Received: 23 Aug 2023 | **Accepted:** 13 Nov 2023 **Genel Tıp Derg. Volume** 34/**Issue** 1 (February), 78-82
DOI: 10.54005/geneltip.1348459

ORIGINAL ARTICLE

Impact of Hemoglobin, Leucocyte and Thrombocyte Levels at Diagnosis on the Survival Outcomes of Chronic Myeloid Leukemia Patients

Kronik Miyeloid Lösemi Hastalarının Tanı Sırasındaki Hemoglobin, Lökosit ve Trombosit Düzeylerinin Sağkalım Sonuçlarına Etkisi

[1]Sinan Demircioğlu, [2]Rafiye Çiftçiler, [1]Taha Ulutan Kars, [1]Atakan Tekinalp

[1]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Hematology
[2]Selçuk University, Faculty of Medicine, Department of Hematology

Correspondence

Rafiye Ciftciler, Selcuk University Faculty of Medicine, Department of Hematology, Konya, Turkey

E-Mail: rafiyesarigul@gmail.com

How to cite ?

Demircioğlu S, Ciftciler R, Tekinalp A, Kars TU. Impact of Hemoglobin, Leucocyte and Thrombocyte Levels at Diagnosis on the Survival Outcomes of Chronic Myeloid Leukemia Patients. Genel Tıp Derg. 2024;34(1):78-82.

ABSTRACT

Background: Since the development of tyrosine kinase inhibitors (TKIs), the prognosis for chronic myeloid leukemia (CML) has significantly improved. Several predicted prognostic scores and indicators at diagnosis have been used to predict the prognosis of chronic phase chronic myeloid leukemia (CML-CP) during the TKI period. When CML patients are first diagnosed, hemogram parameter aberrations are rather prevalent in clinical practice although it is still unknown how those parameters affect the prognosis. This study aims to evaluate the hemogram parameters at diagnosis on the survival outcomes of CML-CP patients.
Materials and Methods: One hundred thirty-seven patients who were diagnosed with CML-CP and received treatment were assessed between the years 2006 and 2020.
Results: There were 65 (47.4%) males and 72 (52.6%) females with a median age of 50 (range: 18-78) years at diagnosis. Median hemoglobin level was 12.1 gr/dL (4.3-17.4), leucocyte count was 66.2 ×109 /L (7.5-520.2), and thrombocyte count was 362 ×109 /L (18-3.496) for all patients. The median progression-free survival (PFS) was 16.7 (2.0-106.4) months and the median overall survival (OS) was 63.8 (0.43-166.2) months for all patients.
Conclusion: This study is valuable in terms of predicting the prognosis of CML patients with hemoglobin, leukocyte, and platelet values at the time of diagnosis. While emphasizing the importance of platelet count at the time of diagnosis, similar to the previously defined risk scores, it showed that leukocyte and hemoglobin values at the time of diagnosis did not have a statistically significant effect on OS and PFS.

Keywords: Chronic myeloid leukemia, Hemoglobin, Leucocyte, Thrombocyte, Risk score

