

# Chronic Myeloid Leukemia (CML) at National Referral Hospital in Indonesia

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## ABSTRACT

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome and BCR-ABL fusion oncogene. CML is one of the illnesses that may be treated using Tyrosine Kinase Inhibitors (TKIs), a type of targeted therapy. Since TKIs are the standard of therapy, long-term survival of CML has improved compared to chemotherapy and interferon-alpha. For the first-line treatment for CML, there are four commercially available TKIs that serve as an integral part of the disease management. However, there are many challenges in diagnosing, treating, and monitoring patients with chronic phase CML in Indonesia. This study highlights the epidemiology data of chronic phase CML patients, particularly at Dr. Cipto Mangunkusumo General Hospital, an Indonesian national referral hospital, and how to diagnose, select first-line TKIs, and monitor the response of treatment after TKIs administration.

**Keywords:** Chronic phase chronic myeloid leukemia; epidemiology; diagnosis; treatment; monitoring (Siriraj Med J 2022; 74: 530-536)

## INTRODUCTION

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia (Ph) chromosome. The BCR-ABL fusion gene is produced by a reciprocal translocation between the ABL region of chromosome 9 and the breakpoint cluster region (BCR) section of chromosome 22 [t(9;22)(q34;q11)].<sup>1,2</sup> Cell proliferation, cytoskeletal disorganization, decreased cell apoptosis, enhanced mitogenic signaling, decreased cell differentiation, decreased cell adhesion, and increased cell motility are all caused by the BCR-ABL gene, which codes for transcripts with strong tyrosine kinase activity.<sup>3,4</sup>

Most CML patients present asymptomatic cases and are diagnosed in the early chronic phase. However, most patients in Indonesia and other Asia are symptomatic and diagnosed in the late chronic phase.<sup>3</sup> In Asian countries, CML tends to affect younger people than in Western countries.<sup>5</sup> The diagnosis is usually established by conventional cytogenetics and Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of BCR-ABL.<sup>2</sup>

Treatment of CML has changed drastically, and in the 1980s, Busulfan, allogeneic bone marrow transplantation, and interferon-alpha were used as therapy for CML. After that, hydroxyurea was used as standard therapy of CML,

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and in the 2000s, the first-generation TKI, Imatinib, was used as the first-line therapy.<sup>6</sup> There are four commercially available TKIs as first-line therapy: Imatinib, Dasatinib, Nilotinib, and Bosutinib.<sup>7</sup> The most appropriate first-line therapy is selected based on the patient's characteristics and the availability in each nation or healthcare facility. Currently, only Imatinib, Nilotinib, and Ponatinib are available in Indonesia.

Dr. Cipto Mangunkusumo General Hospital is a national referral hospital that receives referrals from all provinces. This study determines CML's epidemiology, establishes the diagnosis of chronic phase CML, treats and monitors treatment response, and compares the findings to other countries.

