HEMATOLOGICAL TOXICITY IN CHILDREN WITH ACUTE LIMPHOBLASTIC LEUKEMIC (ALL) IN BANDUNG

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ABSTRACT

Hematological toxicity is one of the side effects of chemotherapy that may occur in children with acute lymphoblastic leukemia (ALL). This causes a disruption in blood cell formation, and if not detected early, can cause death. However, this is still not the concern of health workers, especially nurses. The aim of this study was to know the description of hematological toxicity in children with leukemia who are undergoing chemotherapy. This research was conducted at a hospital in Bandung in December 2016. Designed of this study was descriptive with retrospective approach. This study was conducted on 198 respondents taken from medical records from January to July 2015 by using purposive sampling. Data was analyzed using univariate test. The results showed that the occurrence of hematological toxicity occurred in 64.6% of children with ALL post-chemotherapy, while 35.4% did not experience hematological toxicity. Hematological toxicity that occurs in children with leukemia in this study were leukopenia, thrombocytopenia, and anemia. Hematological toxicity that occurs can lead to prolonged hospitalization and delay the next schedule of chemotherapy, so it is important for nurses to collaborate with physician to perform early detection and monitoring of hematological toxicity in children with leukemia post chemotherapy.

Keywords: acute lymphoblastic leukemia, children, hematological toxicity.

I. INTRODUCTION

Cancer in children is one of the health problems in the world. Although the incidence of cancer in children around the world is still quite rare and when calculated only 1% of the total number of cancer patients in the world. But cancer in children is one of the leading causes of death of 80,000 children (ages 0-14 years) in 2012 (American Cancer Society, Global Cancer Fact & Figures 3rd Edition, 2015). There are more than 200,000 children have cancer in the world each year (World Child Cancer, 2014). According to Union for International Cancer Control (UICC) data, there are approximately 176,000 children diagnosed with cancer each year, the majority coming from low- and middle-income countries (Center for Data and Information Ministry of Health, 2015).

In Indonesia, it is estimated that 2-4% of total cancer in Indonesia attack on children (PERSI-Center of Data and Information, 2012). Based on the results of Basic Health Research in 2013, stated that prevalence of cancer in Indonesian children aged 0-14 years about 16,291 cases. Based on the data of Child Cancer Registry of Children Department in Dharmais Hospital from 2006-2014, the incidence of cancer in children always increased, although in 2007 had decreased but then increased every year which then increased drastically in 2011 and in 2015 there were about 11,000 cases cancer of children every year in
Cancer in children consists of various types, but the most common cancer found in children is acute leukemia. The incidence of acute leukemia per year is 3 to 4 cases found per 100,000 children under 15 years of age (Wong, Eaton, Winkelstein, Wilson, & Schwartz, 2009). Based on data from the Ministry of Health of the Republic of Indonesia (2011), acute leukemia is 30-40% of children's malignancy which peak occurs at the age of 2-5 years with an average incidence of 4-4.5 / 100,000 children per year. Leukemia cancer death rate in 2015 is still high, with the death of acute lymphoblastic leukemia (LLA) there are 1450 cases of 6,250 cases found (Siegel, Miller, & Jemal, 2015). Based on data from Dharmais Cancer Hospital (RSKD), it is known that in 2006-2010 the leukemia child mortality rate is 20-30% of all types of cancer (Center for Data and Information Ministry of Health, 2015).

According to American Fact and Figure (2016), the success rate of leukemia patients to survive is as much as 85%, with acute lymphoblastic leukemia (LLA) being 89% and having a very good prognosis compared to acute myeloblastic leukemia (LMA) 65%. This is also supported by Tanjung (2011) who stated that children with 2-3 year-old LLA who undergo intensive therapy programs have a good life expectancy in which patients can survive longer even until someone can be more than 20 years old.

Many methods of treatment to improve the life expectancy of children with leukemia such as using chemotherapy therapy, radiation or bone marrow transplant. However the main leukemia treatment today is chemotherapy (Wong, Eaton, Winkelstein, Wilson, & Schwartz, 2009). Chemotherapy is done to kill cells especially fast-growing cells such as cancer or leukemia cells. The goal of therapy is healing or at least a prolonged remission. The administration of these chemotherapy drugs is usually given with single or combination therapy according to the protocol used (Morrison & Hesdorffer, 2012).

