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ORIGINAL ARTICLE

Event-free Survival in Patients with Chronic Myeloid Leukemia Receiving Front-line Imatinib Mesylate

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ABSTRACT

Objective: Chronic myeloid leukemia (CML) prognostication at the time of diagnosis is critical to determine the intensity of initial treatment. Event-free survival (EFS) has become a prominent concept of prognosis in the patients with chronic phase CML (CML-CP). The aim of this study is to assess the prognostic impact of bone marrow (BM) and peripheral blood (PB) cellular components, in correlation with the clinical parameters.

Materials and Methods: One hundred forty-three patients with CML-CP on the front-line imatinib mesylate therapy were recruited into this study. Clinical and laboratory characteristics, therapeutic responses were recorded. Sokal, Euro/Hasford, The EUropean Treatment Outcome Study (EUTOS) and The EUTOS long-term survival (ELTS) scores were calculated for the studied patients.

Results: Median follow-up time was 84 (IQR: 54-125) and median front-line therapeutic duration was 56 (IQR:23-89) months. Five-year EFS rate was 62.3% (95% CI: 53.9-70.7). The blast percentage in the BM, EUTOS scores, and basophil percentage in PB were related with the poor therapeutic outcomes in frontline therapy (p=0.002, p=0.002 and p=0.042, respectively). Although Sokal risk classification showed that the intermediate class had a higher event risk compared to the low-risk class (p=0.001), the predictive association disappeared in high-risk classes.

Conclusion: EUTOS score system has better predictive capability for front-line imatinib therapy comparing with other indices. Higher blast percentage in BM and increased basophil percentage in PB are independent risk factors, adversely related with EFS in patients with CML.

Keywords: CML, event-free survival, EFS, first-line, imatinib

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have game changer effects on the clinical course of chronic myeloid leukemia (CML). Although imatinib mesylate constitutes the major option in the front-line treatment, resistance or intolerance may occur in 50% of patients, which leads to escalation in therapeutic scheme [1,2]. Therefore, CML prognostication at the time of diagnosis is critical to determine the intensity of initial TKI treatment.

Various indices derived from baseline clinical and laboratory features have been used to determine prognosis in CML [3]. Sokal and Euro/Hasford scoring systems which were developed before the TKI era, have been widely used for risk assessment [4,5]. However, it was reported that these scores were less effective than European Treatment and Outcome Study (EUTOS) in event-free survival estimate [6]. Furthermore, a novel predicting system, EUTOS long-term survival (ELTS) score was developed through re-weighing of Sokal score components [7]. Due to improved response rates with TKI treatment, event-free survival (EFS) has become a prominent concept in patients with chronic phase CML (CML-CP). Nevertheless, present scoring systems still need to be improved for perfect EFS estimation.

The aim of this study is to assess the prognostic impact of bone marrow (BM) and peripheral blood (PB) cellular components, correlated with clinical parameters. Our hypothesis was that certain laboratory parameters such as bone marrow blast percentage in addition to current prognostic indices could be effective tools to predict EFS in patients with CML. Elucidation of the exact prognostication in CML could facilitate decision-making in therapeutic management of the patients.

MATERIALS AND METHODS

Ethical approval

During this study, all the ethical considerations was followed in accordance with the 1964 Helsinki Declaration.

Study Population

In our study, one hundred forty-three patients with CML-CP, applied to our clinic between January 2005 and July 2018 were recruited. Exclusion criteria were being under 18 years of age, having a follow-up of less than 24 months, receiving front-line therapy other than imatinib mesylate, and initiating TKI treatment more than 6 months after diagnosis.

Clinical characteristics and laboratory results were collected through electronic record system and patient files, retrospectively. Demographic features, comorbidities, palpable spleen size, complete blood count, BM characteristics, PBS distribution and therapeutic responses were recorded. Sokal, Euro/Hasford, EUTOS and ELTS scores were calculated according to their respective equations [4,5,7,8].

Hematologic, molecular, and cytogenetic responses, primary and secondary resistance were defined through 2013 European LeukemiaNet (ELN) criteria [9]. EFS describes the time between initiation of TKI treatment, and determination of primary or secondary resistance, progression to accelerated phase (AP) or blastic crisis (BC), or moderate to severe adverse event occurrence. Overall survival (OS) defines duration from CML diagnosis to death, by any cause.

