RESEARCH ARTICLE

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Predictive Factors for Molecular Response in Chronic Myeloid Leukemia: Reduction Ratio and Halving Time of *BCR::ABL1* IS Transcript Levels

Kronik Myeloid Lösemide Moleküler Yanıtı Öngörücü Faktörler: *BCR::ABL1* IS Transkript Seviyelerinin Azalma Oranı ve Yarılanma Zamanı

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Abstract

Objective: Achieving an early molecular response (EMR) is crucial for improving the prognosis of patients with chronic myeloid leukemia (CML). The halving time (HT) and reduction ratio (RR) of *BCR::ABL1* transcript levels have recently emerged as additional prognostic indexes besides the *BCR::ABL1* International Scale (IS). We aimed to investigate the prognostic role of *BCR::ABL1* transcript levels, HT, and RR on molecular response kinetics at 3 months in patients with newly diagnosed chronic-phase (CP)-CML.

Materials and Methods: Forty patients with CP-CML who received first-line imatinib treatment were included in this study. *BCR::ABL1* transcript levels and molecular responses at baseline and at 3, 6, 12, and 24 months of treatment were evaluated retrospectively. Major molecular response (MMR) at 12 months and event-free survival (EFS) were determined as primary endpoints and the effects of treatment kinetics on these parameters were examined.

Results: Of the 40 patients, *BCR::ABL1* IS was ≤10% at 3 months in 72.5%, representing EMR. The rate of event occurrence was 45.5% in patients with *BCR::ABL1* IS of >10%, whereas it was 6.9% in those with *BCR::ABL1* IS of ≤10% (p=0.004). MMR was detected in 62.1% of the patients with EMR and in 9.1% of those without EMR (p=0.003). The cut-off value for achieving MMR was 24 days for HT and 0.04 for RR. Deep molecular response (DMR) at 24 months was associated with HT of ≤24 days and RR of ≤0.04. EFS was found to be significantly better in the group with *BCR::ABL1* IS of ≤10% and HT of ≤24 days (p=0.001) and in the group with *BCR::ABL1* IS of ≤10% and RR of ≤0.04 (p=0.007) compared to others.

Öz

Amaç: Kronik myeloid lösemili (KML) hastaların prognozunu iyileştirmek için erken moleküler yanıtın (EMR) elde edilmesi çok önemlidir. Son zamanlarda *BCR::ABL1* IS değerinin yanı sıra yarılanma zamanı (HT) ve azalma oranı (RR) gibi kavramlar ek prognostik göstergeler olarak ortaya çıkmıştır. Bu çalışmada yeni tanı kronik faz (KF)-KML hastalarında 3 ayda *BCR::ABL1* IS transkript düzeyi, HT ve RR ile moleküler yanıt kinetiklerinin prognostik rolünü araştırmayı amaçladık.

Gereç ve Yöntemler: Birinci basamak imatinib tedavisi alan KF-KML'li kırk hasta bu çalışmaya dahil edildi. Bazal, 3, 6, 12 ve 24 aylardaki *BCR::ABL1* transkript seviyeleri ve moleküler yanıtlar retrospektif olarak değerlendirildi. On ikinci ay majör moleküler yanıt (MMR) ve olaysız sağkalım (EFS) sonlanım noktaları olarak belirlendi ve bu parametreler üzerindeki tedavi kinetiklerinin etkileri incelendi.

Bulgular: Kırk KF-KML hastasının %72,5'inde 3. ayda *BCR::ABL1* IS ≤ %10'du (EMR). Üçüncü ayda *BCR::ABL1* IS>%10 olanların %45,5 inde olay varken, ≤%10 olanların %6,9'u olaya sahipti (p=0,004). EMR elde edilen hastaların %62,1'inde, elde edilemeyenlerin %9,1'inde MMR saptandı (p=0,003). Bu çalışmada MMR sağlanmasında eşik değeri HT için 24 gün ve RR için 0,04 olarak saptandı. Yirmi dördüncü ay derin moleküler yanıt (DMR), HT ≤24 gün ve RR ≤0,04 olmasıyla ilişkiliydi. *BCR::ABL1* IS ≤%10 ve HT ≤24 gün olan grupta (p=0,001) ve *BCR::ABL1* IS ≤%10 ve RR ≤0,04 olan grupta (p=0,007) diğer gruplara göre EFS belirgin olarak daha iyi bulundu.