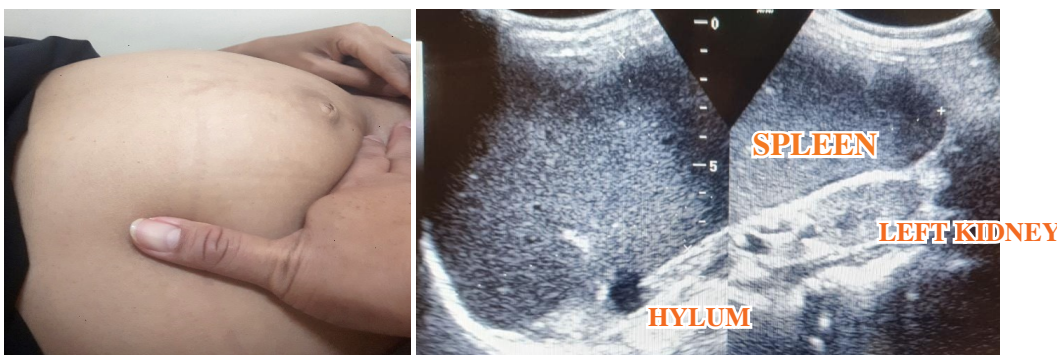
### Epidemiology

The proportion of CML is about 15% of all adult leukemia cases.<sup>2</sup> In the USA, the median age of diagnosis is 67 years, and between 60 to 65 years in Europe.<sup>1,2</sup> CML is less common in Asia than in Western countries, and it tends to strike at a younger age.<sup>5,8</sup> The median age in China, Hongkong, India, Philippines, Singapore, South Korea, Thailand, and Malaysia is between 36-55 years.<sup>8-10</sup> These countries showed a higher occurrence in males than females.<sup>8,10</sup> Indonesia has a similar situation, with a median age of 34-35 years (mean 36 years) and a male to female ratio of 1.5:1.<sup>9</sup> At Dr. Cipto Mangunkusumo General Hospital, the mean (SD) age of diagnosis is 39 (13) years old.<sup>11</sup> A previous study conducted between 2003 and 2008 revealed comparable findings, with the median age of diagnosis being 37 years and a male to female ratio of 1.2:1.<sup>12</sup> Based on these data, the epidemiology of CML patients at Dr. Cipto Mangunkusumo General Hospital and Indonesia is similar to Asia.

CML is a triphasic disease consisting of chronic, accelerated, and blast crisis phases. Patients in the chronic phase are frequently asymptomatic, and symptoms are mainly attributable to anemia and splenomegaly. The most common symptoms are fatigue, unexplained weight loss, left upper quadrant abdominal discomfort or pain, and early satiety. In the chronic phase, bleeding manifestations

or priapism are infrequent, although splenomegaly is often observed on physical examination (40-50%).<sup>2</sup> Severe leukocytosis with a shift to the left, «myelocyte bulge» (more myelocytes than mature metamyelocytes), blast <2%, basophilia, eosinophilia, and increased platelet count (thrombocytopenia only in advance cases) are common laboratory results.<sup>13</sup> The World Health Organization defines accelerated phase CML as having one or more of the following characteristics: persistent or increasing white blood cells (WBC) >10x10<sup>9</sup> cells/L, persistent or increasing splenomegaly, persistent thrombocytosis or thrombocytopenia unresponsive to therapy, >20% basophils in peripheral blood, 10-19% blast in peripheral blood or bone marrow, and additional clonal chromosome abnormalities.<sup>14</sup> Meanwhile, CML is characterized as being in the blast phase when there is more than 20% blast in the peripheral blood or bone marrow or extramedullary involvement (excluding liver and spleen).<sup>2</sup>

The majority (90-95%) of CML patients are diagnosed in chronic phase CML (CP-CML)<sup>3</sup>, and approximately 50% in the USA and Europe are asymptomatic.<sup>2,3</sup> CML is usually detected during a routine physical examination or blood tests.<sup>3</sup> In the study conducted by Tadjoeidin, 72.7% of CML patients at Dr. Cipto Mangunkusumo General Hospital are classified as chronic phase, 23.9% accelerated phase and 3.4% blast crisis phase.<sup>15</sup> Most patients (83.3%) at Dr. Cipto Mangunkusumo General Hospital came with symptoms such as fatigue, night sweating, abdominal discomfort, and abdominal mass. Splenomegaly was detected in 82% of CML patients<sup>11</sup>, and uncommon signs such as priapism and hyperleukocytosis were discovered owing to leukemic cell aggregation in the corpus cavernosum and the dorsal vein of the penis.<sup>16</sup> The majority of patients with chronic phase CML are symptomatic, and the proportion of splenomegaly is higher than in America and Europe. Laboratory also showed similar results from Western countries, which are leukocytosis with basophilia, immature granulocytes (promyelocyte, myelocyte, metamyelocyte), few blasts, mild anemia, and thrombocytosis.<sup>11</sup>



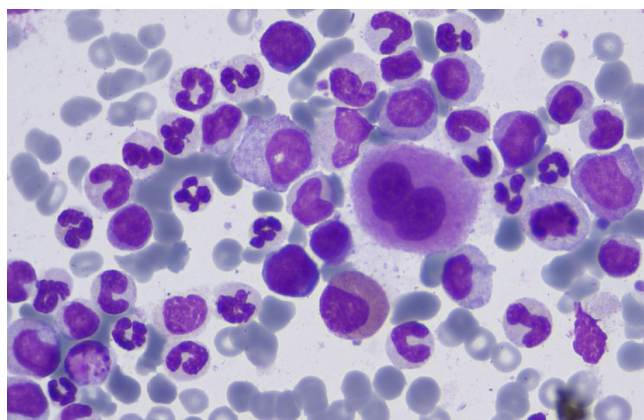
**Fig 1.** The percentage of splenomegaly in chronic phase CML patients at Dr. Cipto Mangunkusumo General Hospital was 82%. Splenomegaly can be detected clinically by palpation (left) or by bedside ultrasound (right).