ÖZ

Giriş ve Amaç: İmatinib ve diğer tirozin kinaz inhibitörlerinin (TKİ'ler) geliştirilmesinden bu yana, kronik miyeloid löseminin (KML) prognozu önemli ölçüde iyileşti. TKİ döneminde daha az tedavi yanıtları ve sonuçları olan kronik faz kronik miyeloid lösemi (KML-KF) bireylerini belirlemek için tanı sırasında tahmin edilen çeşitli prognostik skorlar ve göstergeler kullanıldı. KML hastalarına ilk tanı konduğunda klinik pratikte hemogram parametrelerinde anormallikler oldukça yaygındır, ancak bu parametrelerin prognozu nasıl etkilediği henüz bilinmemektedir. Bu çalışmanın amacı KML-KF hastalarının tanı anındaki hemoglobin, lökosit ve trombosit düzeylerinin sağkalım sonuçlarına etkisini değerlendirmektir.
Gereç ve Yöntem: 2006-2020 yılları arasında KML-KF tanısı alan ve tedavi gören 137 hasta değerlendirildi.
Bulgular: Tanı anındaki ortanca yaş 50 (18-78) yıl olan 84 (%45,9) erkek ve 99 (%54,1) kadın hasta değerlendirildi. Tüm hastaların ortanca hemoglobin düzeyi 12,1 gr/dL (4,3-17,4), lökosit sayısı 66,2×109/L (7,5-520,2), trombosit sayısı ise 362×109/L (18-3,496) saptandı. Medyan progresyonsuz sağkalım (PFS) tüm hastalar için 16,7 ay 16,7 (2,0-106,4) ve medyan genel sağkalım (OS) 63,8 ay (0,43-166,2) idi.
Sonuç: Bu çalışma KML hastalarının tanı anındaki hemoglobin, lökosit ve trombosit değerleri ile prognozunu öngörmesi açısından değerlidir. Tanı anında trombosit sayısının önemi vurgulanırken, daha önce tanımlanan risk skorlarına benzer şekilde, tanı anındaki lökosit ve hemoglobin değerlerinin OS ve PFS üzerinde istatistiksel olarak anlamlı bir etkisinin olmadığı gösterildi.

Anahtar Kelimeler: Kronik miyeloid lösemi, hemoglobin, lökosit, trombosit, risk skoru

Introduction

Chronic myeloid leukemia (CML) is a member of the myeloproliferative neoplasia (MPN) subgroup, which is defined by the uncontrolled proliferation of myeloid cells at various stages of maturity. CML begins with the first description of the Philadelphia Chromosome and the discovery of leukemia and ends with the achievement of remission without treatment following targeted drugs (1). BCR-ABL1 is a key factor in CML's pathogenesis, and its oncoprotein production causes the hematopoietic cells that carry this fusion gene to grow clonally (1). The majority of CML cases are caused by a BCR-ABL1 breakpoint, which creates a 210 kDa BCR-ABL1 oncoprotein by joining exons 13 or 14 of the BCR with exon 2 of ABL1 (p210) (2). Pathology, cytogenetics, reverse transcriptase-polymerase chain reaction (RT-PCR), and the identification of the Ph chromosome by fluorescence in situ hybridization (FISH) is used to make the diagnosis of CML (3). Unspecific CML symptoms might include fever, exhaustion and weight loss, which are frequently brought on by anemia and splenomegaly. Only after routine blood testing may the condition be detected in half of the chronic phase CML (CML-CM) patients who have no symptoms. The Sokal, Hasford, EUTOS, and ELTS scores are among today's most often utilized prognostic indicators in risk classification (4). These scores take into account

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
Complaints: geneltip@selcuk.edu.tr

Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
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factors such as age, spleen, platelet, and blood myeloblast levels; hemogram measures other than platelet are not included. When CML patients are first diagnosed, hemogram parameter aberrations are rather prevalent in clinical practice although it is still unknown how those parameters affect the prognosis. This study aims to evaluate the hemoglobin, leucocyte and thrombocyte levels at diagnosis on the survival outcomes of chronic phase chronic myeloid leukemia (CML-CP) patients.

Materials and Methods

Study design and data collection

This study has been performed in a retrospective manner. In our hematology clinic between the years 2006 and 2020, 137 CML patients who were diagnosed with CML and received treatment were assessed. All clinical information was gathered from hospital medical files. It has been determined from the patient records that all of the studied patients gave informed consent at the time of hospitalization by other pertinent diagnostic/therapeutic standards of care, by the applicable standards of the hospitals of our care center before the administration of chemotherapy. The Ethics Committee of Necmettin Erbakan University approved this study (2021/3133-05.03.2021).