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Abstract

Conclusion: Our findings revealed that MMR could be predicted via EMR as well as by HT and RR. Additionally, HT of ≤24 days and RR of ≤0.04 were more important than *BCR::ABL1* IS of ≤10% in achieving DMR at 24 months, and the combination of *BCR::ABL1* IS of ≤10% with both HT of ≤24 days and RR of ≤0.04 has the best predictive value for EFS.

Keywords: Chronic myeloid leukemia, *BCR::ABL1* IS, Halving time, Reduction ratio, Molecular response

Öz

Sonuç: Bulgularımız, MMR'nin, EMR'nin yanı sıra HT ve RR ile de tahmin edilebileceğini gösterdi. Ayrıca, HT ≤24 gün ve RR ≤0,04 olması 24. ay DMR elde edilmesinde *BCR::ABL1* IS ≤%10 olmasından daha önemliydi ve *BCR::ABL1* IS ≤%10 olmasının hem HT ≤24 gün hem de RR ≤0,04 ile kombinasyonu, EFS için en iyi belirleyici değere sahipti.

Anahtar Sözcükler: Kronik myeloid lösemi, *BCR::ABL1* IS, Yarılanma zamanı, Azalma oranı, Moleküler yanıt

Introduction

The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of patients with chronic myeloid leukemia (CML) and life expectancy is now approaching that of healthy individuals of similar age and sex [1,2]. According to the European LeukemiaNet (ELN), achieving *BCR::ABL1* International Scale (IS) values of ≤10% at 3 months, ≤1% at 6 months, ≤0.1% at 12 months, and ≤0.1% any time after 12 months are milestones for an optimal response of chronic-phase (CP)-CML. A second test is required to confirm IS of >10% at 3 months before treatment intervention [2]. Molecular response at 3 months may differ among patients due to various factors such as treatments for relevant comorbidities and intolerance or resistance to TKIs. This has led to a need for developing assessment methods that reflect individual differences in response to therapy. Thus, the halving time (HT) and reduction ratio (RR) of *BCR::ABL1* IS transcript levels have recently received much attention as prognostic markers of imatinib response and outcome in patients with CML [3,4,5,6,7,8,9].

Achieving a major molecular response (MMR) as a result of using TKIs is considered a milestone in patients with CP-CML. Obtaining *BCR::ABL1* IS of ≤10% at 3 months as a marker of early molecular response (EMR) is predictive for achieving MMR and deep molecular response (DMR). *BCR::ABL1* IS of ≤10% at 3 months and ≤1% at 6 months are predictive for overall survival (OS), event-free survival (EFS), and progression-free survival [1,10,11,12,13]. Although second-generation TKI therapies provide earlier achievement of optimal responses, they have not made any difference in OS in the long term [2]. This study aimed to investigate the association between *BCR::ABL1* IS early response kinetics at 3 months and MMR, DMR, and EFS in patients receiving first-line imatinib.

Materials and Methods

A total of 40 newly diagnosed CP-CML patients who received first-line imatinib treatment (400 mg/day) in two centers between March 2013 and January 2018 and underwent molecular evaluation at 3 months were retrospectively analyzed. Treatment responses were evaluated according to the 2013 ELN recommendations. Molecular analyses of peripheral blood samples were performed using quantitative real-time polymerase chain reaction (RT-PCR). Molecular follow-up was performed at the time of diagnosis and at 3, 6, 12, 18, and 24 months after starting treatment. *ABL1* was used as the control gene and the molecular data were converted to IS values using the Ipsogen *BCR::ABL1* Mbcr RGQ RT-PCR Kit. MMR and DMR were defined as *BCR::ABL1* IS transcript levels of ≤0.1% and ≤0.01%, respectively. Patients with 4-log reduction (MR4) and 4.5-log reduction (MR4.5) in transcript levels were included in the DMR group. Exclusion criteria were pregnancy and double cancer at diagnosis.

The primary endpoints were the achievement of MMR at 12 months and EFS during follow-up. According to the 2013 ELN failure recommendations, EFS was defined as the period between the initiation of treatment with imatinib and the date of the first incidence of any event. An event was defined as a change of therapy for any reason other than toxicity, progression to an advanced stage, or death from any cause.