Although chemotherapy is an effective treatment in the current treatment of leukemia in Indonesia, but each child has a different reaction at the time of treatment. Side effects arising from chemotherapy are sometimes more severe than the symptoms of leukemia itself (Ariawati, Windiastuti, & Gatot, 2007). Chemotherapy kills cells that develop rapidly, but chemotherapy also kills normal-developing cells, such as in hair cells, mucosal tissue cells in the mouth, gastrointestinal tract and spinal cord. One of the side effects that often occur after chemotherapy is the suppression of bone marrow activity (myelosuppression) which resulted in the emergence of hematological toxicity (Metha & Hoffbrand, 2012).

Hematological toxicity according to Cancer Agency (2015) is one of the main side effects of chemotherapy drug administration that occurs due to myelosuppresion that can inhibit the development of normal blood stem cells where the number of white blood cells, red blood cells and platelets become disturbed by the sign of leucocytosis, leukopenia, Anemia and thrombocytopenia. According to some studies such as Pinontoan, Malik and Rampengan (2013), Pertiwi (2013) it is known that there are haematological disorders in LLA patients during chemotherapy either in the induction or consolidation phase that changes every week ie leukopenia, leukocytosis, thrombocytopenia and anemia. Based on
the research of Isnani, Perwitasari, Andalusia et al (2014), hematological toxicity events in LLA patients due to the use of chemotherapy drugs according to Common Toxicity Criteria most are at degree 1 is anemia 86.99%, leukopenia 21.74% and thrombocytopenia 13.04%.

Although based on the results of the study revealed that children who undergo chemotherapy LLA will experience hematological toxicity, but this has not become more attention by health workers, especially by nurses. In fact according to Metha and Hoffbrand (2012), hematological toxicity can cause adverse effects on patients if not addressed immediately ie the infection and bleeding. In addition, the existence of hematological toxicity can also lead to delayed treatment and also reduction of doses of chemotherapy drugs (Cancer Agency, 2015). According to Alcazar, Enrique, Ruiz et al (2013) also, hematological toxicity can also cause complications such as infection and bleeding, but can also increase the risk of relapse due to neutropenia, thrombocytopenia and the effects of cessation. Also known about 1 to 2% of children LLA died due to toxic effects during treatment (Hunger & Mullighan, 2015). Therefore, it is important for nurses to observe the presence of hematological toxicity during patients undergoing chemotherapy. However, the assessment of hematology in LLA child patients is sometimes only used as an indicator of the general state of the patient before and after undergoing chemotherapy. So nurses tend not to pay much attention to hematological toxicity after chemotherapy and do not even make nursing efforts such as monitoring or health education in anticipating the effects of hematological toxicity to the patient's parents or prevention efforts (Karch, 2011).

Based on data in 2015 known that the cancer in children in West Java Province were 1783 cases with the most cases are leukemia (822 cases). Leukemia cases in children consist of LLA which is the most cases of 745 children, LMA cases are 57 children, and non-specific leukemia there are 20 children. Throughout 2016 it was known that the case of leukemia in hospital in Bandung increased every month with the average LLA patients per month is +55 cases. In addition, based on data from 2015-2016 it was known that the highest mortality rate in children was due to treatment during chemotherapy treatment. Based on observations in one hospital in Bandung, almost all of leukemic's children experienced hematological toxicity during the consolidation phase. So patients should be given transfusions either blood transfusions or thrombocytes, leukogens to raise leukocytes, antibiotics as a treatment / prevention of infection and also other drugs. This tends to increase the length of hospitalization of LLA-treated children with chemotherapy. In addition, sometimes after a week patients complete chemotherapy will come back to the hospital for treatment due to leukopenia or anemia and thrombocytopenia.

This study was aimed to determine the hematological toxicity post-chemotherapy in children with acute lymphoblastic leukemia in Hospital in Bandung.

II. METHOD

This research is a desctiptive study with retrospective approach. The sample of this research were children with leukemia lymphoblastic acute who underwent chemotherapy during consolidation and maintenance phase during January-July
2016 in one hospital in Bandung. Method of data collecting were study of documentation. Data taken from medical record.

