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| RESEARCH ARTICLE

Myeloid Cell Leukemia-1 (MCL-1) and Its Correlation with the Prognostic Scoring System in Chronic Myeloid Leukemia

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| ABSTRACT
The prognostic scoring system is used to assess the prognosis of Chronic Myeloid Leukemia (CML) patients to get the right treatment strategy. Poor prognosis, treatment resistance, and tumorigenesis have been associated with the overexpression of Myeloid Cell Leukemia-1 (MCL-1), an anti-apoptotic protein in several hematologic malignancies, including CML. Research on the correlation between MCL-1 levels and the scoring system prognostic in patients with CML is still limited. This study aims to evaluate the correlation between MCL-1 levels and the prognostic scoring system in chronic phase CML patients. This research was conducted on chronic phase CML patients who came to the Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Hasan Sadikin Hospital Bandung, Indonesia. Data is collected from medical records of patients examined for MCL-1 protein levels from previous studies and results of prognostic scoring systems (Sokal, Hasford, and EUTOS. Data were analyzed to evaluate the correlation between the MCL-1 level and the prognostic scoring system. Forty patients had a male-female ratio of 1.5. The average age is 40±11 years, with an age range of 19 to 61 years. The median MCL-1 protein level was 0.27 (min 0.02-max 4.1). Statistical analysis showed no significant correlation between MCL-1 levels and Sokal, Hasford, and EUTOS scores in chronic phase CML patients (p=0.285; p=0.923 and p=0.663, respectively).

| KEYWORDS
Myeloid Cell Leukemia-1 (MCL-1), Prognostic Scoring Systems, Sokal, Hasford, EUTOS, CML

| ARTICLE INFORMATION
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1. Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative disease that develops from multipotent stem cells, characterized by the presence of the Philadelphia chromosome (Ph). The Philadelphia chromosome (Ph), also known as the BCR-ABL1 fusion gene, is caused by a reciprocal translocation between the ABL1 locus on chromosome 9 and the BCR area on chromosome 22, which produces a protein that deregulates the activity of tyrosine kinase and is an oncogene [Ahn, 2022] [Szeto, 2022]. If not treated, the disease will progress abnormally from the chronic phase to the accelerated phase and then to the blast phase within 3 to 5 years [Salas, 2015]

The discovery of *tyrosine kinase inhibitor* (TKI) repairs the prognosis of patient CML, with the level of patient CML reaching 100 percent after 6-7 years [Xia, 2015]. *Imatinib* has significantly improved therapeutic efficacy in patients with chronic phase CML [Sakurai, 2020]. In treating CML patients, newer generations of TKIs, including nilotinib, dasatinib, and bosutinib, can be used as first-line therapy [Szeto, 2022].

Many prognostic scoring systems have been developed to stratify the risk in CML patients. Calculation of an important prognostic index for CML, including assessing survival. Three prognostic scoring systems are widely accepted for clinical practice worldwide: Sokal, Hasford, and the European Treatment and Outcome Study (EUTOS). This prognostic scoring system method classifies patients into low, moderate, and high-risk disease groups based on patient age, spleen size, platelet count, and various peripheral cell counts, used as a basis for clinical decisions and predicting therapeutic response. The Sokal and Hasford scoring systems are based on the CML patients undergoing interferon-alpha and/or hydroxyurea/busulfan treatment. Although this scoring system was developed before the development of imatinib, it is still effective for predicting the prognosis in chronic phase CML patients [Uz, 2013], [Iriyama, 2013]

In chronic phase, CML patients who take imatinib as the first line, the EUTOS prognostic scoring system that developed during the imatinib era predicts even-free survival (EFS) better than the Euro/Hasford and Sokal system. Likewise, according to other studies, the best scoring system for predicting EFS, progression-free survival (PFS), and CML-related mortality among chronic phase CML patients receiving current imatinib was scores EUTOS [Iriyama, 2013], [Sato, 2020]