The rate of change in the *BCR::ABL1* IS transcript level was evaluated after 3 months of imatinib treatment. HT was determined by calculating the number of days required for *BCR::ABL1* IS to reach half of its baseline value. HT was calculated using the formula of Branford et al. [4]. RR was calculated as the *BCR::ABL1* IS transcript level at 3 months/baseline [3].

The relationships of *BCR::ABL1* IS, HT, and RR with MMR and DMR were analyzed. In addition, the relationship between HT and RR cut-off values and event risk was evaluated and EFS analysis was performed.

Statistical Analysis

Categorical variables were compared using chi-square or Fisher exact tests. Receiver operating characteristic curve analysis was performed, and the Youden index was used to compute the optimal cut-off values for HT and RR. EFS was determined using the Kaplan-Meier method. The log-rank test was used to identify significant differences between curves. Cox regression was used

to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) to analyze the associations between cut-off levels and molecular responses. An overall p-value of less than 0.05 was considered to signify a statistically significant result. Statistical analyses were performed using SPSS 20. Cumulative incidence analyses were performed using the cumulative incidence of competing events and the Gray test in EZR, which is a graphical user interface of R version 4.1.2.

Results

Demographic data and disease characteristics of the 40 patients with a mean follow-up of 58 months are shown in Table 1.

One patient died because of adenocarcinoma; this patient did not achieve EMR. During follow-up, drugs were changed for six patients owing to treatment failure. Patients who achieved the optimal response were followed with RT-PCR.

BCR::ABL1 IS transcript levels at diagnosis were available for all patients. The HT and RR cut-off values to achieve MMR at 12 months were found to be 24 days (specificity: 85.7%, sensitivity: 78.8%, AUC: 83%) and 0.04 (specificity: 82.3%, sensitivity: 73.6%, AUC: 85%), respectively. At 3 months, none of the patients with *BCR::ABL1* IS of >10% had HT of ≤24 days or RR of ≤0.04. HT was >24 days in only one of the 18 patients who achieved *BCR::ABL1* IS of ≤10% and MMR. During follow-up, the event rate was 6.9% in patients with *BCR::ABL1* IS of ≤10% and 45.5% in those with *BCR::ABL1* IS of >10% (p=0.011). Furthermore, 71.4% of the events occurred in the group of patients with *BCR::ABL1* IS of >10%. EFS was significantly shorter in the groups with *BCR::ABL1* IS of >10%, HT of >24 days, and RR of >0.04 (p=0.002, p=0.001, and p=0.007, respectively).

BCR::ABL1 IS transcript levels, HT and RR cut-off values, response status at 6 and 12 months, and total events are shown in Table 2.

MMR could not be achieved in 37.9% of the patients with *BCR::ABL1* IS of ≤10%, 22.7% of the patients with HT of ≤24, and 15.8% of the patients with RR of ≤0.04 at 3 months. The relationships among HT and RR cut-off values, *BCR::ABL1* IS transcript levels, and MMR and DMR at 12 and 24 months are presented in Table 3. *BCR::ABL1* IS of ≤10%, HT of ≤24 days, and RR of ≤0.04 were found to be significantly associated with

Table 1. Patient characteristics.

Parameters	n=40
Age (years), median (range)	54 (24-79)
Sex, male/female (n/%)	16/24 (40/60)
Sokal score, low-intermediate/high	32/8
EUTOS* score, low-intermediate/high	34/6
ELTS** score, low-intermediate/high	36/4
Baseline *BCR::ABL1* IS transcripts (%), median (range)	73.514 (11.448-278.329)
BCR::ABL1 IS transcripts (%) at 3 months, median (range)	3.645 (0.006-305.895)
BCR::ABL1 IS of ≤10% at 3 months (n/%), EMR-positive	29 (72.5)
HT, median (range)	20.383 (7.498-117.254)
RR, median (range)	0.482 (0.0002-62.831)

*European Treatment and Outcome Study.
**EUTOS Long-Term Survival.

Table 2. Relationships among *BCR::ABL1* IS transcript levels at 3 months, HT and RR cut-off values, response status at 6 and 12 months, and total events.