Laboratory results to be viewed based on Common Criteria for Adverse Event (CTCAE v3) with toxic (grade 1-5) and non-toxic (grade 0) criteria. Data analysis used in this study was univariate analysis by distribution of frequency.

RESULTS

The characteristic of subjects of the study can be seen in table 1:

Table 1
Distribution of Childhood LLA Characteristics undergoing Chemotherapy (n = 198)

<table>
<thead>
<tr>
<th>No</th>
<th>Characteristics</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>118</td>
<td>59.6</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>80</td>
<td>40.4</td>
</tr>
<tr>
<td>2.</td>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1 year</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1-6 year</td>
<td>112</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td>6-11 year</td>
<td>51</td>
<td>25.8</td>
</tr>
<tr>
<td></td>
<td>&gt;11 year</td>
<td>34</td>
<td>17.2</td>
</tr>
<tr>
<td>3.</td>
<td>Chemotherapy phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consolidation</td>
<td>71</td>
<td>35.9</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>127</td>
<td>64.1</td>
</tr>
</tbody>
</table>

Based on table 1, it can be seen that the characteristics of LLA children who underwent chemotherapy, children with male (59.6%) was higher compared with female (40.4%). More than half (56.6%) was 1-6 years old and the ongoing phases of chemotherapy were mostly in the maintenance phase of 127 respondents (64.1%).

Hematological toxicity that occurs in patients after chemotherapy has two criteria that is toxic and non toxic. Toxic and non-toxic criteria based on grade of modified Common Toxicity Criteria ie grade 0 are non toxic and grade 1-5 are toxic. The most hematological toxicity were mostly experience were leukopenia/leukositos, then trombositopeni and anemia. In this study there were 128 respondents (64.6%) were experience hematological toxicity and 70 respondents (35.4%) were not experience hematological toxicity (showed in table 2)

Table 2
Hematological Distribution of Toxicity Post-Chemotherapy of LLA Children
In Dr Hasan Sadikin Bandung General Hospital from January to July 2016 (n = 198)

<table>
<thead>
<tr>
<th>Hematological Toxicity</th>
<th>n</th>
<th>f (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Toxic</td>
<td>70</td>
<td>35.4</td>
</tr>
<tr>
<td>Toxic</td>
<td>128</td>
<td>64.6</td>
</tr>
</tbody>
</table>
IV. DISCUSSION

LLA children who underwent chemotherapy in this study more than half (59.6%) were male and nearly half (40.4%) were female. Leukemia is more common in men than in women (Wong, Eaton, Winkelstein, Wilson, & Schwatz, 2009). Studies of children with LLA suggest that LLA is more common in boys than girls. According to research Sulastriana, Young and Jemadi (2012) note that children with acute leukemia more commonly found in men compared with women with a ratio of 1.4:1.

According to Hossain's research, Xie and McCahan (2014) also note that male in LLA children is the most abundant. Also in this study it was found that male sex had a poor prognosis even with a probability of 1.29 times more likely to result in death than women. Males have a poor initial response to experience remission compared to women. Other studies suggest that resistance to chemotherapy is associated with sex caused by differences in drug metabolism in which boys are more tolerant of cumulative dose of mercaptopurine than girls, allowing for earlier relapse. So men have a higher risk for relapse, especially in hematologic than in women. Nevertheless, according to research by Isnani, Perwitasari and Andalusia (2014) it is known that sex does not affect the decrease of hemoglobin value (p=0.499), leukocytes (p=0.554) and platelets (p=0.349) after chemotherapy treatment.

In this study, 56.6% respondents were aged 1-6 years, 0.5% were <1 year, 25.8% were age 6-11 years and 17.2% were >11 years old. Previous study stated that leukemia were common in children over 1 year and its peak occurrence occurs between the ages of 2 and 6 years (Wong, Eaton, Winkelstein, Wilson, & Schwatz, 2009). According to de Sousa's study, Ferreira Felix, Et al (2015) who found that most (75%) of LLA children aged 1-9 years, only a small part (2.6%) Children under 1 year and a small portion (22.4%) children over 9 years. According to Bangun (2012), the average age of children with leukemia were in school age (mean=6.37 years). According to Ninuri and Ariawati (2013) also found that LLA children who experience haematological disorder after chemotherapy treatment mostly (88.2%) were aged 1-10 years.

