RESEARCH ARTICLE / *Araştırma Makalesi*

Imatinib Mesylate Treatment in Chronic Myeloid Leukemia

Kronik Miyeloid Lösemide İmatinib Mesilat Tedavisi

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Abstract

Objective	To evaluate retrospectively the efficacy of treatment in chronic myeloid leukemia (CML) patients followed up in our center and receiving imatinib treatment.
Materials and Methods	Eighty-five chronic phase CML patients with adequate clinical and laboratory data were included in this study. Patients received imatinib treatment as a first-line treatment.
Results	Forty-eight (56.47 %) patients were male, and 37 (43.53 %) of them were female. The median age at diagnosis was 52 years (19-79). The mean follow-up period was 45 (12-158) months. In the follow-up, 6 of the chronic phase patients progressed to a blastic and accelerated phase. In the third month of imatinib treatment, 77 (90.59 %) patients had a complete hematologic response, and 85 (100 %) patients had a full hematologic response at 18 months. In our study, cytogenetic data of 78 patients with adequate metaphase (≥ 20) could be evaluated within the first 18 months after the diagnosis was made. At the end of 18 months, 68 (87.18 %) of 78 patients had complete cytogenetic response.
Conclusions	Imatinib is well tolerated and an alternative to other therapies.
Keywords	Chronic myeloid leukemia; imatinib mesylate; treatment.

Öz

Amaç	*Merkezimizde takip edilen ve imatinib tedavisi alan kronik miyeloid lösemi (KML) hastalarında tedavinin etkinliğini retrospektif olarak değerlendirmek.*
Gereç ve Yöntemler	*Bu vaka kontrol çalışmasına klinik ve laboratuvar verileri tam olan 85 kronik evre KML hastası dahil edildi. Hastalar imatinib tedavisini birinci basamak olarak almışlardır.*
Bulgular	*Kırk sekiz (% 56,47) hasta erkek, 37 (% 43,53) hasta kadındı. Tanı sırasındaki hastaların yaşlarının ortancası yaş 52 idi (19-79). Ortalama takip süresi 45 (12-158) aydı. İzlemde kronik faz hastalarının 6'sı blastik ve hızlandırılmış faza ilerlemiştir. İmatinib tedavisinin üçüncü ayında, 77 (% 90,59) hasta tam hematolojik yanıt aldı ve 85 (% 100) hasta 18 ayda tam hematolojik yanıt aldı. Çalışmamızda, uygun metafazlı (≥ 20) 78 hastanın sitogenetik verileri, tanı konulduktan sonraki ilk 18 ay içinde değerlendirildi. 18 ayın sonunda 78 hastanın 68'inde (% 87.18) tam sitogenetik yanıt vardı.*
Sonuç	*İmatinib, KML hastaları tarafından iyi tolere edilir ve alternatif bir tedavi yöntemidir.*
Anahtar Kelimeler	*Kronik miyeloid lösemi; imatinib mesilat; tedavi.*

Introduction

In the treatment of chronic myeloid leukemia (CML), cell-reducing cytotoxic treatments (mainly hydroxyurea and busulfan), which do not alter the biological course of the disease, were initially used.[1] Subsequently, biological response regulator drugs [interferon-alpha (IFN-α) and IFN-α/ARA-C combination] were used to achieve cytogenetic remission.1 After observing the leukemic transformation of BCR-ABL protein in ABL-related tyrosine kinase activity, studies have started to develop molecular targeted therapies for CML.[2]

In 1998, after the specific BCR/ABL tyrosine kinase inhibitor (TKI) imatinib mesylate (STI571, Glivec) entered the clinical practice as a drug, the "Imatinib Period" and the TKI era was started in the treatment of CML.[3] Imatinib can provide hematological, cytogenetic or even molecular remission at daily doses of 400 mg, especially in the chronic phase. Imatinib is very well tolerated orally. According to available data, lifelong treatment should be given. Its side effects, such as edema, skin rashes, cytopenias are well tolerated. Imatinib is being used at 600-800 mg doses in the accelerated and blastic phases.[4] In a randomized IRIS study, imatinib mesylate and IFN-α / ARA-C combination were compared in newly diagnosed CML patients.5 In 1106 newly diagnosed CML patients included in this study, the primary cytogenetic response rate was 83% in patients receiving imatinib at the end of the first year. Since the IFN-α/ARA-C combination produced only 20% of responses during the same period, imatinib mesylate has become the standard of treatment for CML. Cytogenetic responses obtained during the follow-up of 48-month IRIS patients have been shown to be durable and continuous.[6] Today, the only treatment with curing potential in CML is allogeneic bone marrow transplantation, but it can be applied to very few people due to the lack of appropriate donor, and resistance or intolerance to IFN-α treatment in patients without donors suitable for transplantation limits the treatment options in CML.

