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Hematologic Recovery in Pediatric Patients with Acute Lymphoblastic Leukemia After Induction Chemotherapy

Sony Wicaksono[1], Mia Ratwita Andarsini[1*], I Dewa Gede Ugrasena[1], Andi Cahyadi[1], Maria Christina Shanty Larasati[1], Susanto Nugroho[2]

[1]Hematology-Oncology Division, Department of Pediatrics, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;
[2]Hematology-Oncology Division, Department of Pediatrics, Faculty of Medicine, Universitas Brawijaya/ Dr. Saiful Anwar Hospital, Malang, Indonesia.

*Corresponding author:
Mia Ratwita Andarsini;
Hematology-Oncology Division, Department of Pediatrics, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;
mia-r-a@fk.unair.ac.id

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Introduction: Myelosuppression in Acute Lymphoblastic Leukemia (ALL) children was associated with high morbidity and mortality. Chemotherapy was aimed to achieve remission conditions, including the elimination of blast cells in the bone marrow. However, the evidence of hematologic recovery after induction chemotherapy was poorly described. This study aimed to evaluate the profile of peripheral blood and the outcome of children with ALL after induction chemotherapy.
Methods: A prospective study was conducted in the Hematology-Oncology Pediatric Department at Saiful Anwar Hospital Malang. Patients <15 years old who were newly diagnosed as ALL were enrolled in this study. Peripheral blood examinations were performed on the 1st, 2nd, 4th, and 6th weeks. Clinical outcomes were evaluated by remission status. Comparison and correlation analysis were done by IBM SPSS for Windows, version 26. P-value <0,05 was considered significant.
Result: There were 27 children included in this study. The median age was 5 years. There were 15 males and 17 females, 18 patients with LLA-L2 and 9 patients with LLA-L1. All patients received chemotherapy regimens according to the 2018 National Protocol for ALL. The median hemoglobin level was significantly increased after induction chemotherapy ($p < 0.05$). Meanwhile, the reticulocyte count increased in the 2nd week after induction chemotherapy. The Absolute Neutrophil Count (ANC) significantly improved and reached the normal limit in 4th week after chemotherapy induction. The platelet count and Immature Platelet Fraction (IPF) also increased significantly ($p < 0.05$) and reached the normal limit in 4th week after induction of chemotherapy.
Conclusion: Three cell lines regenerate at different rates at induction chemotherapy, with rapid erythrocyte recovery and slow neutrophil and platelet recovery.

Keywords: chemotherapy, childhood acute leukemia, hematologic recovery.
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INTRODUCTION

Acute leukemia is the most common childhood malignancy, representing 30% of all cancer in children under the age of 15 years and 12% of cancer cases in those ages 15 to 19 years old. In the United States, approximately 2500 new cases are diagnosed annually; 80% of these are acute lymphoblastic leukemia (ALL), 15% are acute myelogenous leukemia (AML), and 5% belong to the chronic leukemia category.[1] The incidence of ALL is relatively low in Indonesia, while the incidence of AML is similar to incidences reported from Western countries. In a multicenter study in Indonesia, it was reported that the prevalence of ALL was 77% and AML was 23%.[2] The survival rates of children with acute leukemia have increased dramatically in the last years because the successful of chemotherapeutic regimens. However, such intense chemotherapy with cytotoxic drugs usually results in myelosuppression and usually arise during the first course of induction chemotherapy.[3]

Patients typically present with symptoms related to anemia, thrombocytopenia, and neutropenia due to the replacement of the bone marrow with the tumor. The period of low blood counts is associated with morbidity, such as the need for transfusion therapy and antibiotic treatment. Furthermore, this period is associated with a risk of serious and life-threatening complications; thus, there is an induction mortality of 1%, mostly from bacteremia and occasionally from severe bleeding.[4] Induction chemotherapy aimed to achieve remission, including the elimination of blast cells in bone marrow. The decrease in blast cells was characterized by an improvement in hematopoietic function. As leukemia is cleared, the normal bone marrow can regenerate, resulting in normal peripheral counts. This process of regeneration is important as a sign of the treatment effect.[5]

The evidence of hematologic recovery during induction chemotherapy is not well described. This study evaluated the correlation between peripheral blood profile and the outcome of children with ALL during induction chemotherapy in pediatric patients with acute lymphoblastic leukemia.

