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Analysis of factors predicting the efficacy of Imatinib in patients with Chronic Myeloid Leukemia: A retrospective analysis

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ABSTRACT

Objective: Imatinib is a commonly used first generation tyrosine kinase inhibitor for patients with chronic myeloid leukemia (CML). The efficacy has been reported as very high even in recent studies.

Material and methods: A retrospective analysis was made of newly diagnosed CML patients treated with Imatinib as a first-line agent from January 2010 to January 2020. The patients were classified as those who obtained an adequate response and those for whom treatment was discontinued due to inadequate efficacy. The two groups were compared to analyze factors predicting the efficacy of the agent.

Results: Evaluation was made of a total of 47 CML patients, comprising 20 females (42.6%) and 27 males (57.4%) with a median age of 55 years. Imatinib was discontinued in 19 patients because of inadequate response, and 28 patients were still continuing the treatment at the end of median 33.3 months follow-up duration. At the end of follow-up, there were 44 survivors (93.6%), and 3 non-survivors (6.4%). Median Bcr-Abl (IS, %) at the time of diagnosis in patients with response was higher than patients in discontinued group (67.6 [0.0-291.4] vs 41.9 [0.0-208.5], p=0.022). All other disease and demographic characteristics were similar in both groups (p>0.05).

Conclusion: Almost 10 years of follow-up demonstrated that there is still an unmet need to determine factors predicting the response to Imatinib in CML patients. Larger population-based studies are required to specify patients with high risk at the time of diagnosis to monitor closely.

Keywords: chronic myeloid leukemia, CML, Imatinib, efficacy, response

INTRODUCTION

Chronic myeloid leukemia (CML) is defined as a chronic myeloproliferative disease. CML is characterized by clonal proliferation in myeloid cells due to abnormal tyrosine kinase activity (TKA), which is also a fatal disease after its transformation from chronic phase (CP) to accelerated phase (AP) and blastic phase (BP) if untreated. The permanently active TKA is caused by the Bcr-Abl (breakpoint cluster region- Ableson leukemia virus) fusion gene, resulting from an abnormal genetic translocation between chromosomes 9 and 22 (1).

Tyrosine kinase inhibitors (TKIs) inhibit the protein's enzyme activity by strongly blocking the interaction between Bcr-Abl 1 onco-protein and adenosine triphosphate (ATP), thereby controlling immortal TKA and malignant clonal proliferation. When the disease course of patients diagnosed with CML with a tyrosine kinase inhibitor, which is defined as targeted therapy, was examined, the survival rate reached 90% and almost approached the normal population (2-4). Imatinib mesylate is a selective inhibitor of Bcr-Abl tyrosine kinase, which plays a key role of the pathogenetic mechanism of CML. It also prevents ATP's interaction with ABL protein and protein phosphorylation. The IRIS [International Randomized Study of Interferon and STI571] demonstrated the superior cytogenetic and hematological responses of Imatinib than interferon alfa and cytarabine, Imatinib became the first TKI agent to be used in CML patients (5).

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This study aimed to determine whether there is a possible early predictor of response to Imatinib treatment by evaluating the response analysis after Imatinib treatment in CML patients, including demographic and disease characteristics.

MATERIAL AND METHODS

A retrospective analysis was made with newly diagnosed CML patients who were treated with Imatinib as a first-line agent from January 2010 to January 2020 in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital. We classified the patients as those who achieved adequate response and those who were discontinued due to inadequate efficacy (6).

Patients in whom Imatinib was cessated due to adverse events or other causes were excluded. Two groups were compared to analyze factors predicting the efficacy of the agent. While the "Independent Sample-t" test (t-table value) is used to compare the measurement values of two independent groups in the data with normal distribution; "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in the data that do not have a normal distribution X2-cross tables were used to examine two qualitative variables.

