Annals of Medical Research

Original Article

DOI: 10.5455/annalsmedres.2019.08.449 2019;26(9):1737-43

Imatinib mesylate in first-line treatment of chronic myeloid leukemia

Omer Ekinci[1], Ismet Kizilkaya[2]

[1]Firat University Faculty of Medicine, Department of Hematology, Elazig, Turkey
[2]Yuzuncu Yil University Faculty of Medicine, Department of Hematology, Van, Turkey

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,

Received: 03.08.2019 **Accepted:** 05.09.2019 **Available online:** 26.09.2019
Corresponding Author: Omer Ekinci, Firat University Faculty of Medicine, Department of Hematology, Elazig, Turkey
E-mail: dromere@hotmail.com

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 (STI57I) into clinical practice, the era of imatinib in the treatment of CML began (9). After publication of the "International Randomized Study of Interferon and STI571" (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 × 10^9/L, platelets: < 450 × 10^9/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 laboratorial checkups 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 (68.7%) 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 musculoskelatal 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

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

LDH; lactate dehydrogenase, IS; International Scale System

Tablo 2. Complete hematologic response, complete cytogenetic response and major molecular response rates by month of patients with CML

Parameters	3rd month	6th month	12th month	18th month
Complete hematologic response, %				
Yes	97.1	100	100	100
No	2.9	0	0	0
Complete cytogenetic response, %				
Yes	18.8	57.6	73.4	77.8
No	81.2	42.4	26.6	22.2
Major molecular response, %				
Yes	9	59.1	68.7	78.1
No	91	40.9	31.3	21.9

Table 3. Reasons for switching to second generation TKIs in patients with CML

	Patient number (n)	Rate (%)
Imatinib intolerance/ adverse events	4	22.2
Absence of cytogenetic response	4	22.2
Loss of cytogenetic response	2	11.1
Absence of molecular response	5	27.8
Loss of molecular response	3	16.7
Total	**18**	**100**

DISCUSSION

In this study, we evaluated 69 patients with CML with regard to demographic characteristics, disease status, treatment response rates, and adverse events. CML accounts for 15% of adult leukemia cases and its incidence increases with age. To the literature median age was reported as 65 years and there was a predominancy for males (female/male:1.2/2) (2), but in our study our patients were younger (median age: 49,3) and there was a female predominancy (female/male:1.46/1).

The majority of patients with CML are diagnosed in the chronic phase; progression to the accelerated and/or blastic phase occurs within 3-6 years when the disease is untreated and left to its natural course. In general, 80-85% of CML patients are diagnosed in the chronic phase and 10% each in the accelerated and blastic phases (9). Sahin F. et al., in their study of 1133 patients diagnosed with CML, reported that at the time of diagnosis 94.9% were in the chronic phase, 4.1% in the accelerated phase and 1.1% in the blastic phase (15). In our study, 67 patients (97.1%) were in the chronic phase and 2 (2.9%) in the accelerated phase at the time of diagnosis; our results for the percentage of patients presenting in the chronic phase were consistent with rates reported in the literature.

Prognostic models have been developed to determine different risk groups in CML; of these, the most frequently used is the Sokal risk score (16). Although another prognostic scoring system, the Hasford risk score, exists, the Sokal score is more common in daily practice (17). In the ENESTnd study conducted by Saglio et al., in which nilotinib and imatinib treatment responses were compared, the percentage of patients with low, middle, and high Sokal scores in all three treatment arms were 37%, 36%, and 28%, respectively (18). Sahin F. et al. evaluated 1133 patients with CML and reported low, intermediate, and high Sokal risk rates of 69.2%, 24.2%, and 6.6%, respectively, at the time of diagnosis (15). In our study, patients were classified according to both the Sokal and Hasford risk scores. For the Sokal score, 39 patients (56.5%) were low risk, 24 (34.8%) were intermediate, and 6 (8.7%) were high risk. The risk scores based on the Hasford method identified 42 patients (60.9%) as low, 25 (36.2%) as intermediate, and 2 (2.9%) as high risk. The Sokal risk scores calculated for our patients at the time of diagnosis were concentrated in the low and intermediate risk groups, similar to findings reported in the literature.