## Diagnosis

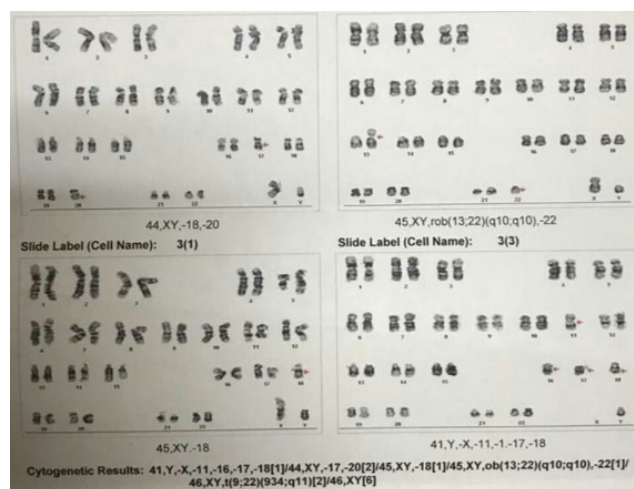
CML is suspected when there is unexplained leukocytosis, which is validated by bone marrow aspiration and biopsy and qualitative RT-PCR on peripheral blood cells. Bone marrow aspiration and biopsy samples are sent for cytogenetics and morphology examination. Morphology examination is essential to distinguish CML phases: chronic phase, accelerated phase, and blastic crisis phase.<sup>7,17</sup> Furthermore, qualitative RT-PCR is required to identify the BCR-ABL transcripts while monitoring therapeutic response.<sup>7</sup> Fluorescent in situ hybridization (FISH) is needed when Ph-chromosome is undetected in cytogenetics evaluation.<sup>2,7</sup>

At Dr. Cipto Mangunkusumo General Hospital, bone marrow aspiration was routinely performed for morphology and conventional cytogenetics evaluation. The sample was sent to Dharmas Hospital, the National Cancer Centre, or a private laboratory for qRT-PCR. In addition, the Philadelphia chromosome was evaluated using cytogenetic karyotyping. BCR-ABL transcripts are measured by multiplex reverse transcriptase-polymerase chain reaction (RT-PCR).

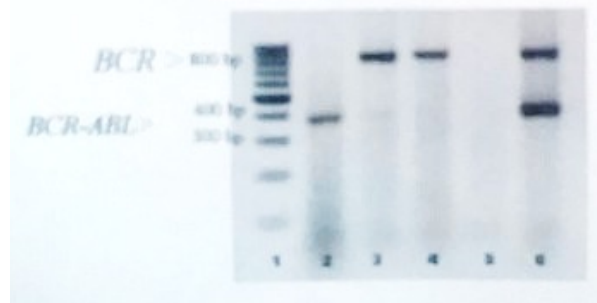
In addition to confirming the diagnosis, the risk of every CML patient before treatment was calculated. The three most common prognostic scores are Sokal, Hasford/Euro, and EUTOS Long-Term Survival (ELTS), as depicted in Table 1. Sokal score was introduced in 1984 during the chemotherapy era, while Hasford/Euro score came during the interferon-alpha era and ELTS score during the TKI era. Sokal and Hasford scores calculate overall survival probabilities, disease progression and predict therapeutic response. Meanwhile, the ELTS score calculates the probabilities of death due to CML.<sup>18</sup> All prognostic scores classify CML patients into low, intermediate, and high-risk profiles. Sokal and ELTS scores



**Fig 2.** Bone marrow morphology of patients with chronic phase CML showed dwarf megakaryocytes, mature granulocytes (segments and bands), immature granulocytes (promyelocytes, myelocytes, metamyelocytes), and a few blasts.



**Fig 3.** Conventional cytogenetics of a patient with chronic phase CML who progressed into accelerated phase after first-line treatment of Imatinib which showed complex karyotype abnormalities including Philadelphia chromosome.



