Imatinib mesylate in first-line treatment of chronic myeloid leukemia

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Abstract
Objective: Chronic myeloid leukemia (CML) is a myeloproliferative disease characterized by clonal proliferation of myeloid cells. In this study we aimed to present our experience in patients with CML who used imatinib mesylate, a tyrosine kinase inhibitor (TKI).

Aim: Sixty nine patients who were diagnosed with CML and were treated with first-generation TKI (in the form of imatinib mesylate) as initial treatment between 2006 and 2018 were included in this retrospective study. The demographic characteristics, response rates (hematologic, cytogenetic and molecular), adverse events and overall survival (OS) rates were retrospectively analyzed.

Results: There were 28 male and 41 female patients with a median age of 49.3. Hematologic, cytogenetic and molecular responses to TKI treatment were evaluated according to the 2013 guidelines of European Leukemia Net (ELN). The complete hematologic response (CHR) rate at three months was 97.1%, the complete cytogenetic response (CCR) rate at 12 months was 73.4%, and the major molecular response (MMR) at 18 months was 77.8%. The most common adverse events were cytopenia (13%), edema (10.1%), nausea/vomiting (7.2%), and musculoskeletal pain (5.8%). The mean follow-up period was 40.4 months for all CML patients, with an overall survival (OS) rate of 84.6% during follow-up.

Conclusion: As a real life data in our population, our results were consistent with those reported in the literature. Drug-related adverse events were minimal and tolerable. Long-term survival and disease-free survival can be achieved with proper cytogenetic and molecular monitoring under imatinib treatment and, if necessary, a change in medication.

Keywords: Chronic myeloid leukemia; tyrosine kinase inhibitor; imatinib.

INTRODUCTION
Chronic myeloid leukemia (CML) is characterized by abnormal clonal proliferation of myeloid cells and accounts for 20% of all adult leukemias (1). Its incidence is 1-2 per 100,000, and it occurs more frequently in males than in females, with most patients diagnosed in their 50s or 60s (2). The molecular defect that causes the disease is the formation of the BCR-ABL fusion gene encoded by the Philadelphia (Ph) chromosome, which is formed by translocation between chromosomes 9 and 22. Molecules encoded by the BCR-ABL fusion gene cause an increase in tyrosine kinase activity. The result is the development of a disease profile characterized by excessive proliferation of Ph positive cell clones and reduced apoptotic activity (3). CML presents in the form of three distinct clinical phases: chronic phase (CP-CML), accelerated phase (AP-CML), and blastic phase (BP-CML). While the vast majority of patients are diagnosed in the chronic stage, progression to AP and/or BP is observed when the disease is untreated and left to its natural course or when there is no response to treatment and/or due to disease progression (4). Clinical findings differ in the diagnosis of CML and may vary depending on the stage of the disease at the time of diagnosis. Twenty to fifty percent of patients are asymptomatic and are diagnosed incidentally in routine blood tests. In symptomatic patients, clinical findings are fatigue, weakness, weight loss, excessive sweating, abdominal distension, and bleeding attacks related to platelet dysfunction (5).

Prior to the use of imatinib in the treatment of CML, busulfan, hydroxyurea, interferon, and allogeneic stem cell transplantation were used. In the event of treatment failure, patients died within an average of 4-5 years by progressing from chronic stage to accelerated and/or blastic stage (6). With the use of imatinib mesylate, a tyrosine kinase inhibitor (TKI), in the treatment of CML,
long survival time became the expectation, a goal that was ultimately achieved (7,8). In 1998, following the introduction of the specific BCR-ABL1 tyrosine kinase inhibitor imatinib mesylate (STI571) into clinical practice, the era of imatinib in the treatment of CML began (9). After publication of the “International Randomized Study of Interferon and ST1571” (IRIS) study, imatinib mesylate started to be accepted as the standard treatment for chronic phase CML. In IRIS study, imatinib response was evaluated in patients who were resistant to or intolerant of interferon. Imatinib showed less toxicity and higher hematologic and cytogenetic response rates. According to the 5-year data of the IRIS study, a 97% complete hematologic response and 82% complete cytogenetic response were obtained with imatinib mesylate therapy in CML. The overall survival (OS) rate was reported to be 90%, while the survival rate in the chronic stage was 93%. Following widespread use of imatinib, some patients developed imatinib unresponsiveness (in the form of additional mutation or resistance) or intolerance. Thereafter, second generation tyrosine kinase inhibitors (dasatinib, nilotinib and bosutinib) and third generation TKI (ponatinib) were introduced (10-12).

