropenia, and thrombocytopenia were 77.2%, 56.4%, and 26.7%, respectively. These findings are in line with a previous study, where the most prevalent hematological toxicities among 23 ALL maintenance phase patients were anemia (95.7%), followed by neutropenia (47.8%), and thrombocytopenia (17.4%).[16] Albeit not life-threatening, anemia was the most common hematologic complication of chemotherapy.[17] Anemia was the most prevalent event in this study. This may be attributed to the disease factor, wherein blast cell growth inhibits normal cell maturation in ALL patients' bone marrow, resulting in anemia, neutropenia, and thrombocytopenia.[18]

Neutropenia occurred more frequently than thrombocytopenia in this study. Similar to the study by Smid, et al, grade 3-4 neutropenia was the most common toxicity in this study.[19] White blood cells, especially neutrophil precursors, are most likely influenced by chemotherapy, owing to the rapid proliferation and short lifespan (6–12 h) of these cells. Platelets (a lifetime of 10 days) are also influenced, but to a lesser extent compared to neutrophils.[17]

Based on the literature, neutropenia may result from failure of neutrophil production in the bone marrow or from their peripheral destruction. Some of the factors causing neutropenia include infection, nutritional deficiency, protein malnutrition, immune reaction, and chemotherapy-induced neutropenia.[8,9] This study showed that age, gender, BMI, nutritional status, and disease stratification were not found to be related to neutropenia. These observations are in line with the study by Badr, et al, where patient (age, gender, and BMI) and disease (disease risk stratification and stage) characteristics were not associated with the occurrence of neutropenia in pediatric cancer patients.[20] However, a significant difference in anemia toxicity was noted based on gender and risk stratification. In accordance with previously reported findings, the occurrence of anemia was greater in males than in females in this study.[10,21–23] Moreover, most (95%) of the anemia cases were grades 1–2, with only 5% of cases presenting as grades 3–4. This might attributable to differences in normal limits between genders, as a higher number of males presented with grade 1 anemia in this study. However, this did not affect patient dose adjustment.

Age was shown to be associated with the occurence of anemia and thrombocytopenia. Younger patients had higher occurence of anemia and thrombocytopenia. In contrast to this result, Beaumais, et al, found higher 6-thioguanine nucleotide (6TGN) concentration, active metabolite of 6MP, in older patients as compared to younger patients. Their result showed that the mean concentration of 6TGN in younger children (aged ≤6 years) was 493 pmol/8 x 10^8 RBC, whereas 600 pmol/8 x 10^8 RBC in older children.[24] However, Dubinsky, et al, found that 6TGN level of >450 pmol/8 x 10^8 RBC was associated with myelotoxicity.[25]

In this study, the occurrence of anemia, neutropenia, and thrombocytopenia were not affected by serum albumin levels. More than 90% of patients with toxicity had normal albumin levels. However, we could not ascertain serum albumin levels from all the subjects because it was not a mandatory examination for this population. 6MP, the main drug provided to the patients during the maintenance phase,[26] suppresses blast cells and causes myelosuppression. In addition, this drug has a low binding affinity to plasma proteins. As a result, low serum albumin levels do not influence the concentration of free 6MP, and therefore do not affect the hematotoxicity.[27]

No association between BMI and hematological toxicity was noted in the current study. More than 95% of patients with hematological toxicity presented with normal to overweight BMI. This observation is in line with the study by Hijiya, et al, and Butturini, et al, BMI was not associated with the occurrence of toxicity in ALL children.[28,29]

Myelosuppression risk factors for cancer patients could be classified into 3 categories: disease factors; patient characteristics (age, comorbidity: kidney, liver, heart disease, hypertension, infections, sepsis disorders, abnormal laboratory results before therapy, and nutrition); and therapeutic factors (types and doses of chemotherapy).[7,17] In this study, patient characteristics, including gender, nutritional status, serum albumin levels, and disease stratification, did not affect hematotoxicity. Several studies conducted in childhood ALL patients have demonstrated that polymorphisms

in the enzymes that metabolize 6MP, major drug used during the maintenance phase, influenced hematotoxicity. Patients with thiopurine methyl trasferase (TPMT) enzyme polymorphisms had higher 6-thioguanine (active metabolite of mercaptopurine) levels, leading to an increase in the risk of hematotoxicity.[26,23,30] The American Society for Clinical Pharmacology and Therapeutics has recommended adjusting the starting dose of 6MP, based on patient's TPMT genotype, in order to avoid hematotoxicity.[31]

Conclusions

In conclusion, the hematotoxicity occurrence was high in ALL patients who underwent 6MP treatment during the maintenance phase in this study. Grades 3 and 4 neutropenia were most commonly observed among the patients. Age, disease stratification, BMI, and serum albumin levels did not affect thrombocytopenia or neutropenia occurrence. Anemia occurred more frequently in males, among the younger patients, and in those with standard risk stratification. Further studies investigating the role of genetic polymorphism in ALL patients undergoing 6MP treatment are warranted, particularly in those with hematotoxicity.

Declaration of Interest

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