	BCR::ABL1 IS of >10% at 3 months (%, n=11)	*BCR::ABL1* IS of ≤10% at 3 months (%, n=29)	p	HT of >24 days (%, n=18)	HT of ≤24 days (%, n=22)	p	RR of >0.04 (%, n=21)	RR of ≤0.04 (%, n=19)	p
BCR:: ABL1 IS of ≤1% at 6 months	18.2 (2)	82.8 (24)	0.000	27.8 (5)	95.5 (21)	0.000	38.1 (8)	94.7 (18)	0.000
BCR:: ABL1 IS of ≤0.1% at 12 months	9.1 (1)	62.1 (18)	0.003	11.1 (2)	77.3 (17)	0.000	14.3 (3)	84.2 (16)	0.000
Total events	45.5 (5)	6.9 (2)	0.011	38.9 (7)	0 (0)	0.001	33.3 (7)	0 (0)	0.006

MMR at 12 months. Additionally, HT and RR were associated with DMR at 24 months. The probability of achieving DMR at 24 months was significantly higher in the group of patients with HT of ≤24 days and RR of ≤0.04 (HR=0.221, 95% CI: 0.048-1.010 and HR=0.284, 95% CI: 0.077-1.049, respectively). Risk groups were not predictive of achieving MMR or DMR. There was no correlation between the risk groups based on HT or RR.

In this study, the patients were divided into two groups: those with HT of ≤24 days and those with HT of >24 days. The MMR rates differed between the short and long HT groups (p=0.000). MMR was achieved at 12 months in 77.3% of the patients with short HT, and this value was statistically significant when compared with that of those with longer HT (11.1%) (p=0.000). Of the patients who achieved MMR at 12 months, 94.7% had *BCR::ABL1* IS of ≤10% and 89.5% had HT of ≤24 days at 3 months (p=0.003 and p=0.000, respectively). The patients were divided into two groups according to the RR cut-off value with groups for RR of ≤0.04 and RR of >0.04. The MMR rates were also different between these two groups. MMR was detected at 12 months in 84.2% of the patients with low RR (p=0.000).

The cumulative molecular response rates according to the *BCR::ABL1* IS, RR, and HT cut-off values are illustrated in Figure 1A. Non-CML-related deaths and temporary interruptions of imatinib due to toxicity were considered as competing risks in the analysis. MMR and DMR at 12 and 24 months were calculated using the cumulative incidence and the competing risks. The cumulative incidence graphs for MMR and DMR are shown in Figure 1B.

The patients were also divided into three groups based on the combined evaluation of *BCR::ABL1* IS transcript levels and HT and RR. EFS analysis was performed based on these groups. EFS was significantly higher in patients in the first group compared to the others (p=0.003 and p=0.005, respectively) (Figure 2). It was lower in patients with *BCR::ABL1* IS of >10%.

In the first year, none of the patients with *BCR::ABL1* IS of ≤10% experienced any events, whereas three patients with *BCR::ABL1* IS of >10% had events. One of these patients had a loss of hematological response at 4 months and two patients had IS of >10% and Ph chromosome of >35% at 6 months as ELN 2013 failure criteria. These patients received full-dose imatinib and were compliant to therapy. Additionally, their HT and RR values were >24 and >0.04, respectively.

The evaluation of the correlations among *BCR::ABL1* IS transcript levels, HT, and RR and risk groups revealed a relationship with *BCR::ABL1* IS of >10% only in patients with high European Treatment and Outcome Study (EUTOS) scores (p=0.039). In addition, according to the Sokal score, 50% of the patients in the high-risk group had *BCR::ABL1* IS of >10%, whereas 75% had HT of >24 days and RR of >0.04; however, the differences were not statistically significant. Cytogenetic test results at diagnosis were not available for some of the patients. Therefore, the presence of additional chromosomal abnormalities could not be evaluated. Twelve patients had comorbidities (hypertension, diabetes mellitus, hypothyroidism, and coronary artery disease).

There was no statistical significance between baseline *BCR::ABL1* IS transcript levels and MMR, DMR, or EFS.

Discussion

The results of this study confirmed that the HT and RR of *BCR::ABL1* IS transcript levels at 3 months of imatinib treatment are significant in predicting molecular response rates and EFS. Although various TKI treatments are currently available, the early detection of patients who may require alternative treatments remains an important issue. Recent studies have reported that the rate of decline in the *BCR::ABL1* IS transcript level may be a better predictor of treatment response [6,7,8,9,14,15].