Hematologic, cytogenetic, and molecular responses are all evaluated in the follow-up of CML patients. In the physical examination, splenomegaly, complete blood count, and peripheral blood smear are analyzed to evaluate hematologic response. Cytogenetic and molecular monitoring are performed using fluorescence in situ hybridization (FISH) analysis and reverse-transcriptase polymerase chain reaction (RT-PCR) (13). The fundamental goal is to obtain cytogenetic, molecular, and hematologic treatment responses in CML. Diagnosis, treatment, and follow-up of CML should be conducted in light of current studies. Adverse events, the development of resistance, cost effectiveness of the drug, and the demographic characteristics of patients should be evaluated as a whole in treatment of the disease (14). In this study, we aimed to evaluate the demographic characteristics and treatment response rates of patients diagnosed with CML who received follow-up care and treatment with imatinib mesylate in our hematology clinic.

MATERIAL and METHODS

Patients
This study included CML patients who were newly diagnosed in our clinic between 2006 and 2018 and were given first generation tyrosine kinase inhibitor imatinib mesylate as the first-line treatment. Patients for whom hematologic, cytogenetic, and molecular test results could not be obtained after diagnosis, those who did not receive regular follow-up and controls, and individuals under 18 years of age were excluded from the study. Demographic data at the time of diagnosis, disease stage, spleen size (distance from the costal angle in cm), laboratory findings, clinical course, treatment responses and adverse events were evaluated retrospectively. Sokal and Hasford risk scores were used to identify the risk status of the patients.

Treatment response evaluation
Hematologic, cytogenetic, and molecular responses were assessed according to the criteria of European Leukemia Network (ELN; 2013). Evaluations were made based on the time elapsed since the treatment start date. The patients’ hematologic, cytogenetic, and molecular responses were assessed at 3, 6, 12, and 18 months. Patients who did not respond to imatinib or underwent treatment changes due to adverse events were also evaluated retrospectively.

Patients were evaluated with regard to the following: complete hematologic response (CHR), normalization of leukocyte and platelet counts within 3 months of treatment (leukocytes: < 10 × 10⁹/L, platelets: < 450 × 10⁹/L), less than 5% of myelocyte and metamyelocytes in the peripheral blood smear, no detection of blasts or promyelocytes, no involvement of the extramedullary, whether the spleen was non-palpable, and no signs of accelerated or blastic phase.

Cytogenetic response was assessed according to the percentage of Ph positive metaphases calculated using the FISH method. Complete cytogenetic response (CCR) was defined as 0% identified as Ph positive metaphase, partial cytogenetic response as 1-35%, minor cytogenetic response as 36-65%, minimal cytogenetic response as 66-94%, and no response as 95% and above.

Molecular response was evaluated based on BCR-ABL1 levels as determined by the RT-PCR method. Prior to 2012, quantitative BCR-ABL transcript levels were measured by RT-PCR in our hospital. According to the method, major molecular response (MMR) is defined as a 3-log decrease in the level of BCR-ABL transcripts and complete molecular response (CMR) as the absence of detected BCR-ABL transcripts. After 2012, the international scale system (IS), a more sensitive method calculated on the basis of international standardization, was introduced. The IS values for definitions of response are 0% for CMR and < 0.1% for MMR.

Ethics consent
Ethics approval was obtained from the non-invasive clinical research ethics committee of the medical faculty (date/number: 31.01.2018/003). All aspects of the study, including periodical clinical and laboratory checks were performed according to the principles of the declaration of Helsinki (64th, 2013).
Statistical Analysis
For statistical analysis of the data, SPSS (ver: 21) statistical package program was used. Descriptive statistics were used for continuous variables, expressed as median, standard deviation, and minimum and maximum values, while categorical variables were expressed as numbers and percentages. The Student's t-test was used to compare group medians for continuous variables. In addition, the Kaplan-Meier method was used to determine the median survival time of the patients. The level of statistical significance was set at a value of \( p < 0.05 \).