CML is asymptomatic in the majority of patients and is diagnosed by leukocytosis detected in routine tests, which is present in nearly all CML patients. In peripheral blood smear examination, cells from all stages of the granulocytic series, from blast to neutrophils, are detected. The platelet counts increased in more than half of the patients and platelets could vary in shape. Although

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 × 10^9/L, the median platelet count was 375 × 10^9/L, and the median hemoglobin level was 12 g/dL (18). Sahin F. et al. reported a median leukocyte count of 101 × 10^9/L, a median platelet count of 275 × 10^9/L, and a median hemoglobin level of 11.5 g/dl (15). In the present study, the median leukocyte count was 115.24 × 10^9/L, the median platelet count was 461.8 × 10^9/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, 64% 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 inital 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).*

Omer Ekinci ORCID: 0000-0002-4636-3590
Ismet Kizilkaya ORCID: 0000-0002-6977-5117

REFERENCES

1. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. New Engl J Med 1999;341:164–72.
2. Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011;105:1684-92.
3. Serpa M, Sanabani SS, Dorliac-Llacer PE, et al. Molecular measurement of BCR-ABL transcript variations in chronic myeloid leukemia patients in cytogenetic remission. BMC Blood Disord 2010;10:7.
4. Hoffman R, Benz EJ, Shattil SJ, et al . Hematology basic principles and practice 5th Edition. Churchill, Livingstone, Elsevier; 2005. p.1247-53.
5. Melo JV, Hughes TP, Apperley JF. Chronic myeloid leukemia. Hematology Am Soc Hematol Educ Program 2003:132-52.
6. Silver RT, Woolf SH, Hehlmann R, et al. An evidence -based analysis of the effect of busulfan, hydroxyurea, interferon and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. Blood 1999;94:1517-36.
7. O Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
8. Hughes TP, Kaeda J, Branford S, et al. International Randomised Study of Interferon versus STI571 (IRIS) Study Group. Frequency of majör molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-32.
9. Deininger M, O Brien SG, Guilhot F. et al. International randomized study of interferon vs. STI571 (IRIS) 8 year follow up: sustained survival and low risk for progression of events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood 2009;114:3376-81.
10. Cornelison AM, Kantarjian H, Cortes J, et al. Outcome of treatment of chronic myeloid leukemia with second-

generation tyrosine kinase inhibitors after imatinib failure. Clin Lymphoma Myeloma Leuk 2011;11:101-10.
11. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013;369:1783-96.
12. Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in Chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.
13. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. Blood 2012;120:1390-7.
14. Kantarjian HM, Cortes J, Guilhot F, et al. Diagnosis and management of chronic myeloid leukemia: a survey of American and European practice patterns. Cancer 2007;109:1365-75.
15. Sahin F, Saydam G, Cömert M, et al. Turkish Chronic Myeloid Leukemia Study: Retrospective Sectional Analysis of CML Patients. Turk J Haematol 2013;30:351-8.
16. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
17. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. J Natl Cancer Inst 1998;90:850-8.
18. Saglio G, Kim DW, Issaragrisil S, et al. ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362:2251-9.
19. Goldman JM. Chronic myeloid leukemia: a historical perspective. Semin Hematol 2010;47:302-11.
20. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. Br J Haematol 1997;96:111-6.
21. White DL, Hughes TP. Predicting the response of CML patients to tyrosine kinase inhibitor therapy. Curr Hematol Malig Rep 2009;4:59-65.
22. Karaman A, Solmaz Medeni S, Sevindik OG, ve ark. Kronik Myeloid Lösemi Tanılı Hastalarımızın Retrospektif Değerlendirilmesi. DEU Tip Fakultesi Dergisi 2016;30:103-12
23. Zhao Y, Liu L, Wang Y, et al. Efficacy and prognosis of chronic myeloid leukemia treated with imatinib mesylate in a Chinese population. Int J Hematol 2009;89:445-51.
24. Radich JP, Kopecky KJ, Appelbaum FR, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood 2012;120:3898-905.
25. Baccarani M, Deininger MW, Rosti G, et al. European Leukemia Net recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013;122:872-84.