Statistical Analyses

The normality of the variable distributions was examined by Kolmogorov-Smirnov test. For categorical variables, proportions and for continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) were reported based on normality. To evaluate differences in continuous variables, student's t test or Mann-Whitney U test were used based on normality. For the categorical variables, Chi- square or Fisher's exact tests were used. Survival analyses were performed through Kaplan-Meier test, and factors related with EFS were examined through Cox Proportional Hazards Regression Analysis for univariate analysis and backward multivariate adjustments. Statistical analyses were performed using IBM SPSS Statistics (version 25; SPSS, Armonk, NY), probability values were 2-sided and considered statistically significant when $p<0.05$.

RESULTS

General characteristics

One hundred forty-three patients (70 women, 73 men) were enrolled in our study (Figure 1). Median follow-up time was 84 (IQR: 54-125) months and median front-line therapeutic duration was 56 (IQR:23-89) months. At the time of diagnosis, median age was 48 (IQR: 35-59) years. General characteristics of the study population were summarized in Table-1.

During front-line TKİ therapy, 95.3% of the patients achieved complete hematologic response and 83.6% reached major molecular response.

Prognostic scores

All four prognostic scores were calculated for each patient and summarized in Table 1. Sokal scores were positively correlated with Euro/Hasford, EUTOS and ELTS scores (r=0.77, r=0.45, r=0.64 respectively, $p < 0.001$ for all).

Survival analyses

In front-line therapy, the treatment of 66 (46.2%) patients had to be switched to another TKI. Moderate and severe therapeutic adverse events were described in 16 (11.2%) patients. While primary TKI resistance was observed in 19 (13.3%) patients, secondary TKI resistance occurred in 22 (15.4%) patients.

During follow-up at our center, death of any kind occurred in 6 (4.2%) patients. While the 10-year OS rate was 95.2% (95% CI: 90.6-99.8), 5-year EFS rate was determined as 62.3% (95% CI: 53.9-70.7).

Predictive factors for EFS

The results of the univariate regression analyses to determine the factors predicting EFS rate were summarized in Table 2. Although Sokal scores showed that the intermediate class had a higher event risk compared to the low-risk class (HR: 3.117 [95% CI:1.584-6.135], p=0.001), the predictive association disappeared at higher scores (p=0.061). Therefore, numerical scores rather than classifications were used to determine prognosis to avoid lower statistical power due to the limited number of CP-CML patients with high-risk scores. EUTOS score showed a prognostic relationship with EFS, which remained the same after multivariate analyses (Table 2).

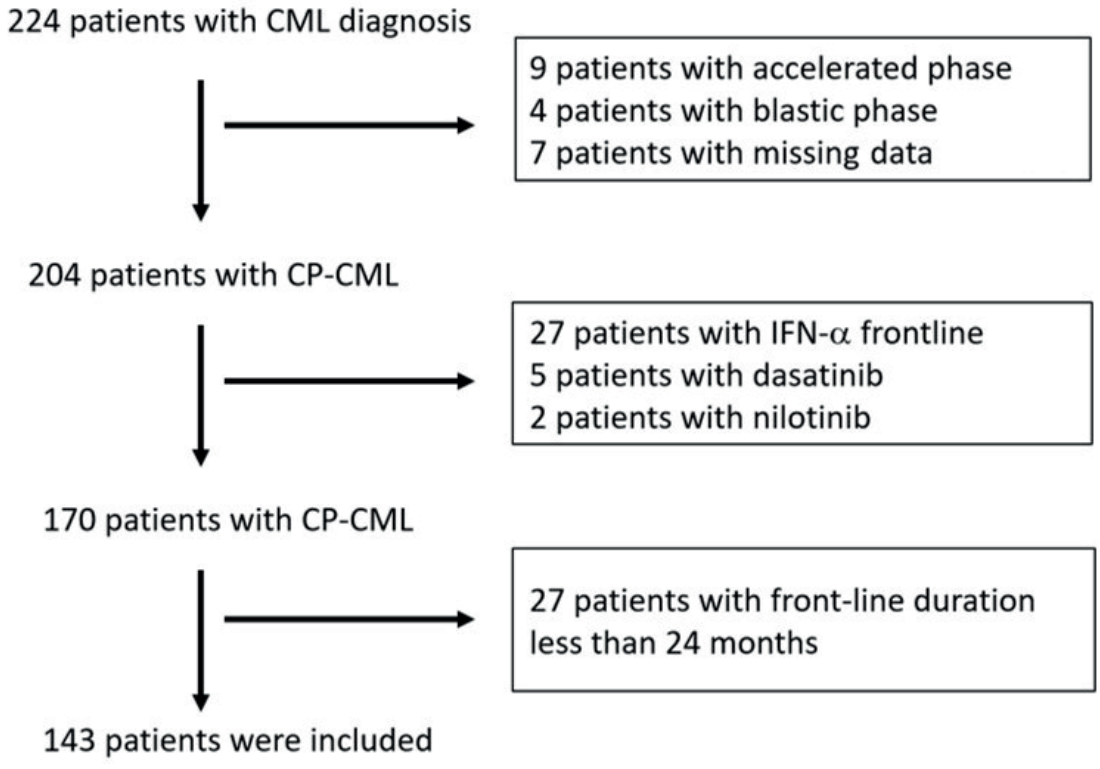

Figure 1. Inclusion diagram

Table 1. Comparison of baseline clinical and laboratory characteristics in different event states