RESULTS

Demographic and clinical characteristics of the CML patients
Our study included 69 patients (median age: 49.3 ± 12.3 years), of whom 28 (40.6%) were males and 41 (59.4%) females, with median ages of 48.4 ± 13.1 and 49.5 ± 14.4 years, respectively. Seven patients (10.1%) had additional chronic diseases such as diabetes mellitus and hypertension. The median leukocyte count at the time of admission was 115.2 × 10^9/L, the median platelet count was 461.8 × 10^9/L, and median hemoglobin level was 12.7 g/dl. The median basophils and median eosinophils percentages were 1.4% and 1.7%, respectively. Physical examination revealed a median splenomegaly size of 3.8 cm. Based on the diagnostic criteria of the World Health Organization (WHO), 67 patients (97.1%) had chronic phase and 2 patients (2.9%) had accelerated phase CML, while none had blastic phase. The median lactate dehydrogenase level was 918 IU/L (range; 321-3288). At the time of diagnosis, the median IS score measured using the RT-PCR method was 80.6% (range: 12-376). The patients’ risk statuses were determined based on their Sokal and Hasford risk scores. According to the Sokal risk scores, 39 (56.5%) patients were low risk, 24 (34.8%) were intermediate risk, and 6 (8.7%) were high risk, while the Hasford risk scores identified 42 (60.9%) patients as low risk, 25 (36.2%) as intermediate risk, and only 2 (2.9%) as high risk. There was no significant relationship between Sokal risk score and the CHR, CCR and MMR in the 3rd, 6th, 12th, or 18th month. While CHR developed in 39 patients with low Hasford risk scores in the 3rd month and in one patient in the 6th month, in those with intermediate risk scores CHR developed in 19 patients in the 3rd month and 6 patients in the 6th month. CHR occurred in only one patient with a high Hasford risk score in the 3rd month. A significant relationship between the Hasford risk score and imatinib treatment response was observed; as the former increased, a decrease in the latter was detected (\( p = 0.022 \)) (Table 1).

Treatment and outcomes of CML patients
The first TKI administered to all patients treated for CML was imatinib mesylate. The patients' response rates to the TKI treatments are presented in Table 2. Patients who were initially treated with imatinib but used second generation TKI due to insufficient response, intolerance, or loss of response were also included. At the time of the final follow-up appointments, 51 patients (73.9%) were receiving imatinib and 18 patients (26.1%) were receiving second generation TKIs.

Hematologic response: Sixty-seven patients (97.1%) showed a complete hematologic response (CHR) within three months following initiation of imatinib treatment. In the sixth month, CHR was observed in all patients taking imatinib.

Cytogenetic response: Cytogenetic responses were evaluated by medians of the FISH test. In the 3rd month, complete cytogenetic response (CCR) was obtained in 13 patients (18.8%) and major cytogenetic response (MCR) in 15 patients. Sixty-six patients were evaluated for cytogenetic response in the 6th month, of whom 38 (57.6%) showed CCR and 52 (78.8%) had MCR. At 12 months, 64 patients were evaluated for cytogenetic response, with 47 patients (73.4%) showing CCR and 61 (95.3%) with MCR. CCR occurred in 77.8% of patients receiving follow-up in the 18th month.

Molecular response: The RT-PCR test for the BCR-ABL1 gene product from the patients’ peripheral blood was examined for molecular response levels. The results were classified according to ELN criteria. In the 3rd month, major molecular response (MMR) was achieved in 6 (9%) out of 54 patients, but no complete molecular response (CMR) was obtained. Of the 66 patients evaluated in the 6th month, 39 (59.1%) had MMR and 8 (12.1%) showed CMR. In the 12th month, 64 patients were evaluated, of whom MMR was achieved in 44 (67.8%) patients and CMR was achieved in 21 (32.8%) patients. At the end of the 18th month 50 (78.1%) patients had still and 31 patients (48.4%) had CMR.

Management of imatinib treatment failure
There were 18 patients who received second generation TKIs due to imatinib intolerance, nonresponse, and/or loss of treatment response. Of these, 14 were switched to dasatinib and 4 were switched to nilotinib. The switch to second generation TKIs was related to imatinib intolerance or serious adverse events in 4 patients, cytogenetic unresponsiveness in 4 patients, loss of cytogenetic response in 2 patients, molecular unresponsiveness in 5 patients, and loss of molecular response in 3 patients (Table 3). Transformation to blastic phase was detected upon evaluation of the loss of cytogenetic and hematologic response in one patient under imatinib treatment at 6 months. The patient was administered high-dose chemotherapy plus dasatinib as TKI, and proceeded to allogeneic stem cell transplantation.