At this stage, imatinib therapy has alternatively been used in clinical practice. The aim of this study was to evaluate retrospectively the efficacy of imatinib treatment in CML patients followed up in our center and receiving imatinib as a first-line treatment.

Materıals and Methods

Study design: The approval of the Sakarya University Institutional Review Board (715224733/050.01.04/150 number / 15 May 2018) had been obtained before this retrospective study. The demographic characteristics, clinical course, and treatment responses of our patients who were treated with CML between the years of 2012-2019 were evaluated retrospectively. Eighty-five CML patients with adequate clinical and laboratory data were included in the study.

These patients received imatinib treatment as a first-line treatment. Imatinib treatment was used at a dose of 400 mg/day. In the case of leukopenia and thrombocytopenia, the dose was reduced to 300 mg/day or discontinued. Hematological parameters were monitored once a week during the first month of the drug onset, and later intervals were adjusted according to the hematological parameters. Enzyme monitoring was performed for liver toxicity. Toxicity assessments were made according to the World Health Organization (WHO) scale. Grade 3-4 toxicity was determined as the indication for the cessation of the drug. Cytogenetic Chromosome analysis of bone marrow or peripheral blood was performed by FISH (fluorescent in-situ hybridization) method.

The European LeukemiaNet (ELN) has developed recommendations for the medical management of patients with CML in daily clinical practice. The response is assessed with standardized real quantitative polymerase chain reaction and/or cytogenetics at 3, 6, and 12 months. BCR-ABL 1 transcript levels ≤ 10% at 3 months, < 1% at 6 months, and ≤ 0,1% from 12 months onward define optimal response, whereas > 10% at 6 months and >1% from 12 months onward define failure, mandating a change in tre-

atment. Similarly, partial cytogenetic response (PCyR) at three months and complete cytogenetic response (CCyR) from 6 months onward define optimal response, whereas no CyR (Philadelphia chromosome-positive [Ph+] >95%) at 3 months, less than PCyR at 6 months, and less than CCyR from 12 months onward define failure.

Treatment response was considered to have been lost if one of the following criteria was found: 1) loss of complete hematological response, or 2) loss of complete cytogenetic response, or 3) 30% or more increase in bone marrow Ph + rate at three-month intervals, or 4) development of new cytogenetic abnormalities.[7]

Results

A total of 85 patients were included in the study. Demographic and clinical characteristics of patients are presented in Table 1. Forty-eight (56.47%) patients were male, and 37 (43.53%) of them were female. The median age at diagnosis was 52 years (19-79). The mean follow-up period was 45 (12-158) months.

Table 1. Demographic and clinical characteristics of patients.

Variable	
Male / Female	48 / 37
Age (years) [mean (min-max)]	52 (19-79)
Follow-up (months) [mean (min-max)]	45 (12-158)
Duration of imatinib treatment (months) [mean (min-max)]	12.4 (3-18)
Hemoglobin (mean) (g / dl)	11.4 ± 1.6
Leukocyte [mean (min-max)] (/ mm^3)	94000 (9100 - 530000)
Platelet [mean (min-max)] (/ µl)	410000 (34000 - 1200000).
Sokal prognostic score (low / intermediate / high)	28 / 30 / 27
IQR= Interquartile range; SD= Standard deviation.	

When the average laboratory data of all patients were evaluated, the mean hemoglobin value was 11.4 ± 1.6 g / dl, and the mean leukocyte value was 94.000 / mm^3 (range, 9.100 - 530.000). The mean platelet value was 410,000 / µl (range, 34,000 to 1,200,000).

At the time of diagnosis, 66 patients (77.6%) were in the chronic phase, 16 patients (18.8%) were in the accelerated phase and three patients (3.6%) were in the blastic phase. In the follow-up, 6 of the chronic phase patients progressed to the blastic and accelerated phase. Sokal prognostic score was low in 28 patients, intermediate in 30, and high in 27.

Hematologic and cytogenetic response rates of patients under imatinib treatment are given in Table 2. In the third month of imatinib treatment, 77 (90.59%) patients had a complete hematologic response and 85 (100%) patients had a full hematologic response at 18 months. In our study, cytogenetic data of 78 patients with adequate metaphase (≥ 20) could be evaluated within the first 18 months after the diagnosis was made. At the end of 18 months, 68 (87.18%) of 78 patients had a complete cytogenetic response.

Table 2. Hematologic and cytogenetic response rates of CML patients to imatinib treatment.

