Introduction

Leukemia is the most common childhood malignancy, accounting for more than one-third of all childhood cancers. Most of the leukemia cases do not have some inherited genetic predisposition but from somatic genetic alterations. Many of these alterations have been characterized at the molecular level, which has pursued the identification of oncogenes and tumor suppressor genes that are closely tangled in leukemogenesis. Molecular analysis has both enhanced perceptive of the pathogenesis and treatment management of childhood leukemia [1]. Molecular genetic testing helped to establish submicroscopic classification as well as minimal residual disease follow-up, considered to be responsible for relapse.

One of the popular genes involved in leukemogenesis is BCR-ABL1 fusion gene, a key regulator of the tyrosine kinase activity in leukemic cells. BCR-ABL1 fusion gene resulted from chromosomal translocations involves the breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (ABL) genes, a potent oncogene that drives leukemia. This translocation t(9;22) (q34; q11.2) is commonly named with the Philadelphia chromosome (Ph), which is defined as shortened chromosome 22 resulting in a translocation of chromosome 22 and 9 which leads to a juxtaposition of protooncogene c-abl and bcr on chromosome 22 [2]. The most common translocations generate fusion protein products with molecular weights of 190 and 210 kDa [3]; both protein variants have driven different signaling pathways in the leukemic cell [4,5]. These differences...
could underlie the distinct leukemogenic process induced by these two protein variants.

BCR-ABL1 can play an important role in addressing the issue of prognostic prediction and treatment choice. BCR-ABL1 fusion gene transcript engendered a protein that leads to constitutive active tyrosine kinase. Hence, BCR-ABL1 testing avails to identify patients with a good prognosis in CML patients or those with a high risk of treatment failure in ALL, who are considered for alternative therapy such as bone marrow transplantation [2]. With an upgraded understanding of BCR-ABL1 activity, Tyrosine Kinase Inhibitors like imatinib, nilotinib, and dasatinib have been developed, which specifically inhibit the activity of the BCR-ABL1 protein.

The objective of this study was to investigate the profile of childhood leukemia patients who have had a positive BCR-ABL1 fusion gene in “Dharmais” Cancer Hospital. This paper provides preliminary data and highlights the importance of BCR-ABL1 examination for the clinical management of childhood leukemia by a pediatric oncologist.

**METHODS**

This retrospective study had been ethically approved by The Health Research Ethics Committee of “Dharmais” Cancer Hospital in April 2020 with number 053/KEPK/IV/2020. Data were collected using epidemiology data which were obtained from Cancer Registry Data of “Dharmais” Cancer Hospital. The inclusion criteria were childhood leukemia patients who performed the BCR-ABL1 examination at “Dharmais” Cancer Hospital from March 2008 to August 2018. We analyzed the demographic data, leukemia types, BCR-ABL1 examination results, and protein isoforms generated by BCR-ABL1 fusion gene itself. Descriptive data analysis was performed using Statistic Package for Social Service (SPSS) version 22.

All samples were peripheral blood or bone marrow, then processed quickly into Mononuclear Cell (MNC). The status of the BCR-ABL1 rearrangement in all patients was assessed using Polymerase Chain Reaction (PCR) technique. Finally, electrophoresis was carried out for data visualization at the end steps.

**RESULTS**

Samples enrolled in this study were 79 respondents, 43 of whom were from other institutions. Among 79 samples, 65.8% (52/79) of them were males and 34.2% (27/79) were females. Most of them were in the age group of 6 to 18 years. A total of 74.7% (59/79) samples were diagnosed with CML, 21.5% of whom were diagnosed with ALL (17/79), and the lowest proportion was AML, which only included 3 patients.

| Characteristics | n (%) |
|-----------------|-------|
| **Gender** (n=79) | |
| Males | 52 (65.8) |
| Females | 27 (34.2) |
| **Leukemia Types** | |
| ALL | 17 (21.5) |
| CML | 59 (74.7) |
| AML | 3 (3.8) |
| **Age** (Median, years) | |
| ALL | 15 (3–18) |
| CML | 16 (0.16–18) |
| AML | 14 (4–17) |

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CML: chronic myeloid leukemia

Among all leukemia types, the BCR-ABL1 fusion gene was detected in 2 among 17 ALL samples, 43 (72.9%) among 59 CML patients, and none among AML samples. Based on the protein isoforms generated by BCR-ABL1 fusion, 210-kDa protein was mostly found in our samples, rather than 190-kDa protein isoforms.

| Leukemia Types | n (%) |
|----------------|-------|
| **CML (n=59)** | |
| BCR-ABL (+) | 43 (72.9) |
| > p210 | 42 (97.7) |
| > p190 | 1 (2.3) |
| BCR-ABL (-) | 16 (27.1) |
| **AML (n=3)** | |
| BCR-ABL (+) | 0 (0) |
| BCR-ABL (-) | 3 (100) |