Patients and disease characteristics

We retrospectively analyzed CML patients diagnosed and treated between 2006 and 2020. In this study, the patients included were as follows: age >18 years at the time of diagnosis, patients who were in the chronic phase at diagnosis. Patients with deficient data, patients with accelerated or blastic phase at diagnosis, and patients who took medication irregularly were not included in this study.

Progression-free survival (PFS), the primary endpoint was defined as the time from the initiation of TKI treatment (first generation) until progression to accelerate or blastic phase or switching to second-generation TKI therapy due to loss of response (according to cytogenetic and molecular response) to first-generation TKI therapy. Overall survival (OS), the secondary endpoint, was determined as the time interval between CML diagnosis and death resulting from any cause or the end of follow-up.

Molecular and cytogenetic analyses

After 24-hour cultures had been processed, bone marrow samples underwent cytogenetic analysis. For karyotypic analysis, at least 20 metaphase studies per patient using the R banding method were used. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to measure the molecular reactions in peripheral blood, and the results were shown as the International Scale (IS) ratio of BCR-ABL to ABL. After receiving tyrosine kinase inhibitor (TKI) therapy, molecular responses were gathered at 3, 6, and 12 months. The optimal response was determined as BCR-ABL1 (IS) 10% at 3 months, BCRABL1 (IS) 1% at 6 months, and BCR-ABL1 (IS) 0.1% at 12 months based on National Comprehensive Cancer Network (NCCN) guidelines (5-7).

Statistical analyses

Statistical analyses were performed using the SPSS software version 26. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they were normally distributed or not. Statistical comparisons were made using Chi-square for categorical data. A student t-test (for two independent samples) was used for the comparison of continuous numerical data. Survival analyses were made using the Kaplan-Meier test. P values less than 0.05 were regarded as statistically significant.

Results

Baseline characteristics of CML patients

Between 2006 and 2020, 137 consecutive patients with CML-CP were screened for this study. There were 65 (47.4%) males and 72 (52.6%) females with a median age of 50 (range: 18-78) years at diagnosis. Median hemoglobin level was 12.1 gr/dL (4.3-17.4), leucocyte count was 66.2 ×109 /L (7.5-520.2), and thrombocyte count was 362 ×109 /L (18-3.496) for all patients. The median progression-free survival (PFS) was 16.7 months 16.7 (2.0-106.4) and the median OS was 63.8 months (0.43-166.2) for all patients. Patient characteristics are summarized in Table 1.

Table 1. Clinical characteristics of patients at diagnosis of CML

Number of patients (n)	137
Age (median, range)	50 (18-78)
Gender (male/female)	65 (47.4%)/72 (52.6%)
Hemoglobin (gr/dL)	12.1 (4.3-17.4)
MCV	87.3 (52.4-106.2)
MCHC	33.1 (21.2-38.8)
MCH	29.1 (9.9-35.6)
Leucocyte (median, range)	66.2 (7.5-520.2)
Neutrophile (median, range)	51.0 (4.4-468.4)
Lymphocyte (median, range)	5.1 (0.6-83.2)
Eosinophile (median, range)	0.7 (0-21.8)
Basophile (median, range)	0.8 (0-20.4)
Thrombocyte (median, range)	362 (18-3.496)
PFS (median, range), months	16.7 (2.0-106.4)
OS (median, range), months	63.8 (0.43-166.2)

Clinical characteristics and survival outcomes of patients according to hemoglobin level at diagnosis of CML

Patients with hemoglobin ≤12 gr/dL had higher white blood cell counts (<0.001), higher neutrophil counts (<0.001), and a high Sokal risk (<0.001) than patients with Hb >12 gr/dL. However, there is no impact of Hb levels on OS (p:0.61) and PFS (p:0.74) (Fig 1). Table 2 shows the findings of a study conducted on our patients with low and high hemoglobin levels.