Table 3. MMR and DMR rates according to *BCR::ABL1* IS and HT and RR cut-off values at 3 months.

	MMR at 12 months (%)	p	DMR at 12 months (%)	p	MMR at 24 months (%)	p	DMR at 24 months (%)	p
***BCR::ABL1* IS of ≤10% at 3 months**	62.1	0.003	17.2	0.298	72.4	0.035	37.9	0.076
***BCR::ABL1* IS of >10% at 3 months**	9.1		0		36.4		9.1	
HT of ≤24 days	77.3	0.000	18.2	0.355	86.4	0.001	45.5	0.018
HT of >24 days	11.1		5.6		33.3		11.1	
RR of ≤0.04	84.2	0.000	15.8	0.654	89.5	0.001	47.4	0.023
RR of >0.04	14.3		9.5		38.1		14.3	

Two patients who had *BCR::ABL1* IS of >10% at 3 months and whose drugs were changed were considered as non-responders in the analysis.

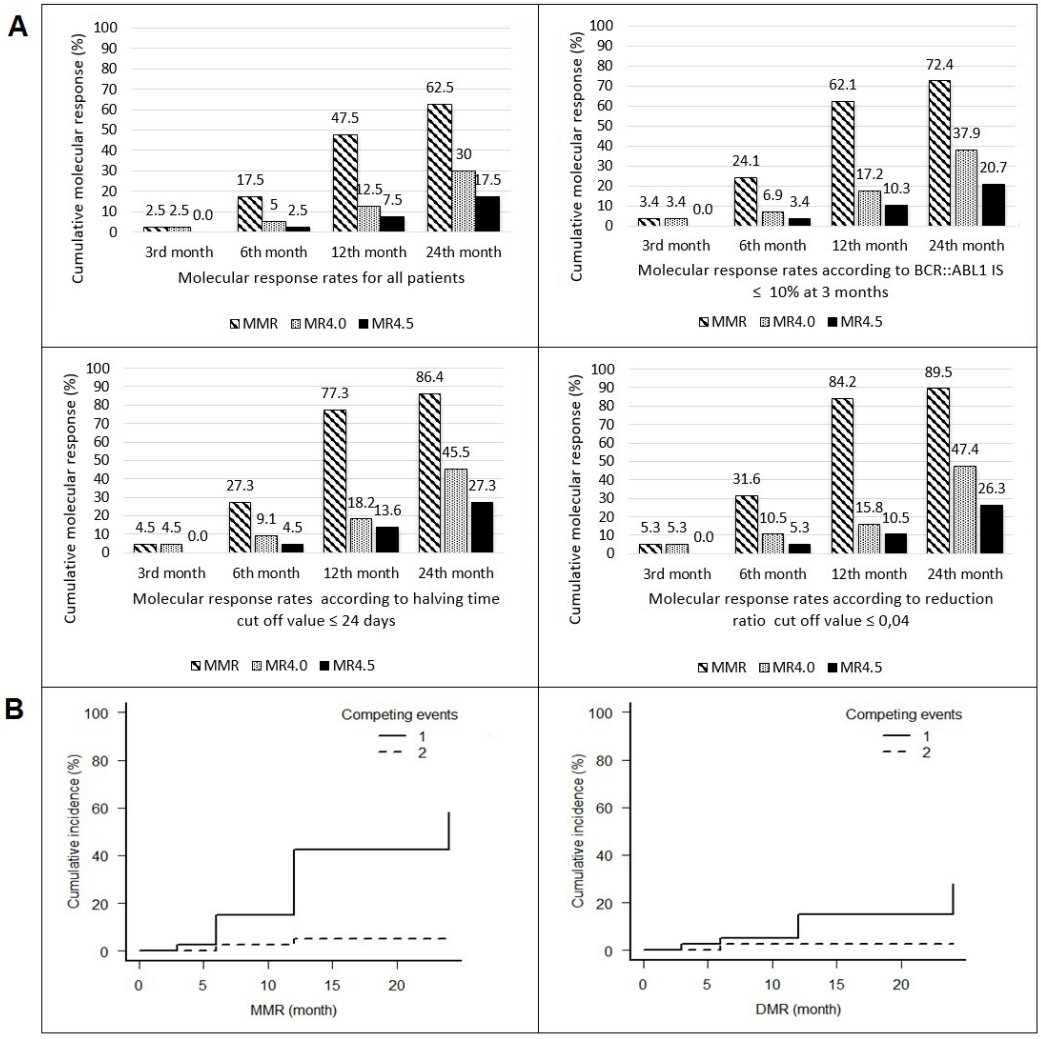

Figure 1. (A) Cumulative molecular response rates according to *BCR::ABL1* International Scale (IS), reduction ratio (RR), and halving time (HT) cut-off values. **(B)** Cumulative incidence graphs for major molecular response (MMR) and deep molecular response (DMR). Non-chronic myeloid leukemia-related deaths and temporary interruptions of imatinib due to toxicity were considered as competing risks in the analysis.

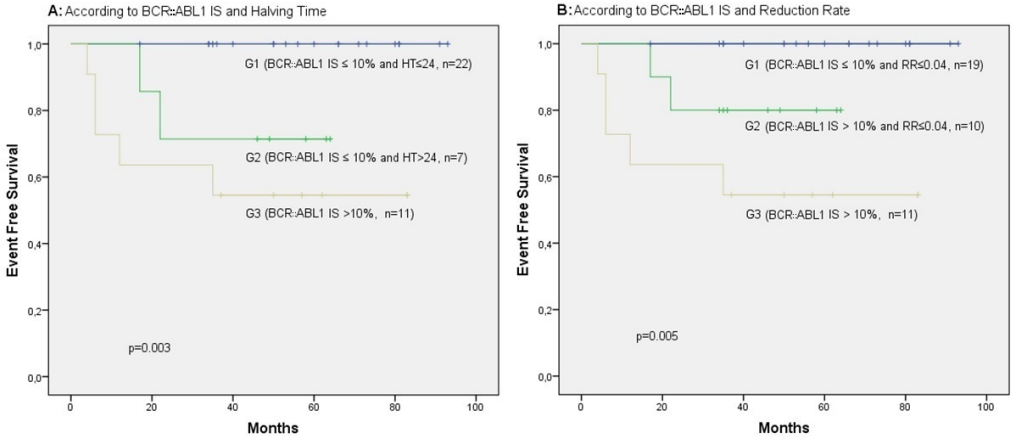

Figure 2. Patients were divided into three groups based on the combined evaluation of *BCR::ABL1* International Scale (IS) transcript levels and halving time (HT) and reduction ratio (RR). Event-free survival (EFS) analysis was performed based on these groups.

Knowing the baseline *BCR::ABL1* IS transcript level enables the evaluation of early transcript kinetics [3,6]. The baseline level is important for the calculation of *BCR::ABL1* kinetics, such as HT and RR at 3 months. A decrease in transcript levels observed before and after TKI treatment may be predictive of EMR and has been shown to have prognostic value in recent years [3,4,6,7]. Our study found that in patients with imatinib-treated CP-CML, the HT cut-off