METHODS

We conducted a prospective study of patients with ALL who underwent their induction chemotherapy as inpatients at the Pediatric Department, Saiful Anwar Hospital, Malang, Indonesia. Inclusion criteria were patients with a confirmed diagnosis of ALL by hematologic and bone marrow aspiration smears, less than 15 years of age, and willingness to participate in the study after informed written consent by parents. Exclusion criteria were patients with comorbid conditions such as diabetes, hypertension, chronic renal failure or cardiac diseases, patients with a history of bone marrow transplant and evidence of clinical infections before chemotherapy. The study protocol was approved by the Institutional Ethical Committee of Saiful Anwar Hospital.

The diagnosis of ALL is based on morphological investigations of bone marrow samples and peripheral blood smears based on The French-American-British (FAB) criteria.[6] Data about age at diagnosis, sex, treatment protocol, and other parameters described were collected and compiled for each patient. The day a patient received chemotherapy was defined as day one of that cycle. All patients were observed during the induction phase of chemotherapy. The peripheral blood test was performed in the first, 2nd, 4th, and 6th weeks to evaluate the myelosuppression and hematologic recovery.

Demographic data were expressed as medians, ranges, and percentages. A comparison between continuous variables was performed. A p-value < 0.05 was taken as significant. All statistical analysis was done using the software package SPSS, version 23.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

There were 27 patients enrolled in this study, 15 males and 12 females. The median age was 5 years old, with an interquartile range of 7. The most common presentation at the first time of diagnosis was pale, followed by fever, organomegaly and bone pain. Several patients have bleeding manifestations (gum bleeding and epistaxis) at diagnosis. Morphological examination of bone marrow showed 9 patients had ALL-L1 and 18 patients had ALL-L2, based on French-American-British (FAB) criteria. Based on risk stratification, there were 12 patients in Standard Risk and 15 patients in High-Risk regimen. Demographic data of patients are shown in Table 1.

Patients were followed up during the induction phase of chemotherapy. Peripheral blood analysis was performed during treatment. Median and Inter Quartile Range/IQR hemoglobin, reticulocyte count, leukocyte count, ANC, platelet count, and IPF in 27 subjects in weeks 1, 2, 4, and 6 are shown in Table 2. Significant improvement ($p < 0.05$) in hemoglobin levels in the study was shown during all weeks of observation. Significant reticulocyte differences were only found in weeks 1 and 2 ($p = 0,039$). Statistical analysis for leukocyte count showed significant differences during induction, except for weeks 4 and 6, while the ANC was significantly different in the first and second week compared to the end of induction ($p < 0.05$). Hyperleukocytosis (Leukocyte > 100.000/uL) were found in 5 children. Significant platelet count differences were found ($p < 0,05$), except for weeks 4 and 6. A significant difference in IPF was found in weeks 2 and 4 (Table 2).

The median hemoglobin level significantly increased gradually after induction chemotherapy. The reticulocyte count increased in the 2nd week after induction chemotherapy, and there was no significant difference during follow-up (Figure 1a). The median leucocyte count was decreased significantly after induction chemotherapy. The absolute neutrophil count increased significantly and reached the normal limit in 4th week after chemotherapy induction (Figure 1b). The platelet count and immature platelet count

Table 1. Demographic data of patients

Characteristics	Value
Age, median (IQR)	5 (7)
Sex, n	
Male	15
Female	12
ALL classification, n	
L1	9
L2	18
Chemotherapy Protocol Risk Stratification, n	
Standard risk	12
High risk	15