**Fig 4.** Multiplex RT-PCR for BCR-ABL

were calculated based on the patient's age, spleen size, platelet count, and blast percentage in peripheral blood. In addition to the variables above, data on eosinophil and basophil are needed to calculate the Hasford score.<sup>1</sup> According to Tadjoein, CML patients at Dr. Cipto Mangunkusumo General Hospital, are divided into three groups: low risk (39.8%), intermediate-risk (22.7%), and high risk (37.5%) Sokal score.<sup>15</sup> For patients with intermediate to high risk, the most contributing factors are splenomegaly, followed by thrombocytosis. The risk stratification according to these scores, along with disease duration, history of treatment with hydroxyurea, and the phase of CML correlates with the response to therapy with TKI, particularly Imatinib.<sup>15</sup>

## Treatment

There are many revolutionary changes in CML treatment before Tyrosine Kinase Inhibitors (TKIs) therapy. In 1960, busulfan was used as a CML therapy, followed by hydroxyurea, which is superior to busulfan. Then in 1980, interferon-alfa became the standard therapy for CP-CML. During 1990, allogeneic hematopoietic stem



**TABLE 1.** Comparison of Sokal, Hasford/Euro, and ELTS Scores.

	Sokal	Hasford/Euro	ELTS
Factors	Age, spleen size, platelet count, blast percentage	Age, spleen size, platelet count, blast percentage, basophils percentage, eosinophils percentage	Age, spleen size, platelet count, blast percentage
Formula	$\text{Exp } 0.0116 \times (\text{age}-43.4) + 0.0345 \times (\text{spleen}-7.51) + 0.1880 \times [(\text{platelet count}/700)^2 - 0.563] + 0.0887 \times (\text{blasts} - 2.10)$	$(0.6666 \times \text{age} [0 \text{ when age } < 50 \text{ years; } 1, \text{ otherwise}] + 0.0420 \times \text{spleen} + 0.0584 \times \text{blasts} + 0.0413 \times \text{eosinophils} + 0.2039 \times \text{basophils} [0 \text{ when basophils } < 3\%; 1, \text{ otherwise}] + 1.0956 \times \text{platelet count} [0 \text{ when platelets } < 1,500 \times 10^9 / \text{L}; 1, \text{ otherwise}]) \times 1,000$	$0.0025 \times (\text{age}/10)^3 + 0.0615 \times \text{spleen} + 0.1052 \times \text{blasts} + 0.4104 \times (\text{platelet count}/1000)^{-0.5}$
Risk	Low risk: <0.8 Intermediate risk: 0.8–1.2 High risk: >1.2	Low risk: ≤780 Intermediate risk: 781–1,480 High risk: >1,480	Low risk: ≤1.5680 Intermediate risk: 1.5680–2.2185 High risk: >2.2185

cell transplantation became the first-line therapy for CP-CML patients below 50 years old, while interferon-alpha (IFN- $\alpha$ ) is indicated for those who are contraindicated to transplantation. In the meantime, in 1986, BCR-ABL oncoprotein was discovered, resulting in TKI targeted therapy. Firstly, Imatinib was used only as therapy for IFN- $\alpha$  resistant patients. However, in 2000, Imatinib 400 mg/day was designated as the first-line therapy for CP-CML after the International Randomized Study of Interferon and STI 571 (IRIS) revealed that Imatinib outperformed IFN- $\alpha$  in terms of cytogenetic response, event-free survival, progression-free survival, and overall survival.<sup>6</sup>

The United States Food and Drug administration (FDA) and European Medicines Agency (EMA) have authorized four TKIs as first-line therapy: one first-generation TKI (Imatinib) and three second-generation TKIs (Dasatinib, Nilotinib, and Bosutinib). In South Korea, Radotinib, the fifth TKI, has been approved<sup>7</sup> and TKIs are effective as CP-CML therapy. However, second-generation TKIs are associated with lesser disease progression and faster cytogenetic and molecular responses. There are no differences in terms of overall survival<sup>1</sup>, and based on data from phase 3 study RERISE, Radotinib results in earlier and more profound molecular responses than Imatinib.<sup>19</sup> Ponatinib, a third-generation TKI, may be therapy for those with BCR-ABL mutation or resistance