Myeloid Cell Leukemia-1 (MCL-1) is an important regulator of mitochondrial homeostasis, which is an anti-apoptotic oncoprotein from one of the most studied members of the BCL-2 family [Xiang, 2018]. MCL-1 is required for the survival of many cells, especially of the hematopoietic lineage [Pereira-Castro, 2020] [Senichkin, 2019]. In general, MCL-1 may undergo genetic alterations and overexpression associated with drug resistance in various human cancers, including CML, and is particularly associated with drug resistance [Mittal et al. 2021]. Studies show that MCL-1 is overexpressed in leukemia cell lines in myeloblastic humans during the early phases of differentiation observed in various types of cancer [Pereira-Castro, 2022] [Senichkin, 2019].

MCL-1 inhibitors, in particular, have recently started clinical trials for some hematological malignancies but not for CML [Malyukova, 2021]. Overexpression and amplification of MCL-1 are usually associated with poor prognosis and resistance to anticancer treatment. MCL-1 influences disease development and progression by helping cancer cells avoid apoptosis and proliferation [Xiang, 2018].

Although TKI therapy has increased the survival of patients with chronic phase CML, certain patients still do not respond to this standard therapy [Malyukova, 2021]. Increased activity of various independent BCR-ABL1 signaling pathways, one of which is through the MCL-1 pathway, is hypothesized as the mechanism underlying TKI resistance in CML patients [Malyukova, 2021]. Therefore, the MCL-1 level may be included in assessing the prognosis of CML, especially when combined with the additional factors considered by the Sokal, Hasford, and EUTOS prognostic scoring system. We have examined MCL-1 levels in chronic phase CML to determine the correlation between this protein level and a prognostic scoring system.

Not many studies have investigated the correlation between MCL-1 levels and prognostic scoring systems in the context of chronic phase CML patients. This study aims to explore this correlation and determine whether MCL-1 levels can provide additional valuable information in evaluating the prognosis in patients with chronic phase CML.

2. Methods

This is a cross-sectional study conducted at the Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Hasan Sadikin Central General Hospital, Bandung, Indonesia, after obtaining approval from the Research Ethics Committee of Padjadjaran University, Bandung (Identification Number: 1100/UN6. KEP/EC/2018). The study period was from April 2018 to June 2019. The study population was chronic phase CML patients, and data were collected from patient records, including MCL-1 levels and prognostic scoring system results (Sokal, Hasford, and EUTOS). The 2013 ELN criteria were used to determine the diagnostic criteria [Baccarani, 2013]. At the time of diagnosis, the risk was categorized using Sokal, Hasford, and scores EUTOS [Nicolini, 2018], [Gołos, 2011]. The statistical analysis evaluated the correlation between MCL-1 levels and the prognostic scoring system.

3. Results and Discussion

Forty patients were found in this study, where the male-female ratio was 1.5. The mean age was 40±11 years, with an age range of 19 to 61 years. In epidemiology, CML patients are slightly more male than female. The sex ratio in studies in Asian countries ranged from 1.5-1.7:1, while in Caucasian countries (United States, United States of America, and surrounding races), it was around 1.3-1.6:1 [Reksodiputro, 2015], [Au, 2009]. Chronic myeloid leukemia is more common in Western countries than in Asia and tends to develop at an older age [Hochhaus, 2020] [Rajabto, 2022]. The average diagnostic age in the US is 67 years, while in Europe, it is between 60 and 65 years [Deininger, 2021] [Hochhaus, 2017]. In Indonesia, China, Hong Kong, India, the Philippines, Singapore, South Korea, Thailand, and Malaysia, the average age is between 36 and 55 years, and the incidence is higher in men than women [Au, 2009], [Rajabto, 2022], [Kuan, 2018].