Table 2. Clinical characteristics of patients according to hemoglobin level at diagnosis of CML

	Hb <12 gr/dL	Hb ≥12 gr/dL	p
N (%)	67 (48.9%)	70 (51.1%)	
Median age, years	49 (18-78)	53 (18-76)	0.11
Gender (female/ male)	37/30 (55.2%/44.8%)	35/35 (50%/50%)	0.54
MCV	86 (52-106)	88 (63-98)	0.19
MCHC	32 (21-38)	33 (24-37)	0.82
MCH	28 (11-35)	29 (9-34)	0.5
WBC	116 (9-520)	47 (7-213)	<0.001
Neutrophil	102 (6-478)	35 (4-190)	<0.001
Eosinophil	1.4 (0-21.8)	0.5 (0.1-7.2)	0.001
Lymphocyte	5.9 (0.6-83)	4.5 (1.6-25)	0.04
Basophile	1.2 (0-20)	0.6 (0-6.1)	0.002
Thrombocyte	369 (18-3496)	330 (114-2009)	0.35
Myeloblast (%)	0 (0-9)	0 (0-6)	0.19
Ph chromosome	90 (23-100)	80 (8-100)	0.01
BCR-ABL	33 (0-195)	31 (0-146)	0.78
Sokal score (low/ intermediate/high)	9/22/34 (13.8%/33.8%/52.3%)	27/24/13 (42.2%/37.5%/20.3%)	<0.001
Progression (n, %)	26 (41.9%)	17 (27.4%)	0.08
Exitus (n, %)	10 (14.9%)	12 (17.1%)	0.72

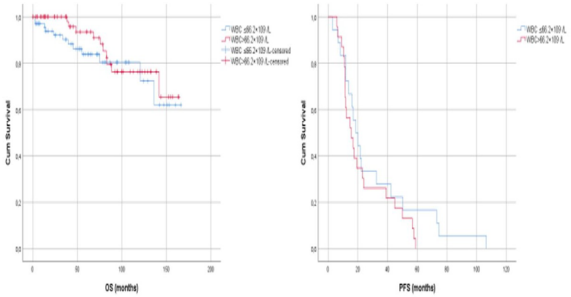

Figure 1. Overall survival (p: 0.61) and progression-free survival (p: 0.74) according to hemoglobin level at diagnosis

Clinical characteristics and survival outcomes of patients according to thrombocyte level at diagnosis of CML

Patients with thrombocyte level PLT ≤362×109 /L had higher MCV (p:0.002), MCHC (p: 0.008), higher MCH (0.005), higher WBC (p: 0.01), and higher neutrophil counts (p: 0.01) than patients with PLT >362×109 /L (Table 3). OS (p:0.005) and PFS (p:0.03) were statistically significantly higher in patients who had thrombocyte levels>362×109 /L at diagnosis than in patients who had thrombocyte levels ≤362×109 /L (Fig 2). With all these results, there was a statistically significant difference between the two groups in terms of the Sokal score (p: <0.001).

Table 3. Clinical characteristics of patients according to thrombocyte level at diagnosis of CML patients

Platelet, ×10⁹ /L (IR)	PLT ≤362×10⁹ /L	PLT >362×10⁹ /L	P
N (%)	69 (50.4%)	68 (49.6%)	
Median age, years	53 (19-76)	49 (18-78)	0.02
Gender (female/ male)	34/35 (47.2%/53.8%)	38/30 (52.8%/46.2%)	0.43
Hb (gr/dL) (median, range)	12.6 (5.7-17.4)	11.9 (4.3-16.4)	0.72
MCV	89 (69-106)	84 (52-102)	0.002
MCHC	33 (28-38)	32 (21-37)	0.008
MCH	30 (9-35)	28 (11-33)	0.005
WBC	87 (9-428)	47 (7-520)	0.01
Neutrophil	79 (6-257)	37 (4-468)	0.01
Eosinophil	0.7 (0-17.5)	0.6 (0.1-21.8)	0.53
Lymphocyte	5.2 (0.6-83)	4.6 (1.6-25)	0.24
Basophile	0.8 (0-20)	0.9 (0-20)	0.74
Myeloblast (%)	0 (0-9)	0 (0-8)	0.16
Ph chromosome	85 (8-100)	86 (12-100)	0.51
BCR-ABL	41 (0-146)	24 (0-195)	0.56
Sokal score (low/ intermediate/high)	18/27/19 (28.1%/42.2%/29.7%)	18/19/28 (27.7%/29.2%/43.1%)	<0.001
Progression (n, %)	25 (39.7%)	18 (29.5%)	0.23
Exitus (n, %)	17 (24.6%)	5 (7.4%)	0.006