Adverse events
The most common adverse events related to treatment were cytopenia (13%), edema (10.1%), nausea/vomiting (7.2%), and musculoskeletal pain (5.8%). The majority of these were grade 1 and 2 side effects that did not necessitate a change in treatment.
Pregnancy in CML patients
During the follow-up period, 5 patients treated with imatinib became pregnant. Interferon treatment was initiated in 2 patients following the diagnosis of pregnancy, while 3 patients persisted in using imatinib, rejected the proposed treatment change and were informed of the risks. CCR and MMR continued in patients who still used imatinib. Loss of CCR and MMR was observed in one of the patients who used interferon; imatinib was subsequently resumed. CCR and MMR were obtained at 6 months following treatment with imatinib. Any problem was observed in patients and infants during and after pregnancy.

Survival
The median follow-up period was 3.4 years (40.4 months, min: 3 - max: 145 months). During the follow-up period, 6 (8.6%) of 69 patients died. Four of these patients died following complications related to their disease due to a lack of response to 1st and 2nd generation TKIs and the absence of appropriate hematopoietic stem cell donors. Two patients died due to secondary malignancy and cardiovascular events. The overall survival (OS) rate was 84.6%.

Table 1. Demographic and clinical characteristics of patients with CML.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median ± SD)</td>
<td>49.3 ± 12.3</td>
</tr>
<tr>
<td>Male, years (median ± SD)</td>
<td>48.4 ± 13.1</td>
</tr>
<tr>
<td>Female, years (median ± SD)</td>
<td>49.5 ± 14.4</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (40.6)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (59.4)</td>
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<tr>
<td>Splenomegaly, cm; median (min-max)</td>
<td>3.8 (2.6-18)</td>
</tr>
<tr>
<td>Leukocyte count, 10^9/L; median (min-max)</td>
<td>115.2 (22-459)</td>
</tr>
<tr>
<td>Basophils, %; median (min-max)</td>
<td>1.4 (1.2-7.4)</td>
</tr>
<tr>
<td>Eosinophils, %; median (min-max)</td>
<td>1.7 (0.7-8.7)</td>
</tr>
<tr>
<td>Platelet count, 10^9/L; median (min-max)</td>
<td>461.8 (21-1728)</td>
</tr>
<tr>
<td>Hemoglobin level, g/L; median (min-max)</td>
<td>12.7 (7.6-16.6)</td>
</tr>
<tr>
<td>Blasts in peripheral blood, %</td>
<td>4.2 (1-9)</td>
</tr>
<tr>
<td>Disease phase at the time of diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic phase</td>
<td>67 (97.1)</td>
</tr>
<tr>
<td>Accelerated phase</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Blastic phase</td>
<td>0</td>
</tr>
<tr>
<td>LDH, IU/L; median (min-max)</td>
<td>918 (321-3288)</td>
</tr>
<tr>
<td>IS score %; median (min-max)</td>
<td>80.6 (12-376)</td>
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<tr>
<td>Sokal risk group, low, n (%)</td>
<td>39 (56.5)</td>
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<tr>
<td>Sokal risk group, intermediate, n (%)</td>
<td>24 (34.8)</td>
</tr>
<tr>
<td>Sokal risk group, high, n (%)</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>Hasford risk group, low, n (%)</td>
<td>42 (60.9)</td>
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<tr>
<td>Hasford risk group, intermediate, n (%)</td>
<td>25 (36.2)</td>
</tr>
<tr>
<td>Hasford risk group, high, n (%)</td>
<td>2 (2.9)</td>
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</tbody>
</table>

LDH; lactate dehydrogenase, IS; International Scale System
Artificial intelligence is a rapidly evolving field that holds tremendous potential for advancements in medicine. It has the potential to revolutionize healthcare by improving diagnostics, personalizing treatments, and enhancing patient outcomes. However, several ethical and societal implications must be considered to ensure that AI is developed and deployed in a responsible manner.

One of the primary implications of AI in medicine is the potential for increased efficiency and accuracy in diagnostic procedures. Artificial intelligence algorithms can analyze vast amounts of medical data, identify patterns, and make predictions that may be more accurate than human professionals. This can lead to faster and more accurate diagnoses, which can result in earlier treatment and better outcomes for patients.

Another significant implication of AI in medicine is the potential for personalized treatment plans. AI can analyze a patient's individual characteristics, such as genetic makeup, lifestyle, and medical history, to develop a tailored treatment plan. This can lead to more effective and efficient treatments, as well as reduced side effects.