This study identified the Sokal score in three risk groups, namely low risk (42.5%), intermediate risk (17.5%), and high risk (40%). The Hasford score identifies groups of low risk (30%), intermediate risk (37.5%), and high risk (32.5%). Two risk categories are assigned to scores EUTOS: low risk (95%) and high risk (5%). Sato et al. reported their study in which a total of 150 (44%), 137 (40%), and 55 (16%) patients were classified as low, intermediate, and high risk according to the Sokal score; 143 (42%), 170 (50%), and 29 (8%) were at low, intermediate, and high risk according to Hasford scores; 293 (86%) and 49 (14%) were at low and high risk according to the scores EUTOS [Sato, 2020].

In this study, the median MCL-1 protein level was 0, 27 (min 0,02-max 4,1). The statistical analysis shows no significant correlation of MCL1 levels with Sokal, Hasford, and EUTOS scores in chronic phase CML patients (p=0.285; p=0.923, and p=0.663, respectively). The distribution of patients according to the prognosis scoring system and MCL-1 level is shown in Table 1.

Table 1. System prognostic scoring and MCL-1 levels

Prognostic scoring system	**Number of patients n (%)**	**MCL-1 Median (range)**	**P**
Sokal Score			
- Low (<0.8)	17 (42.5)	0.43 (0.06-4.10)	0.258[a]
- Intermediate (0.8-1.2)	7 (17.5)	1.36 (0.04-3.29)	
- High (>1.2)	16 (40.0)	0.21 (0.02-2.73)	
Hasford Score			
- Low (<780)	12 (30.0)	0.21 (0.06-4.10)	0.923[a]
- Intermediate (781-1480)	15 (37.5)	0.43 (0.04-1.63)	
- High (>1480)	13 (32.5)	0.26 (0.02-2.78)	
EUTOS Score			
- Low (≤87)	38 (95.0)	0.325 (0.02-4.10)	0.663[b]
- High (>87)	2 (5.0)	0.2 (0.13-0.27)	

[a]Kruskal Walls test [b]Mann Whitney test

Overexpression of MCL-1 seen in several malignancies, including solid tumors and hematological malignancies, and it was the first to be discovered in leukemic cell lines myeloblastic humans in the early phase of differentiation [Pereira-Castro, 2022], [Senichkin, 2019], [Belmar, 2015], [Wei, 2020], and increased expression of this is associated with a poor prognosis [10]. MCL-1 has been shown to play an important role in promoting cell survival in plasma cell myeloma cell lines, acute myeloblastic leukemia (AML), and lymphoma [Wei, 2020], [Wang, 2021]. In addition, it was also found that overexpression of MCL-1 causes resistance to radiation, chemotherapy and also due to BH3-mimetic therapy that targets BCL-2/BCL-XL [Wei, 2020]. Research on the correlation between MCL-1 levels and prognostic scoring systems is limited, but recent investigations have shown that MCL-1 is critical for cancer cell survival and development. High levels of MCL-1 have been reported in hematological malignancies and various solid tumors [Aguanno, 2020]. MCL-1 overexpression in cancer cells disrupts the balance between these proteins, anti-apoptosis and pro-apoptosis [Moujalled, 2019]. This condition prevents cancer cells from undergoing apoptosis and causes their increased proliferation of cancer cells [Wei, 2020] [Moujalled, 2019]. Cancer can develop multi-drug resistance through different molecular pathways [Wei, 2020] [Yue, 2021]. Cancer cells express high amounts of anti-apoptotic proteins to prevent apoptosis and for their survival. Expression of other members of the anti-apoptotic BCL-2 family can be impaired as a result of the inhibition of one member. Increased MCL-1 expression may result from a reaction to long-term selective BCL-2/BCL-XL inhibitor therapy [Wei, 2020].

Although no significant correlation was found between the MCL1 level and the prognostic scoring system in this study, the important role of MCL-1 in cancer development related to drug resistance in some malignancies cannot be ignored. To further investigate this correlation, more samples and additional studies are needed.

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