Age at the time of diagnosis is known to be a prognostic factor in LLA children. According to Hossain's study, Xie and McCahan (2014), LLA children diagnosed with LLA at 1-4 years old are the age group with fewer deaths than infant (0-12 months). Children diagnosed with LLA under 1 year according to some studies have poor outcomes, have very low event free survival (EFS) and death-inducing toxicities (Hilden, et al., 2006; Ibagy, et al., 2013). The hallmark of infant-aged LLA is usually the occurrence of hyperleocytosis at the time of diagnosis and when the patient undergoing chemotherapy treatment dies before achieving remission. According to de Sousa, Ferreira Felix., Et al. (2015) it is well known that children under 1 year old have an unfavorable prognosis associated with high WBC count, Pro-B immunophenotype, CD10 (-), hepatosplenomegaly and poor response to treatment during phase induction. While in the research that researchers do this there is only 1 (0.5%) LLA children who age infant who managed to achieve remission and was doing chemotherapy treatment in the consolidation phase, but from the results...
known LLA children who are undergoing chemotherapy at infant age in this study instead. Having leukopenia with leukocytes 2200 / mm3. However, it is not very clear whether all infant-aged children in the consolidation phase will have leukopenia compared with leukocytosis because the samples found are only 1. However, according to Ibagy, Silva, Seiben, et al (2013) it is known that intensive chemotherapy in infant can cause severe neutropenia for a long time and the patient will become infected and eventually die due to septic shock.

According to Hossain’s research, Xie and McCahan (2014) found that when aged 1-4 years diagnosed and received intensive treatment would be more survive when compared to age 0-12 months or children over the age of 4 years. Children over 9 years are also estimated to have a poor prognosis and is known to have a high relapse incidence and short survival. At the age of children over 9 years it is known that this is associated with high WBC count, T-cell immunophenotype, non-adherence and tolerance to treatment (de Sousa, Ferreira, Felix, & Lopes, 2015).

So in this case it is known that age has an influence on prognosis and is associated with the occurrence of relapse, but based on other studies said that age has no relation to the occurrence of relapse and also the occurrence of hematological toxicity. In the study Bangun (2012) note that the age of LLA children who underwent chemotherapy did not have a significant relationship with the incidence of relapse (p = 0.111). According to the research of Isnani, Perwitasari, Andalusia et al (2014) it is known that age has no effect on hematological toxicity either on the decrease of hemoglobin (p = 0.499), leukocytes (p = 0.752) or platelets (p = 0.349) at the time of chemotherapy. Especially in the maintenance phase.

In the study during January-July 2016 it was found that LLA children who underwent chemotherapy almost half (35.9%) were in the consolidation phase and more than half (64.1%) were in the maintenance phase. Chemotherapy treatment is an effective treatment for LLA children today. Chemotherapy treatment in children LLA consists of three phases namely induction phase, consolidation and maintenance. The consolidation phase is performed when the patient has reached remission after the induction phase treatment, while the maintenance phase is performed when the patient has undergone a consolidation phase treatment. The large number of LLA children undergoing chemotherapy until the maintenance phase indicates that an increasing outcome of therapy outcome for LLA. Although at the time of data collection it is known that there are some respondents who have entered consolidation phase or maintenance experience relapse so it must return to follow treatment in induction phase (re-induction). In addition, from the results of the study was found there are 1 respondent who died during the consolidation phase during chemotherapy treatment. So even if the patient is in remission and in the consolidation or maintenance phase, the need for strict observation and monitoring to avoid the side effects of chemotherapy during this phase that allows for death. Because although chemotherapy treatment is an effective treatment in the treatment of leukemia, the possible side effects of chemotherapy are sometimes more severe
than those of leukemia itself (Ariawati, Windiastuti, & Gatot, 2007).