Number of patients evaluated (n)	Complete Hematologic Response (n=85)	Complete Cytogenic Response (n=78)
3. month	77	7
6. month	5	22
12. month	2	24
18. month	1	15
Total	85	68

When the patients who were not responsive to imatinib treatment were evaluated, and there was no hematologic response in 8 patients at three months. In 5 of these patients, second-generation tyrosine kinase inhibitor treatment was started, and three patients were followed up with the same treatment. The second-generation TKI treatment was initiated in 8 patients in whom deterioration in cytogenetic response during follow-up was detected, and in 2 patients whose cytogenetic response was not achieved. Nilotinib and dasatinib were started in 8 and 15 patients, respectively. In 7 of the patients who started second-generation treatment, third-generation treatment (ponatinib)

was initiated.

When patients were examined for non-CML disease, the non-CML disease was present in 22 (25.9%) patients. Three patients had non-hematologic malignancies (esophagus, lung, breast). Nine patients had DM, hypertension, atrial fibrillation, coronary artery disease or cerebrovascular disease under CML treatment, and 10 patients had heart, kidney or liver failure. Eight of 85 patients (9.4%) died due to CML.

Discussion

Imatinib, which was previously used in chronic phase CML patients with IFN failure or intolerance, has entered the CML treatment protocol as a first-line treatment because it has resulted in good hematological and cytogenetic responses.

Chronic myeloid leukemia accounts for 15% of adult leukemia, and its incidence increases with age. The mean age at diagnosis is 65 years, and the incidence is slightly higher in men than in women.2 In our study, the Male / Female ratio was 1 / 0.7, the median age was 52 and the data were consistent with the literature. Most patients present with chronic phase of CML. The chronic phase lasts for 3-6 years and progresses to accelerated or blastic phase as a result of its natural course. Eighty-85% of CML patients are diagnosed in the chronic phase, 10% in accelerated phase and 10% in the blastic phase.[8] At the time of diagnosis, 66 (77.6%) patients were in the chronic phase, 16 (18.8%) in the accelerated phase and 3 (3.6%) in the blastic phase. In the follow-up, 6 of the chronic phase patients progressed to the blastic and accelerated phase. In our study, the number of patients presenting in the chronic phase at the time of diagnosis was comparable to the literature.

In a study of 150 patients with resistance or intolerance to interferon; Cervantes et al. obtained complete hematologic response in 96 of 97 cases and a complete cytogenetic response was detected in 44%, partial in 22%, and minor in 8% of the patients at 12 months.[9] In a study by Kantarjian et al. compared the results of 187 cases receiving imatinib as the first-line treatment with those receiving interferon, cytogenetic response rates were found to be better in imatinib patients (81% vs. 32%).[10] These results indicate that imatinib provides a superior cytogenetic response than any other treatment except bone marrow transplantation as the sole agent. This led to the emergence of the idea that imatinib treatment can be used even in patients with appropriate donors in the first step.[11] In our study, it was found that imatinib treatment achieved 100% hematologic remission after interferon treatment, and major cytogenetic response could be obtained in 87.2% of the patients who could not achieve even hematological remission with previous IFN+ARA-C treatments.

Allogeneic stem cell transplantation is now applicable available in patients with accelerated phase or blastic phase CML. In addition, allogeneic stem cell transplantation (ASCT) can be performed in selected high-risk chronic phase TKI resistant CML patients in whom all TKI treatments have been tried but could not be tolerated. When ASCT results were evaluated in these patients, survival rates were found to be around 85%.[12]

In a study of the German CML group, when the 3rd year results after ASCT were evaluated, survival rates were found to be 88% in patients with high-risk chronic phase, 94% in imatinib unresponsive chronic phase patients, and 59% in accelerated / blastic phase patients.[13] In our patients, ASCT was applied to 3 patients with CML in the blastic phase. In all patients, firstly, TKI treatment was preferred and ASCT was not preferred priorly in any of the patients. ASCT regressed to third or fourth place in CML treatment after tyrosine kinase inhibitor treatment was initiated. However, it is still the only treatment for the complete cure of CML and is still used in resistant cases.

In our study, the non-CML disease was present in 22 (25.9%) patients. Solid tumors were detected in three pa-

tients. Controlled studies with more patients with solid organ tumors and CML are needed to say that CML patients with solid organ tumors have a worse prognosis.

Conclusion

Imatinib is well tolerated by CML patients and is a superior treatment alternative to other therapies other than bone marrow transplantation in achieving a hematological and cytogenetic response. However, considering the uncertainty of the duration of drug use and the loss of cytogenetic responses during periods of drug treatment the necessity of developing alternatives in the treatment of CML emerges.

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