Table 2. Profile of hematology parameter after induction chemotherapy

Variable	1st week	2nd week	4th week	6th week	p-value
Hb (g/dL)	7.4 (5.7-9.3)	10.0 (7.9-11.3)	11.2 (9.3-11.9)	11.7 (10.8-12.3)	0.000*
Reticulocyte (%)	0.47 (0.20-0.76)	0.89 (0.22-1.90)	0.47 (0.22-1.63)	0.65 (0.30-1.03)	0.278
WBC (cell/μL)	8960 (1960-6430)	8620 (2380-6424)	3810 (1670-6200)	4370 (2870-7500)	0.048*
ANC (cell/μL)	570 (270-1370)	650 (200-2540)	1280 (420-2340)	1910 (1330-3790)	0.001*
Platelet (cells/mm³)	18,000 (10,000-38,000)	37,000 (9,000-111,000)	164,000 (95,000-311,000)	268,000 (144,000-296,000)	0.000*
IPF (%)	3,7 (1,7-4,1)	3,1 (1,1-4,8)	1,7 (0,9-2,7)	1,1 (0,7-2,2)	0.006*

*p < 0.05 was considered to be statistically significant

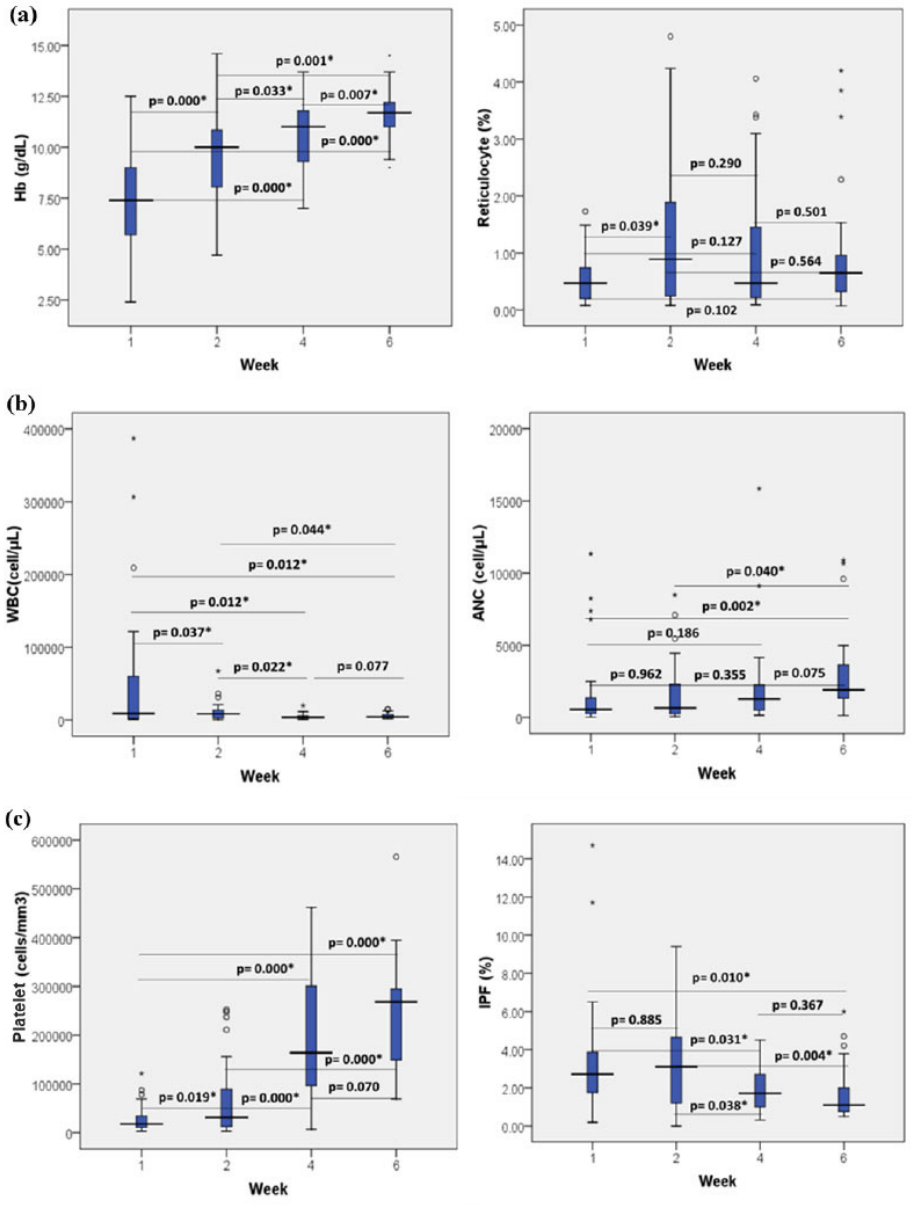

Figure 1. Peripheral blood parameters profile after induction chemotherapy. Hb: hemoglobin, WBC: white blood cell; ANC: absolute neutrophil count; IPF: immature platelet fraction

were also increased significantly ($p< 0.05$). Recovery to normal occurred 4 weeks after chemotherapy induction (Figure 1c).

Seven patients died during observation in the first week of induction chemotherapy. The cause of death was a septic condition, with the source of infection including pneumonia (71.4%), gastroenteritis (14.3%), soft tissue and skin infection (14.3%). In a separate analysis, we found that there were no significant differences in hemoglobin ($p= 0.371$), reticulocyte ($p= 0.495$), leukocyte ($p= 0.686$), ANC $p= 0.815$), platelet ($p= 0.815$) and IPF ($p= 0.932$) between survivor and non-survivor group during the first week of induction.

DISCUSSION

In this study, we described peripheral blood count profiles during induction chemotherapy in children with ALL. According to our findings, recovery from anemia, neutropenia and thrombocytopenia may be expected after two to four weeks after induction chemotherapy. Recovery of the three cell lines during induction chemotherapy was reported in a previous study. A study by Grunnan and Steen reported that after starting chemotherapy for ALL, platelet recovery occurred early after two weeks of induction chemotherapy, while neutrophil recovery lasted three to five weeks after induction chemotherapy. Platelet and lymphocyte count after two weeks of treatment may indicate residual disease after four weeks.