to  $\geq 2$  TKIs.<sup>7</sup> Selecting first-line treatment for patient CML should be based on the patient's age, risk score, comorbidities, response to therapy, side effects, and availability. Disease progression is more common in those with intermediate to high-risk Sokal or Euro scores, therefore, second-generation TKIs are preferred. Second-generation TKIs are also preferred for younger patients, specifically females, due to a faster response that may allow therapy discontinuation for fertility purposes.<sup>1</sup> Imatinib is recommended for older patients, specifically those with comorbidities, as the drug is safer in terms of adverse effects, specifically in patients with cardiovascular disease. Nilotinib usage is contraindicated in those with cardiovascular or metabolic disorders. Meanwhile, Dasatinib is contraindicated in patients with lung disease. Bosutinib should not be chosen as first-line therapy for hepatic or gastrointestinal disease patients.<sup>7,20</sup> Consumption of food with high-fat content and nilotinib should be avoided because of the effect on drug bioavailability.<sup>20</sup>

In the last decade, the therapy of CML has developed significantly. Before 1980, busulfan is the only available agent for the therapy of CML in Indonesia. Around 1987-1988, allogeneic bone marrow transplantation (BMT) was introduced as CML therapy at Dr. Cipto Mangunkusumo General Hospital, Jakarta, with interferon-alpha. Hydroxyurea became available in Indonesia in

1989-1990 and was used as a CML therapy, and in February 2002, first-generation TKI Imatinib mesylate was approved by the Indonesian FDA (Badan Pengawasan Obat dan Makanan/BPOM). In 2003, The Glivec® International Patient Assistance Program (GIPAP) helped patients with chronic phase CML access imatinib by covering Imatinib's cost. It was replaced by Novartis™ Oncology Access (NOA) in 2008, and Indonesia National Health Insurance has covered Imatinib fully since 2009. Second generation TKI, Nilotinib, got approval by the BPOM in 2007, and in 2013, nilotinib was approved by BPOM and fully covered by Indonesian National Health Insurance. Ponatinib gets approved by BPOM in 2019, but Indonesia National Health Insurance does not cover it. Currently, the first-line therapy for CML is Imatinib, with nilotinib as second-line therapy. Nilotinib may be considered initial therapy for those with intermediate to high-risk profiles or younger patients, specifically females, who plan to get pregnant. Before TKI, hydroxyurea was the standard therapy of CML. There were 73.9% CML patients at Dr. Cipto Mangunkusumo General Hospital who received hydroxyurea before Imatinib, with 27.3% for more than 6 months.<sup>15</sup> Recent studies showed an association between administration hydroxyurea for > 6 months with the inability to achieve significant molecular response (Major Molecular Response/MMR).<sup>21</sup>

## Monitoring

A good outcome depends not only on first-line therapy but also on monitoring the response to treatment, ensuring that the milestones are met, and intervening quickly when intolerance or resistance develops.<sup>20,22</sup> According to European LeukemiaNet (ELN) 2020, before

obtaining a complete hematological response, blood cell and differential count monitoring every two weeks is essential.<sup>7</sup> Patient is classified as reaching complete hematological response (CHR) when WBC count <10 x 10<sup>9</sup>/L, no immature granulocytes, basophils <5%, platelet count <450 x 10<sup>9</sup>/L, and no sign and symptoms with the non-palpable spleen.<sup>1,2</sup> Quantitative BCR-ABL (IS) has to be conducted every 3 months, even after the MMR is achieved, to monitor the therapy's molecular response.<sup>1,7</sup> Molecular response of therapy classified to early [BCR-ABL (IS) ≤ 10% on the 3<sup>rd</sup> and 6<sup>th</sup> month], major molecular response (BCR-ABL <0.1% or reduction ≥ 3-log mRNA BCR-ABL from baseline), and deep molecular response [BCR-ABL (IS) ≤ 0.01%].<sup>1</sup> Furthermore, achievement of CHR on 3<sup>rd</sup>, 6<sup>th</sup>, and 12<sup>th</sup> month is associated with MMR on 18<sup>th</sup> month.<sup>15</sup> CML therapy monitoring milestones are based on BCR-ABL transcripts (IS) at 3, 6, and 12 months, where it is classified as ideal (maintain current treatment), warning (close monitoring and consider changing treatment), or failure (change treatment).<sup>7</sup> Adherence to treatment also plays an important role in therapy outcome.<sup>23</sup>

At Dr. Cipto Mangunkusumo General Hospital, CHR was achieved by 74% of CP-CML patients in the 3<sup>rd</sup> month.<sup>12</sup> After completing CHR in the 3<sup>rd</sup> month, monitoring by qRT-PCR is conducted every 6 months. However, it is not covered by Indonesia National Health Insurance, thus, patients should pay for it themselves.