was 24 days and the RR cut-off was 0.04 for achieving MMR at 12 months. HT of ≤24 days and RR of ≤0.04 were significant for achieving MMR at 12 months (p=0.000 and p=0.000, respectively). Our results are consistent with literature data showing the importance of HT and RR [5,6,7,8,16,17]. Baseline *BCR::ABL1* IS transcript level was not associated with Sokal scores, ELTS scores, EFS, MMR, or DMR. These findings are similar to those of previous studies [7,8]. However, Iriyama et al. found a correlation between low baseline *BCR::ABL1* IS transcript levels and MMR [8]. Different reference genes have been used to estimate EMR. More accurate results have been reported with *GUSB*, especially at early time points [18]. Recent comparative studies of *GUSB* and *ABL1* have shown concordant and correlated results; therefore, both control genes are suggested to be used to predict early molecular response [19,20,21]. In general, the *ABL1* control gene is used by the majority of laboratories worldwide.

Hanfstein et al. described the benefit of early reduction of transcript levels in patients treated with imatinib and found that approximately a half-log reduction may be useful in distinguishing disease progression [3]. Branford et al. [4] emphasized that in patients with *BCR::ABL1* IS of >10% at 3 months, HT of >76 days was a critical determinant of poor outcomes. Another study revealed that HT of ≤11 days at 1 month among imatinib-treated patients with high Sokal scores was associated with outcomes equivalent to those of patients with low Sokal scores. Thus, a rapid reduction in the transcript level could be effective in overcoming negative effects in high-risk patients [5]. High-risk patients with short HT may have outcomes similar to those of low-risk patients; however, we could not confirm such results due to the small number of high-risk patients in this study.