	All patients (N=143)	Event (N= 66)	Censored (N=77)	p value
Age, median (IQR), y*	48 (35-59)	46 (34-54)	49 (38-61)	0.09
Male, N (%)	73 (51)	40 (54.8)	33 (45.2)	0.044
Palpable spleen size, median (IQR), cm	0 (0-2)	2 (0-5)	0	<0.001
Hb†, mean (SD), g/dl	12.4 (1.7)	12.2 (1.7)	12.5 (1.7)	0.39
WBC‡, mean (SD), $x10^3/mm^3$	105.9 (95.8)	122 (105.7)	93.2 (85.9)	0.10
Basophil (%) of PBS§, median (IQR)	0.5 (0.1-2.3)	0.8 (0.1-3.3)	0.4 (0.1-1.2)	0.35
Eosinophil (%) of PBS, median (IQR)	1.2 (0.5-2.1)	1.2 (0.5-2.4)	1.2 (0.5-2.0)	0.83
Platelet, mean (SD), $x10^3/mm^3$	499 (385)	535 (450)	470 (327)	0.38
Myeloblast (%) of PBS, median (IQR)	0 (0-2)	0 (0-3)	0 (0-1)	0.001
Blasts percentage in BM‖, median (IQR)	3 (2-4)	4 (3-4)	3 (2-4)	0.01
Sokal classification				
Low, N (%)	55 (47.4%)	16 (32%)	39 (59.1%)	0.019
Intermediate, N (%)	36 (31.0%)	21 (42%)	15 (22.7%)	
High, N (%)	25 (21.6%)	13 (26%)	12 (18.2%)	
Euro/Hasford classification				
Low, N (%)	76 (65.5%)	28 (56%)	48 (72.7%)	0.06
Intermediate, N (%)	32 (27.6%)	17 (34%)	15 (22.7%)	
High, N (%)	8 (6.9%)	5 (10%)	3 (4.5%)	
EUTOS¶ classification				
Low, N (%)	110 (94.8%)	46 (92%)	64 (97%)	0.40
High, N (%)	6 (5.2%)	4 (8%)	2 (3%)	
ELTS** classification				
Low, N (%)	85 (71.6%)	31 (62%)	52 (78.8%)	0.10
Intermediate, N (%)	25 (21.6%)	15 (30%)	10 (15.2%)	
High, N (%)	8 (6.9%)	4 (8%)	4 (6.1%)	

*: year, †: Hemoglobin, ‡: white blood cells, §: peripheral blood smear, ‖: bone marrow, ¶: The EUropean Treatment Outcome Study, **: The EUTOS long-term survival

Table 2. Univariate and multivariate analyses of EFS predictors

	Univariate regression		Multivariate Regression Model 1		Multivariate Regression Model 2	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (year)	0.99 (0.97-1.0)	0.15				
Gender (male vs. female)	0.535 (0.320-0.893)	0.017	0.67 (0.31-1.46)	0.32	0.54 (0.27-1.09)	0.09
Palpable spleen size (cm)	1.055 (1.008-1.105)	0.022	1.09 (0.98-1.21)	0.10		
Hb* (g/dl)	0.93 (0.79-1.1)	0.39				
WBC† ($x10^9$/ml)	1.0	0.15				
Basophil (%) of PBS‡	1.114 (1.005-1.234)	0.04	1.17 (1.006-1.361)	0.042		
Eosinophil (%) of PBS	1.05 (0.89-1.25)	0.55				
Platelet ($x10^9$/ml)	1.0 (0.99-1.0)	0.62				
Myeloblast (%) of PBS	1.08 (0.99-1.19)	0.09				
Blasts% in BM§	1.32 (1.123-1.548)	0.001	1.353 (1.101-1.662)	0.004	1.352 (1.113-1.644)	0.002
Sokal score	1.25 (0.82-1.92)	0.31				
Euro/Hasford score	1.0 (1.0-1.001)	0.08				
EUTOS‖ score	1.012 (1.004-1.021)	0.005			1.017 (1.006-1.027)	0.002
ELTS¶ score	1.49 (0.91-2.43)	0.11				

*: Hemoglobin, †: white blood cells, ‡: peripheral blood smear, §: bone marrow, ‖: The EUropean Treatment Outcome Study, ¶: The EUTOS long-term survival

Similarly, bone marrow blast percentage, spleen size and basophil rates in peripheral blood smear were showed significant predictive relationship. No association was observed between EFS and age, eosinophil percentage or platelet count. In the univariate regression, male patients had a higher risk of events, and their spleen size were significantly higher than women (data not shown). However, the higher risk attributed to gender disappeared in various multivariate regression models.