RESULTS

Totally 47 CML patients with a median age of 55 years were included. There were 20 female (%42,6) and 27 male (%57,4) subjects. Among them, Imatinib was discontinuated in 19 patients because of inadequate response whereas 28 patients were still going on at the end of the median 33,3 months follow-up duration. At the end of follow-up, there were 44 survivors (%93,6), and 3 nonsurvivors (%6,4). There was no mortality in patients who achieved optimal response. Demographic characteristics of the patients were given in **Table1**. Mean Imatinib treatment duration in patients for whom Imatinib was discontinued due to inadequate response was 18,79±20,34 months (median 13,7 months). Evaluation of differences or relationships in hematological and biochemical parameters in Imatinib-responsive and unresponsive patients is given in **Table2**. There is no significant difference among all parameters according to the groups (p>0,05). The comparison of disease characteristics and treatment responses of Imatinib-responsive and unresponsive patients is given in **Table 3**. A statistically significant difference was found between the groups in terms of initial BCR-ABL value. Patients who responded optimally to Imatinib treatment had a statistically significantly higher BCR-ABL value at the time of diagnosis than those discontinued due to insufficient efficacy. (p=0,022). As a result of the Logistic regression model (Backward: LR) revealed no parameter had an impact on response to Imatinib treatment (p> 0.05).

Table 1. The demographic characteristics of the patients

	All patients (N=47)	Optimal Response (n=28)	Inadequate response (n=19)
Gender			
Female	20 (42,5%)	12 (%42,9)	8 (%42,1)
Male	27 (57,5%)	16 (%57,1)	11 (%57,9)
Age, median, range [years]	55 [25-89]	53,32±13,95	55,42±14,52
Follow-up duration			
median,range(month)	33,9[0,23-171,9]	24,9[0,23-138]	44[5,7-171,9]
Final status			
Survivor	44 (93,6%)	28 (100%)	16 (84,2%)
Nonsurvivor	3 (6,6%)	0	3 (15,8)

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Table 2. Evaluation of hematological and biochemical parameters in Imatinib-responsive and unresponsive patients

N=47	İmatinib treatment		*P*
	Inadequate response (n=19)	Optimal Response (n=28)	
Gender			
Female	8 (%42,1)	12 (%42,9)	0,959
Male	11 (%57,9)	16 (%57,1)	
Age (year)	55,42±14,52	53,32±13,95	0,621
Hemoglobin(g/dL) Median [Min-Max]	11,16±3,21	11,60±2,41	0,594
WBC($\times10^3/mm^3$) Median [Min-Max]	155000,0 [8000,0-576500,0]	62400,0 [5100,0-252430,0]	0,260
Neutrophil ($\times10^3/mm^3$) Median [Min-Max]	60103,5 [3970,0-393000,0]	51200,0 [3200,0-214600,0]	0,500
Platelet($\times10^3/mm^3$) Median [Min-Max]	315000,0 [206000,0-1190000,0]	266500,0 [64000,0-3803000,0]	0,335
Basophil ($\times10^3/mm^3$) Median [Min-Max]	220,0 [0,0-25310,0]	330,0 [0,0-21400,0]	0,879
Monocyte ($\times10^3/mm^3$) Median [Min-Max]	2150,0 [400,0-28440,0]	1710,0 [200,0-8600,0]	0,480
LDH(/l) Median [Min-Max]	792,0 [184,0-2287,0]	532,0 [165,0-2253,0]	0,569
Ferritin (ng/mL) Median [Min-Max]	60,0 [4,0-1119,0]	58,0 [2,2-543,0]	0,831
Vitamin B12 (pmol/L) Median [Min-Max]	803,26±578,96	1044,16±540,26	0,163
Platelet/ lymphocyte	57,0 [7,4-172,1]	56,7 [9,1-845,1]	0,982
Lymphocyte/monocyte	3,3 [0,4-10,7]	2,8 [0,7-20,0]	0,889
Neutrophil/lymphocyte	11,0 [1,2-53,0]	8,4 [1,8-33,3]	0,787

Table 3. The comparison of disease characteristics and treatment responses of Imatinib-responsive and unresponsive patients

N=47	Imatinib treatment		*P*
	Inadequate response (n=19)	Optimal Response (n=28)	
Splenomegaly			
No	10 (%52,6)	9 (%32,1)	0,217
Yes	9 (%47,4)	19 (%67,9)	
Bone marrow blast at diagnosis			
<%5	8 (%72,7)	9 (%64,3)	0,889
%5-10	2 (%18,2)	3 (%21,4)	
>%10	1 (%9,1)	2 (%14,3)	
Eutos score Median [Min-Max]	9,5 [0,0-82,0]	13,0 [0,0-131,0]	0,364
Sokal score Median [Min-Max]	0,9 [0,6-2,7]	1,0 [0,6-2,0]	0,963
ELTSeutos score Median [Min-Max]	1,88±0,56	1,68±0,46	0,248
BCR-ABL IS at diagnosis (%) Median [Min-Max]	41,9 [0,0-208,5]	67,6 [0,0-291,4]	**0,022**
Bcr-Abl IS at 3rd month			
≤10	8 (%57,1)	15 (%71,4)	
>10	6 (%42,9)	6 (%28,6)	0,611
Bcr-Abl IS at 6th month			
≤1	7 (%50,0)	17 (%85,0)	
>1	7 (%50,0)	3 (%15,0)	0,054
Bcr-Abl IS at 12th month			
≤0,1	2 (%18,2)	13 (%76,5)	
>0,1	9 (%81,1)	4 (%23,5)	**0,006**
Final status MMR			
Yes	8 (%42,1)	7 (%25,0)	0,339
No	11 (%57,9)	21 (%75,0)	