[5] Other study of ALL bone marrow morphology reported that during induction therapy, there was a decrease in the cellularity of samples at day 15 of therapy, with a further decrease at the end of induction and an increase in the area occupied by adipocytes and the width of sinusoids. However, no correlation was found between clinical presentation, early response to treatment and morphological changes.[4]

Rapid bone marrow recovery is advantageous in terms of morbidity, but according to recent evidence, it may also be a favorable prognostic factor. In adults with ALL, a shorter time to platelet recovery has been associated with better disease free survival and overall survival, possibly reflecting the host ability to overcome minimal residual disease.[7] In children, a low ANC during induction (below median) was associated with more relapse, independent of the amount of minimal residual disease.[8]

Severe bone marrow suppression, by excessive lymphoblast proliferation, leads to impaired erythropoiesis, granulopoiesis, and thrombopoiesis. Therefore the laboratory findings in childhood acute leukemia show a decrease in the number of peripheral blood cells. Decreased bone marrow function is associated with anemia, bleeding, and risk of infection. Induction phase chemotherapy aims to achieve marked remission by blast cell clearance from the bone marrow, achieved by the 7-week treatment. When the blast cells decrease, the bone marrow begins to function so that hematopoiesis returns to normal. System restore hematopoiesis is an important sign of successful therapy and recovery of bone marrow and the consequences of bone marrow insufficiency. Length of a child with ALL in conditions of bone marrow insufficiency, associated with duration of hospitalization, including the need for transfusions, antibiotics, nutritional support, and