DISCUSSION

In this study, increased bone marrow blast percentage, peripheral basophil rates and EUTOS scores significantly related to clinical course prediction of real-life patients with CML-CP on front-line imatinib mesylate therapy. Although spleen size, gender and Sokal risk classification appeared to be associated with therapeutic outcomes, multivariable adjustments had indicated their predictive relationship for event-free survival could be limited. Furthermore, in different Euro/Hasford and ELTS risk groups EFS rates were observed as similar. There was no correlation between event-free survival and age of patients.

The estimation of therapeutic responses by prognostic scores is particularly contentious issue. While some authors described that risk stratification was compatible with EFS, the others identified similar EFS duration in different Sokal or Euro/Hasford scores [6,10-14]. In the current study, we observed that ability to anticipate EFS in Sokal risk classes was limited in patients with imatinib mesylate in the frontline. Although there was a prognostic difference between low and intermediate risk groups, EFS rates of high-risk group was similar with low-risk patients, this result could be linked with limited number of patients with high-risk score in CP-CML group. In addition to Sokal risk classification, we also found a linear relationship between EUTOS risk score and EFS. In addition, various studies reported better prediction capacity in EUTOS scoring system consistent with our results, others indicated validation handicaps in the score [6,10,13,15-17]. As opposed to other studies, EFS results were similar among ELTS subgroups in our study [7,11].

According to ELN 2013, blast rate in bone marrow below 15% is a CP criterion [9]. However, many authors reported that a BM blast rate higher than 10% was associated with unfavorable disease course [18-22]. Some authors have even suggested that an excess of blasts in CP could be an early sign of an accelerated phase [18]. In our study, a linear hazard ratio of blast percentage in bone marrow was described regardless of a specific cut-off point. Despite new technological capabilities, our results suggest that histomorphological assessment in CML is still a valuable art.

It was shown that basophilia is an independent prognostic feature correlated with disease progression and TKI resistance in patients with CML [23-25]. Therefore, basophil rates in PB are frequently used laboratory parameters for prognostic indices [5,8]. We also described the relationship between basophil percentage and event rates. Age is also a common variable in overall survival prediction. However, there was no association between EFS estimation and age in our study. This could be associated with our cohort, which was younger than the typical CML median age.

The current study is subject to some limitations. Firstly, due to the study design, calculation of prognostic scores could not be obtained for all patients. However, the retrospective computation of the scores made it possible to evaluate relatively new prognostic systems, such as ELTS score. Secondly, patients' adherence to imatinib therapy and dosage could not be assessed during follow-up. Nevertheless, the study results might have important implications because of providing real-life data. On the other hand, our study also has some strengths. To minimize confounding factors, our study enrolled only patients who received first-line treatment with imatinib and no interferon therapy. In addition, a minimum follow-up period of at least 24 months was set for enrollment in our study to avoid insufficient observation time and to describe a specific patient cohort that is more common in clinical practice.

However, it is important to note that while patient characteristics may predict clinical course, they are not the only determinant of disease prognosis. In addition to patient characteristics, there are other factors that are critical to treatment

management. For example, there have been numerous studies comparing the efficacy of imatinib and new generation TKI therapies [26-28]. Individualization of therapeutic options is an effective tool that improves our position in disease control. Consequently, harmonization of patient characteristics with pharmaceutical data and available facilities would better guide treatment decisions [29].

In conclusion, our results suggest that the EUTOS score system has improved predictive capability for chronic phase CML patients receiving front-line imatinib mesylate therapy. Moreover, higher blast percentage in bone marrow and increased basophil percentage in peripheral blood smear are independent risk factors, adversely related with event-free survival in patients with CML. Large-scale prospective studies are still required to confirm the results of our study.

Author contribution

Study conception and design: NDE, SA, OIÖ and ICH; data collection: NDE and OEC; analysis and interpretation of results: NDE, YB, NS and HD; draft manuscript preparation: NDE, HG and ICH . All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study protocol was approved by the ethical committee of Hacettepe University (Protocol No. GO 17/540/ July 2017).

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Conflict of interest

The authors declare that there is no conflict of interest.

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