**DISCUSSION**

Leukemia is the most common type of childhood cancer, accounting for more than one-third of all childhood cancers [6]. Leukemia itself is classified into several subtypes, while those discussed in this paper are ALL, CML, and AML subtypes. Of all pediatric leukemia cases, the highest number was ALL subtype; the case is almost 80% among others [6], while CML are the fewest cases. This paper presents demographic data about the number of pediatric leukemia patients who performed a qualitative BCR-ABL examination at
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the “Dharmais” Cancer Hospital from 2008 to 2018. Based on our Cancer Registry Data, a total of 79 samples of pediatric leukemia patients were obtained from our institution. From a total of 79 patients, the majority were CML patients which are accounted for 74.7% (59/79) due to BCR-ABL1 fusion gene as the main characteristics in CML and represented for approximately 95% of cases [7]. Apart from the many cases, the positive BCR-ABL1 in CML is also used to assess therapeutic responses [6]. Hence, the test was conducted more frequently for CML than ALL and AML.

The number of pediatric ALL patients who were checked for their BCR-ABL1 status was only 17 children among 79 patients. The examination of BCR-ABL1 in ALL patients is also important due to its use as a prognostic marker. Children with BCR-ABL1 fusion in ALL represent a subgroup at very high risk for treatment failure, despite intensive chemotherapy [8,9], and only 20-30% of childhood ALL with BCR-ABL1 positive are cured with chemotherapy [10]. However, BCR-ABL1 fusion genes only occur in 2% to 4% of pediatric ALL cases (1,8,11); consequently, the BCR-ABL1 examination is rarely performed in pediatric ALL patients. Positive BCR-ABL1 in childhood ALL is associated with higher leukocyte count and more frequent central nervous system leukemia at diagnosis (12). So, routine BCR-ABL1 examination is important to do for pediatric ALL even though the positive results would be very rare. The small number of pediatric ALL who performed BCR-ABL1 examination was not only due to the small number of BCR-ABL1 positive but also due to quite an expensive price, especially before covered by The Indonesian National Health Insurance. However, right now in our institution, BCR-ABL1 examination has already been covered by the Government. So, the BCR-ABL1 examination has already been established and used for clinical services in our institution since 2008.

Almost similar to ALL, the BCR-ABL1 examination in pediatric AML patients is very rare, only accounted for 3 children from 79 patients. According to Neudendorff et al. [10], positive BCR-ABL-in acute myeloid leukemia (AML) is a rare subtype of AML and the prognosis of AML with BCR-ABL positive seems to depend on the cytogenetic and/or molecular background rather than on BCR-ABL1 itself. It is also stated in those papers that therapy using tyrosine kinase inhibitors (TKIs) is much more active kinase [18,19]. This information explained why pediatric ALL patients, in which the majority is represented for approximately 1%, have shown poor prognosis.

Concerning protein products generated by BCR-ABL1 fusion gene, almost all patients diagnosed with CML carry the p210 protein, whereas p190 is very rare (~1% cases) [16]. In accordance with this, our data show that the proportion of p210 is 97.7% (42/43), whereas p190 is only 2.3% (1/43). In contrast, the p190 protein is prevalent in ALL, notably in pediatric patients [16]. Our data have shown there are 1 of 2 pediatric ALL patients with positive BCR-ABL1 who have p190. In less frequent cases, both transcripts can be coexpressed resulting in p210 and p190 simultaneously, and we have 1 case corresponding to this. Recent research has reported the differences in signaling pathways through p190 and p210 BCR-ABL1 fusion proteins in the leukemic cell [16,17]. The study which investigated direct comparison between p190 and p210 by in vitro kinase activity assays has shown that p190 exhibits higher autophosphorylation than p210, leading to the conclusion that p190 is likely a more active kinase [18,19]. This information explained why pediatric ALL patients, in which the majority is p190, have shown poor prognosis.

This study is based on the data collected from our institution only; thus, the small number of the research subjects is a major limitation for this study. The analysis and conclusion drawing should be carried out carefully. One of the possible reasons is due to the BCR-ABL1 examination has not yet been used for routine diagnosis for all childhood leukemia patients, particularly for both ALL and CML, which has been proven to have a clinical impact. Moreover, further studies should be carried out...
BCR-ABL1 examination was useful for CML and ALL patients to get the right decision for using Tyrosine Kinase Inhibitors (TKIs)-based therapy. CML patients with positive BCR-ABL1 have shown better prognosis, but ALL patients have shown poorer prognosis. The clinical use of specific BCR-ABL1 inhibitors has resulted in a significantly improved prognosis, response rate, overall survival, and patient outcome in CML (20). In ALL, BCR-ABL1 status was also used to determine the use of TKIs, but originally ALL patients with positive BCR-ABL1 have shown worse prognosis than negative ones.

CONCLUSIONS

The proportion of positive BCR-ABL1 fusion gene in CML patients was 73.3%, in ALL patients 11.8%, while none in AML patients. Future studies should more closely examine the association between protein isoforms and patients’ clinical manifestation to assess the differences in the patient clinical impact or response of treatment. The study contributes to our understanding of the importance of routine BCR-ABL1 examination for childhood leukemia, particularly for ALL and CML.

DECLARATIONS

Competing of Interest
The authors declare no potential conflicts of interest.

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