For those with treatment failure, evaluation of BCR-ABL mutation is recommended.<sup>24</sup> Mutation on the BCR-ABL kinase domain is associated with resistance to therapy, disease progression, and poor prognosis. T315I mutation is associated with resistance to Imatinib,

**TABLE 2.** The milestone of therapy based on BCR-ABL transcripts (IS).<sup>7</sup>

	Optimal	Warning	Failure
Baseline	NA	High-risk additional chromosome abnormalities, high-risk ELTS score	NA
3 months	≤ 10%	> 10%	>10%, confirmed within 1-3 months
6 months	≤ 1%	> 1-10%	> 10%
12 months	≤ 0.1%	> 0.1-1%	> 1%
Any time	≤ 0.1%	> 0.1-1%, loss of ≤ 0.1% (MMR)	> 1%, resistance mutations, high risk additional chromosome abnormalities

Adapted from: Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966-84.

Dasatinib, Nilotinib, and Bosutinib. T315A, F317L/I/V/C, and V299L resistant to Dasatinib. F359C/V and Y253H are resistant to nilotinib, while E255K/V, F359C/V, Y235H, and T315I mutations are linked to disease progression and recurrence.<sup>1</sup> According to a 2015 study, the following BCR-ABL mutations were discovered: N231Q, M35IT, E509G, c.661 662insG with 1555 1557insG, V506S, 1152C>T, and Y253H. Those with BCR-ABL mutations had an intermediate to high Sokal risk and did not produce a significant molecular response by the 18<sup>th</sup> month, therefore, BCR-ABL mutation plays a crucial role in disease progression.<sup>15</sup>

Overall survival of CP-CML treated with TKI from IRIS, DASISION, ENESTnd, TOPS, CML IV, and SWOG study varies between 83%-95%.<sup>1</sup> Unfortunately, CP-CML patients' overall survival at Dr. Cipto Mangunkusumo General Hospital is lower, which is 66%.<sup>12</sup> The decreased OS was due to the preponderance of patients arriving in the late chronic phase, with the majority presenting with splenomegaly and a greater Sokal risk.

### CML in The Era of COVID-19

Dr. Cipto Mangunkusumo General Hospital requires patients with chronic phase CML who regularly attend the hematology-medical oncology clinic to monitor their body temperature, wear a mask, and schedule a previous online appointment to minimize crowding. Furthermore, before admitting chronic phase CML to the ward, Dr. Cipto Mangunkusumo General Hospital requires nasopharynx and oropharynx swabs for SARS-CoV-2 PCR test. The General Hospital also obligates vaccination to every medical staff who gives medical services.

There are several reported publications on the CML in the pandemic Era. Generally, patients with hematological malignancies are at increased risk due to immunosuppression and/or comorbidities. However, data from the UK showed that most patients with CML who are infected with SARS-CoV-2 had mild disease and recovered.<sup>25</sup> Another case series from Turkey also showed complete recovery of COVID-19 in CML patients, regardless of their Sokal score.<sup>26</sup> Although these patients might have increased risk for complications of COVID-19, it is hypothesized that TKIs have antiviral effects by blocking viral entry through off-target Abl kinase inhibitor.<sup>25</sup> Currently, there is no sufficient data to conclude the findings. Therefore, American Society of Hematology does not recommend alteration in CML treatment in those who contracted COVID-19., except in severe cases in which the decision should be made on case-by-case basis.

### CONCLUSION

Patients with chronic phase CML in our study tend to be younger than in the West, but equivalent to other Asian countries. Most are symptomatic with high percentage of splenomegaly, leading to intermediate to high-risk Sokal score and lower CHR and MMR.

Imatinib is the first line TKI for patients with chronic phase CML since next-generation TKIs are not widely available in Indonesia. Nilotinib is preserved for those with high Sokal scores, no comorbidities, and women who want to conceive in the nearest future. Monitoring of molecular response should be conducted every 6 months, however this is not covered by our National Health Insurance.

Dr. Cipto Mangunkusumo General Hospital has crucial preventative measures to limit the spread of COVID-19, including immunization of designated personnel and screening of COVID-19 in CML patients. Currently, there is no sufficient data to support the hypothesis that CML patients are at increased or less risk during this pandemic.

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