Murai et al. [7] analyzed RR and HT at 3 months in patients receiving first-line dasatinib therapy and showed that RR of ≤0.018 and HT of ≤12.1 days determined DMR at 12 months. They also reported that RR at 3 months was more decisive than HT and *BCR::ABL1* IS in distinguishing high-risk patients. Another study investigating patients treated with first-line dasatinib found that the optimal responses at 12 months could be predicted in patients with HT of ≤14 days [8]. We did not find any correlation between HT or RR and DMR at 12 months; however, we found associations between HT and RR and DMR at 24 months. We think that this difference could be attributed to the early achievement of DMR with second-generation TKI therapies [22,23]. However, the correlation between the three kinetic parameters and MMR at 12 months was also confirmed in our study (Table 3).

Consistent with previous studies, this research confirmed that there is a significant difference between patients with *BCR::ABL1* IS of ≤10% and those with *BCR::ABL1* IS of >10% at 3 months of treatment [6,12]. Patients with *BCR::ABL1* IS of >10% according to the ELN recommendations demonstrated significantly lower response rates. These results were also supported by the HT and RR cut-off values. In this study, MMR could not be achieved at 12 months in 90.9% of the patients with *BCR::ABL1* IS of >10%, 88.9% of those with HT of >24 days, and 85.7% of those with RR of >0.04.

In the present study, the patients were divided into three groups based on combined evaluations of *BCR::ABL1* IS and HT and *BCR::ABL1* IS and RR, and they were assessed in terms of event occurrence. In both categories, a significant difference in EFS was seen between the patients in group 1 (HT of ≤24 days, *BCR::ABL1* IS of ≤10%, and RR of ≤0.04, *BCR::ABL1* IS of ≤10%) and those in groups 2 and 3 (Figure 2). Fava et al. [6] also showed better EFS in patients with HT of ≤17 days and *BCR::ABL1* IS of ≤10%. Additionally, Zhang et al. [9] found that HT of ≤22 days and a log reduction of >0.61 in the transcript levels of imatinib-treated patients with *BCR::ABL1* IS of ≤10% resulted in a significant difference in EFS.

In recent years, treatment discontinuation studies have become increasingly important. It has been shown that treatment can be terminated in imatinib-treated patients who achieve sustained DMR. Achieving EMR and stable DMR are crucial for discontinuation of TKI therapy [24]. Treatment discontinuation studies have demonstrated that patients with shorter HT achieve DMR earlier and have treatment-free remission (TFR) for longer periods than those with longer HT. The decline rate of the *BCR::ABL1* IS transcript is predictive of sustained TFR [5]. A study by Shanmuganathan et al. [25] established sustained TFR at a rate of 80% in patients with HT of ≤9.35 days. Therefore, HT and RR are promising in terms of their potential as predictors of sustained TFR.

There were some limitations of our study, including its retrospective design and relatively small number of patients.

Conclusion

The findings of this study have confirmed the importance of determining the HT, RR, and *BCR::ABL1* IS transcript levels at 3 months of imatinib therapy in patients with CP-CML. Our data suggest that MMR and DMR can be predicted using a combination of these parameters. Early identification of patients who are in the warning group according to ELN recommendations may allow the detection of those who would benefit from early

administration of alternative therapy to improve their responses and minimize the risk of progression. HT and RR are molecular parameters that can serve as prognostic indicators, and they can be easily calculated; however, it is important to know the baseline *BCR::ABL1* IS transcript level when performing these kinetic calculations.

Ethics

Ethics Committee Approval: This study was conducted in line with the Declaration of Helsinki and approved by the local ethics committee.

Authorship Contributions

Concept: F.C., S.D., İ.D., G.Ö.; Design: F.C., S.D.; Data Collection or Processing: F.C., S.A., M.A.U., G.K., M.G., Ş.B.M.Ö.; Analysis or Interpretation: F.C., M.F., B.Ç.; Literature Search: F.C.; Writing: F.C., S.D.

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