other supportive therapy, including an increased risk of death from infection. In this study, 60% of children were found to have hemoglobin < 8gr/dL. Anemia is an invariable finding at the initial diagnosis of ALL. Severe anemia (Hb < 8gr/dL) is associated with better output compared to children with hemoglobin > 8gr/dL. This pattern is associated with bone marrow suppression, anemia, and child ALL immunophenotype. A more severe degree of anemia is found in children with LLA-B.[9] Hemoglobin improvement occurs earlier than peripheral blood parameters. In the 2nd week, the hemoglobin parameter was > 8gr/dL in 80% of children undergoing chemotherapy. Hemoglobin gradually improved until the end of the induction phase, and all children had hemoglobin > 8gr/dL. The mechanism of anemia in children with ALL is still unknown, but it is associated with decreased erythropoietic function due to lymphoblastic infiltration.[10]

The absolute neutrophil count (ANC) is a common criterion when considering discontinuing chemotherapy, antibiotics, and hospital discharge. Absolute neutrophil count (ANC) evaluation is one method for evaluating granulopoiesis function improvement. Absolute neutrophil count (ANC) decreases in a state of infection so that it can obscure the condition of the bone marrow.[11] Interruption of treatment due to toxicity-induced neutropenia or infection is commonly found in children with ALL. Children with severe neutropenia require special care during chemotherapy, including the use of antibiotics, antifungals, isolation, and other supportive therapy. ALL children with severe neutropenia accompanied by clinically severe infection require consideration of delaying chemotherapy.[5,12] Severe neutropenia is still found in 40% of children with ALL at 2 weeks. Severe neutropenia is known to be associated with an increased risk of infection. Another study in Poland showed a 30% increased risk of death and 33% risk of relapse in children with ALL if there is a delay in chemotherapy before the 8th day, especially in children with high-risk ALL. A study on 149 children with ALL and LMA in South India showed similar results.[13,14]

Thrombocytopenia with a platelet count < 50,000/μL is seen in 80% of children diagnosed as ALL. Although at the end of the induction phase, all children with ALL were found with partial recovery of platelet counts, compared to hemoglobin levels and ANC, platelet count occurred later.[15] At the end of the induction phase, < 90% of children had full peripheral blood recovery. The evaluation results of bone marrow analysis showed all children with ALL experienced remission with good clinical results. This showed the National ALL Protocol 2018 has succeeded in inducing remission in ALL children. However, some children experience anemia, neutropenia, and thrombocytopenia, although they do not require special treatment. Further observations are needed on the research subjects to ensure recovery of peripheral blood due to drug toxicity or lymphoblastic infiltration in the bone marrow. This study also reported (analyzed separately) that there was a high mortality during the first week of induction (20.5%). The incidence of treatment-related mortality in patients with ALL is up to 52%, especially in low-to-middle-income countries. Most of the mortality occurs during the initial induction phase of the treatment, with the most common cause being secondary to infections.[16] As reported in this study, pneumonia, gastroenteritis and skin and soft tissue infection were suggested as sources of infection. Therefore, raising awareness about infection identification and control and antibiotic use during induction therapy among ALL patients is prospective.

CONCLUSION

This prospective study has shown that the three cell lines regenerate at different rates at induction chemotherapy, with rapid erythrocyte recovery and slow neutrophil and platelet recovery. Further studies are needed to investigate whether the changes in peripheral counts during induction may affect treatment response and prognosis.

DISCLOSURES

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Conflict of Interest
None of the authors has any commercial or other conflicts of interest with this work.

Author Contribution
MRA and IDGU involved in concepting, designing and supervising the manuscript. SW conduct the study and analyses the data. All authors prepare the manuscript and agree for this final version of manuscript to be submitted to this journal.

Ethical approval
The study protocol was approved by the Institutional Ethical Committee of Saiful Anwar Hospital.

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