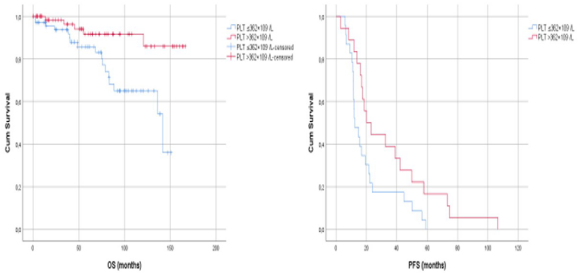

Figure 2. Overall survival (p:0.005) and progression-free survival (p:0.03) according to thrombocyte level at diagnosis

Clinical characteristics and survival outcomes of patients according to white blood cell level at diagnosis of CML patients

Hemoglobin level was statistically significantly lower in the group with higher white blood cell count at diagnosis (p<0.001). However, neutrophil (p: <0.001) and lymphocyte (p: <0.001) counts were statistically significantly higher in the group with higher white blood cell count as expected (Table 4). Except for these results, no statistically significant difference was found between two groups in the terms of OS (p:0.45) and PFS (p:0.23) (Fig 3).

Table 4. Clinical characteristics of patients according to white blood cell level at the diagnosis of CML patients

WBC, ×10⁹ /L	WBC ≤66.2×10⁹ /L	WBC >66.2×10⁹ /L	P
N (%)	69 (50.4%)	68 (49.6%)	
Median age, years	51 (18-77)	50 (18-78)	0.08
Gender (female/ male)	46/23 (66.7%/33.3%)	26/42 (38.2%/61.8%)	0.001

Hb (gr/dL) (median, range)	12.9 (4.3-17.4)	11.1 (5.7-14.8)	<0.001
MCV	86 (52-106)	88 (68-102)	0.05
MCHC	32 (21-36)	33 (24-38)	0.003
MCH	28 (9-33)	30 (21-35)	0.001
Neutrophil	26 (4-57)	117 (55-468)	<0.001
Eosinophil	0.5 (0.1-4.7)	1.8 (0-21.8)	0.003
Lymphocyte	4 (1.2-13.1)	7.5 (0.6-83.2)	<0.001
Basophile	0 (0.7-7)	1.1 (0-20.4)	0.004
Thrombocyte	440 (18-3496)	308 (96-1513)	0.56
Myeloblast (%)	0 (0-9)	0 (0-6)	0.23
Ph chromosome	83 (8-100)	87 (12-100)	0.56
BCR-ABL	24 (0-122)	35 (0-195)	0.32
Sokal score (low/ intermediate/high)	22/22/21 (33.8%/33.8%/32.3%)	14/24/26 (21.9%/37.5%/40.6%)	0.30
Progression (n, %)	18 (30%)	25 (39.1%)	0.28
Exitus (n, %)	12 (17.4%)	10 (14.7%)	0.66

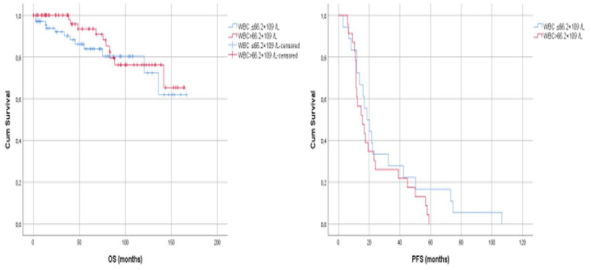

Figure 3. Overall survival (p:0.45) and progression-free survival (p:0.23) according to white blood cell level at diagnosis