However, there are also several ethical and societal implications of AI in medicine that must be addressed. One of the primary concerns is the potential for bias in AI algorithms. If the data used to train AI models is biased, the algorithms may also be biased, leading to unfair treatment of certain groups of people.

Another implication is the potential for job displacement. As AI becomes more advanced, there is a risk that it may replace human professionals in certain fields, leading to job loss and economic disruption.

To ensure that AI is developed and deployed in a responsible manner, it is crucial to establish clear ethical guidelines and regulations. This will help to ensure that AI is used to improve healthcare outcomes, while also protecting patient privacy and ensuring that patients are treated fairly.

In conclusion, AI has the potential to revolutionize medicine by improving diagnostic accuracy, facilitating personalized treatment plans, and enhancing patient outcomes. However, it is essential to address the ethical and societal implications of AI to ensure that it is developed and deployed in a responsible manner.
hemoglobin levels are variable, the frequency of anemia is low (19). In the ENESTnd study, the median leukocyte count at the time of diagnosis was 26 × 10⁹/L, the median platelet count was 375 × 10⁹/L, and the median hemoglobin level was 12 g/dL (18). Sahin F. et al. reported a median leukocyte count of 101 × 10⁹/L, a median platelet count of 275 × 10⁹/L, and a median hemoglobin level of 11.5 g/dL (19). In the present study, the median leukocyte count was 115.24 × 10⁹/L, the median platelet count was 461.8 × 10⁹/L, and the median hemoglobin level was 12.7 gr/dL. In the baseline blood smear, the median basophil percentage was 1.4%, while that of eosinophil was 1.7%. Hematologic parameters were similar to those reported in the literature, and elevated leukocyte level was the most common laboratory finding. Splenomegaly is the most common physical examination finding for chronic myeloid leukemia patients, and is detected in approximately 50% of patients (20). In the literature, spleen was palpated below costal margin as a median 2.2 and 5 cm (21); that of the present study was 3.8 cm. This was also the most common physical examination finding in our study, in accordance with the literature.

Currently, the main therapeutic goals in CML are to achieve and maintain hematologic, cytogenetic, and molecular responses. In their study of 1133 patients diagnosed with CML, Sahin F. et al. found that 95.7% of patients treated with imatinib exhibited a CHR in the 3rd month and 63.8% showed CCR in the 12th month; molecular response rates could not be calculated due to insufficient data (15). Karaman A. et al. reported that 90.9% of the patients treated with imatinib showed a CHR in the 3rd month, 68% exhibited a CCR in the 12th month, and 84% had a MMR in the 18th month (22). In a study by Zhao et al., the CHR rate was 94.1%, CCR rate was 69.6%, and CMR rate was 54.9% in patients with chronic phase CML using imatinib (23). Radich et al. compared imatinib and dasatinib treatment responses in 246 patients, newly diagnosed with CML, reported a CHR rate of 82% in the 3rd month, a CCR rate of 69%, and a MMR rate of 44% expressed as a 3 log reduction with respect to the initial BCR-ABL level (24). In our study, with imatinib treatment, a CHR was observed in 89.4% of patients in the 3rd month, CCR in 73.4% of patients in the 12th month, and MMR in 78.1% of patients in the 18th month. The standard dose of imatinib and the hematologic, cytogenetic and molecular response rates in the specific time periods in our patients were similar to those reported in the literature.

While the 5-year survival rate was only 15% in the period prior to the clinical use of TKI, with the detection of the Philadelphia chromosome in CML patients and the introduction of TKIs, initiating a new era in treatment, the survival rate has increased to 85% (25). According to the 2013 guidelines published by ELN, the disease-free survival rate was 94%, the overall survival rate was 97%, and the 8-year overall survival reported in the IRIS study was 85% (9,25). In a study conducted by Karaman A. et al. in Turkey, the survival rate was 83% and disease-free survival was 8.3 years (22). In our study, the overall survival (OS) rate was 84.6% during follow-up, consistent with the IRIS data. With the use of TKI, CML has now become the first and most successful example of targeted therapies for hematologic diseases. This success in treating CML has subsequently led to the development of new treatment methods.

CONCLUSION
In conclusion, our response rates in CML patients treated with imatinib mesylate were similar to those reported in the literature. Drug-related side effects were minimal and tolerable. Long-term survival and disease-free survival can be achieved in patients with CML with proper cytogenetic and molecular monitoring and, if necessary, by switching to new generation TKIs.

Competing 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.

Ethical approval: The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits (approval number:03, date: 17.01.2018).

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