DISCUSSION

Imatinib is the first and still commonly used TKI for patients with CML. The higher efficacy was reported in many studies even in recent real-life experiences. In a recent study, after approximately 11 years of long-term follow-up, the overall survival rate in patients receiving Imatinib was reported as 83.3%, while the complete cytogenetic remission rate (CCyR) was 83%, and the 10-year major molecular response (MMR) rate was 93% (7). However, long-term results of the IRIS study showed that 33% of the patients who received first-line Imatinib treatment did not have a complete hematological response while 39% of the patients did not achieve major cytogenetic response at the end of 5-year follow up (8). In the current study, 40% of patients could not continue the drug due to efficacy after the first-line Imatinib treatment, and similar results were observed with the studies. Although there are second and advanced-generation TKIs for Imatinib-unresponsive patients, the whole world had no chance to obtain those agents due to financial or other medical reasons. Therefore, it would have been better to know factors that have an impact on Imatinib efficacy, especially those easily obtainable and modifiable risk factors. Sokal, Euro, and European Treatment of Outcome Study (EUTOS) and Hasford scores are used to determine the most appropriate treatment and follow-up program before the treatment (9). According to risk stratification, high and low risk patients not only change their initial TKI agents but also the likelihood of reaching CCyR and MMR values early, which is lower in high risk patients. Furthermore, unfortunately, high-risk patients have a higher chance of the disease transforming into CML-AP or CML-BP. As we know that initial risk stratification of the patients is very important, there is still no consensus about the effect of those scores on long term Imatinib response. It has been shown that the early molecular response (BCR-ABL1 transcripts [IS] <10% at 3 months) has a strong prognostic value and can also be achieved with Imatinib or other TKIs. Studies also state that patients on CCyR under Imatinib treatment have similar survival without reaching MMR. Patients with negative and/or BCR-ABL1 transcripts [IS] <1% by FISH analysis from peripheral blood at 6 or 12 months are likely to be in CCyR (6).

Although ABL seems to be a minimal residual disease marker in CML patients, the Bcr-Abl ratio may give false low transcript rates. The prognostic impact of the 3-month BCR-ABL transcript response may be related to the harshness of treatment response or the tumor burden. Therefore, there are studies suggesting that the half-log reduction rate at the BCR-ABL transcript level in 3 months is more accurate in terms of prediction (10). On the contrary, some studies have determined that patients with high Bcr-Abl transcript levels are less likely to benefit from imatinib treatment (11). Both studies were based on Bcr/Abl/gus IS values, and achieving different results showed that there is still a need for studies on the prognostic prediction of Imatinib treatment. In the current study, a statistically significant difference was found between the groups in terms of initial Bcr-Abl value. Patients who responded optimally to Imatinib treatment had a statistically significantly higher Bcr-Abl value at the time of diagnosis than those discontinued due to insufficient efficacy. However, as a result of the Logistic regression model revealed no parameter had impact on response to Imatinib treatment.

There are also some limitations in our study. Patients diagnosed with CML whose survival rates are close to the normal population with current treatments should have a longer total follow-up period. We obtained patient data from a single center, which may limit the generalizability of the results. Other limitations are that the study is a retrospective design and the need for larger prospective studies to be analyzed.

CONCLUSION

In conclusion, with Imatinib, a commonly used TKI in CML patients, survival rates approached the healthy population statistics and similar results were obtained when the response rates and side effects of the study were compared with the results of real-world studies. Response after Imatinib treatment in CML patients was evaluated, including demographic and disease characteristics and it revealed no impact of any parameter on response to Imatinib treatment. Larger population-based studies are needed to determine significant factors.

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