**Hematological toxicity**

Chemotherapy is sometimes associated with different deaths per phase. Side effects arising from chemotherapy are sometimes more severe than the symptoms of leukemia itself (Ariawati, Windiastuti, & Gatot, 2007). Side effects arising from chemotherapy usually consist of infection, bleeding and other toxicities caused by chemotherapy treatment that can cause death. According to the Pinontoa study, Mantik and Rampengan (2013) it is known that chemotherapy treatment affects the hematology profile of LLA children where the hematology profile of LLA children treated in RS Prof Dr. R. D. Kandau Manado changes every week either leukopenia, leukositosis or thrombocytopenia. According to Asim's research, Zaidi, Ghafoor, et al. (2011) found that in 304 new cases of ALL during 2001-2005, 74 died during chemotherapy and more than half (53%) of LLA children died in the induction phase and nearly half 44%) occurs in the consolidation and maintenance phase.

In this study it was found that more than half (64.6%) of LLA children who underwent chemotherapy in the consolidation and maintenance phase experienced hematological toxicity and nearly half (35.4%) who did not experience hematological toxicity. This is similar to the research of Nisa, Niruri and Ariawati (2013) which is known that from 17 patients LLA 14 children have hematologic disorders while undergoing chemotherapy treatment in the induction phase and consolidation phase.

In this study, when viewed based on the grade of each blood test result in the form of Hb, leukocyte and platelet, it is known that most LLA children who undergo chemotherapy treatment consolidation and maintenance phase are in grade 0, where most (68.2%) did not decrease Hb, Almost half (48.5%) did not decrease leukocytes and most (89.4%) did not decrease platelets. So it is known that most children LLA in this study when viewed from any blood test results did not experience hematological toxicity, but in each patient toxicity occurs different. In one patient it may be only one or two that have decreased or all three have decreased.

In the results of this study it is known that LLA children who underwent chemotherapy in the consolidation phase and maintenance more than half (64.6%) experienced hematological toxicity.

Based on Nisa's research, Niruri and Ariawati (2013), it was found that in 17 LLA patients, different hematologic disorders, 8 patients (47.1%) were known to only decrease Hb alone, 6 patients (35.3%) decreased Hb and decreased platelets, and 3 patients (17.6%) who did not decrease Hb and decreased platelets. According to the research of Isnani, Perwitasari, Andalusia, et al (2014) was also known that the incidence of hematological toxicity that occurs in 23 children who underwent chemotherapy in the maintenance phase is anemia that is 95.66%, while based on the severity according to the Common Toxicity Criteria the occurrence of Hb, The decrease of leukocyte and platelet drop in at most of degree 1 with presentation respectively were 86,96%, 21,74% and 13,04%. So it can be concluded from these studies that LLA children who undergo chemotherapy will mostly experience hematological toxicity despite the different toxicity that occurs.
Hematological toxicity after chemotherapy causes some of the effects that arise in the patient. The impact of hematological toxicity is the presence of infection, bleeding and anemia that cause the patient to be treated longer in the hospital due to blood transfusion, antibiotic treatment and leukogen (as a white blood cell enhancer) should be given gradually and take several days. In addition chemotherapy treatment becomes delay and the dose of chemotherapy is reduced. The worst impact of the existence of hematological toxicity is the relapse and death that became the scourge of the most feared by patients and also parents of patients (Alcazar, Enriquez, Ruiz, Gutierrez, & Arangure, 2013). According to Asim's research, Zaidi, Ghafoor., Et al (2011) found that of 74 LLA children who died during chemotherapy treatment, 63 (85%) died from infection, 8 (10.8%) died of bleeding and 3 %) Due to the other toxicity of chemotherapy treatment. Death caused by infection that occurs consists of infections of the lungs and digestive tract, whereas death caused bleeding due to intracranial hemorrhage, gastrointestinal tract and respiratory tract.

V. CONCLUSION

Results of this study showed that 64.6% of respondents experienced hematological toxicity and 35.4% who did not experience hematological toxicity. Further studies on the effects of hematological toxicity on the quality of life of LLA children should be conducted. It is important for nurses to observe the presence of hematological toxicity during children undergoing chemotherapy. Nurses must tend to pay much attention to hematological toxicity after chemotherapy and made hematological assessment properly. Nurses should continously monitor the effects of hematological toxicity in children as prevention intervention.

REFERENCE


experience. *Journal de Pediatria*, 64-69.