Discussion

Since the development of imatinib and other TKIs, the prognosis for CML has significantly improved. Currently, 83–89% of CML patients in the CML-CP who are receiving imatinib as first-line treatment have a 5-year OS (8). Several predicted prognostic scores and indicators at diagnosis were utilized to identify CML-CP individuals who had less favorable treatment responses and outcomes in the TKI period. One such predictor for chemotherapy is the Sokal score, which was updated once for individuals under the age of 45 despite fewer applications (9). Another score created for interferon alpha is the Hasford score. In CML-CP patients receiving front-line imatinib, Hasford et al. developed the European Treatment and Outcome Study (EUTOS) score, which predicts a complete cytogenetic response (CCyR) and PFS better than the Sokal and Hasford ratings based on spleen size and blood basophil percentage (4, 10, 11). A more precise score, known as the EUTOS long-term survival (ELTS) score, which takes disease-specific fatalities into account, was published by Pfirrmann et al. (4) Lautti et al. also discovered that other chromosomal aberrations in the Philadelphia-positive clone were a poor prognostic predictor for imatinib treatment. Comorbidities may also hinder a patient's ability to adhere to TKI therapy, which might have an impact on survival rates (12, 13).

Patients with CML-CP frequently experience anemia, which may be caused by the disease itself or other concomitant conditions. Hemoglobin levels were predictive in a univariate analysis used to determine the Sokal scores, but they were not significant in a multivariate regression for survival. Hemoglobin levels are therefore rarely mentioned as a baseline prognostic proxy and were not included in the subsequently popular prognostic scoring systems. However, it has recently been discovered that anemia at the time of diagnosis is linked to greater white blood cell counts, more frequent splenomegaly, and more CML-related deaths (14). Anemia at the time of CML-CP diagnosis (baseline hemoglobin 12.0 g/dl) was linked to high-risk characteristics and CML-related mortality, but it was not linked to treatment response, according to a review reported by Jabbour et al. (15).

In this study, the patients with anemia at the time of diagnosis also tended to have higher white blood cell counts, neutrophils, lymphocytes, eosinophils, basophils, and high Sokal scores. Additionally, in the group with anemia at the time of diagnosis, the percentage of Ph chromosomes sent from bone marrow aspiration at the time of diagnosis was found statistically significantly higher. However, no statistically significant correlation was found between both OS and PFS and anemia in this study.

As expected, neutrophil, lymphocyte, basophile, and eosinophile counts were statistically significantly higher in the group with a higher white blood cell count. In addition, it was observed that the white blood cell counts at the time of diagnosis tended to be higher in the male gender. In the group with a high white blood cell count, the median hemoglobin level was statistically significantly lower. Despite these findings, it was observed that OS and PFS patients did not differ significantly in terms of white blood cell counts at the time of diagnosis. However, in terms of OS and PFS, patients with high platelet count at the time of diagnosis had statistically significantly higher OS and PFS than those with low platelet count. Patients with thrombocyte level PLT ≤362×109 /L had higher MCV, MCHC, MCH, WBC, and neutrophil counts and Sokal scores than patients with PLT >362×109 /L. Age tended to be earlier in the group with high platelet count at the time of diagnosis.

Our study has a few limitations. First, this study was retrospective. Second, the number of patients was limited. Third, we do not know the detailed cytogenetic features of these patients, apart from the Ph chromosome. As a result, this study is valuable in terms of predicting the prognosis of CML patients with hemoglobin, leukocyte, and platelet values at the time of diagnosis. While emphasizing the importance of platelet count at the time of diagnosis, similar to the previously defined risk scores, it showed that leukocyte and hemoglobin values at the time of diagnosis did not have a statistically significant effect on OS and PFS.

Conflict of Interests

The authors of this paper have no conflict of interests,

including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Role of the funding source

None.

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