

Hematologic, cytogenetic, and molecular responses to imatinib therapy for chronic myeloid leukemia: a single-center experience in Turkey

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Aim: To validate patient responses to imatinib mesylate, which induces hematologic and cytogenetic remission and, consequently, modifies the progression of chronic myeloid leukemia (CML).

Materials and methods: Between January 2006 and July 2009, 31 patients with chronic-phase CML were treated with imatinib therapy in the hematology unit of Atatürk University Medical Faculty Training Hospital. Imatinib treatment was begun at the standard dose of 400 mg/day, as either first-line or second-line therapy.

Results: At the end of the second month of treatment, all of the patients had achieved complete hematologic response. After 12 months, the rate of complete cytogenetic response was 71%, and after 24 months, the rate of complete molecular response was 85%. The most commonly observed adverse event was edema (facial and/or peripheral). No grade 3 or 4 hematological adverse events were observed during the study period.

Conclusion: Our CML patients' responses to imatinib therapy were similar to those seen in other countries, although our group had a lower rate of adverse events.

Key words: Chronic myeloid leukemia, imatinib, response, survival

Kronik myeloid lösemide imatinibe alınan hematolojik, sitogenetik ve moleküler yanıt oranları: Türkiye'den tek merkez deneyimi

Amaç: İmatinib mesilat kronik myeloid lösemi (KML)de hematolojik ve sitogenetik remisyonu takiben hastalığın ilerlemesinde düzelmeyi indüklemektedir. Biz bu çalışmada tedaviye cevabı değerlendirmek istedik.

Yöntem ve gereç: Çalışmaya Ocak 2006 ve Haziran 2009 yılları arasında Atatürk Üniversitesi Tıp Fakültesi Hastanesi Hematoloji bölümünde KML tanısıyla takib edilen ve imatinib ile tedavi edilen 31 hasta alındı. Hastalara birincil veya ikincil olarak standart 400 mg/gün imatinib başlandı.

Bulgular: Çalışmada 2. ay sonunda tüm hastalarda hematolojik yanıt sağlandı. 12. ay sonunda tam sitogenetik yanıt oranı % 71 ve 24. ay sonunda tam moleküler yanıt oranı % 85'idi. En sık karşılaşılan yan etki ödemi (yüzde ve/veya akral bölgelerde). Çalışma sürecinde hiçbir hastada 3. veya 4. derece hematolojik yan etki gözlenmedi.

Sonuç: Bizim çalışma sonuçlarımıza göre hastalarımızda imatinib tedavisi ile diğer ülkelere bezir oranlarda tedavi başarısı sağlanırken daha düşük oranlarda yan etki ile karşılaşmıştır.

Anahtar sözcükler: Kronik myeloid lösemi, imatinib, cevap, sağkalım

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Introduction

Chronic myeloid leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells that results in increased myeloid cells, erythroid series, and platelets in peripheral blood and marked myeloid hyperplasia in bone marrow (1). This disorder is characterized by a specific cytogenetic abnormality, the Philadelphia (Ph) chromosome. This chromosome, the product of a reciprocal translocation between chromosomes 9 and 22 (2), results in a chimeric BCR/ABL gene expressing an abnormal fusion protein with altered tyrosine kinase activity (3).

The first drug used with consistent activity against CML was busulfan, introduced in 1959. Hydroxyurea became available 10 years later and was probably the first intervention that significantly prolonged survival in patients with CML (4). The first curative therapy results were achieved by allogeneic stem cell transplantation in the mid-1970s (5). The use of interferon, introduced in the mid-1980s, achieved complete cytogenetic responses and long-term survival in only 5% to 20% of patients (5).

Imatinib mesylate (Glivec, Novartis AG, Basel, Switzerland), formerly STI571, is a potent, selective, competitive inhibitor of the BCR-ABL protein tyrosine kinase. Imatinib has been found to induce hematological and cytogenetic remission and thus modify the progression of CML. However, although cytogenetic remission is an important parameter for assessing the therapeutic success of imatinib treatment, patients who achieve such remission can still have residual disease that can be detected only by polymerase chain reaction (PCR) assay (6). Real-time PCR (RT-PCR) assay from cDNA allows quantification of BCR/ABL transcript levels with a sensitivity of 1 in 100,000 cells. In patients with complete cytogenetic remission, quantification of this molecular response by RT-PCR has been correlated with the duration of disease remission (7).

In this study, we aimed to assess the efficacy of imatinib, in terms of both cytogenetic and molecular remission, and to determine its safety in Turkish patients with CML.

Materials and methods

Patients

Between January 2006 and July 2009, we evaluated all patients with chronic-phase CML who received imatinib treatment through the hematology unit of Atatürk University Medical Faculty Training Hospital. Written, informed consent was obtained before imatinib therapy was started.

The disease phase was defined according to criteria recommended by the World Health Organization (WHO) (8). All patients were shown to be Ph-positive via fluorescence in situ hybridization (FISH) analysis, or p210 BCR/ABL transcripts-positive via RT-PCR assay of peripheral blood or bone marrow aspiration samples. FISH analysis was used for evaluating patients' cytogenetic response instead of classical cytogenetic analysis, due to the unavailability of classical cytogenetic analysis in our genetic analysis laboratory.

Assessment of clinical outcomes

Complete blood count (CBC) and blood chemistry data were measured weekly for the first month, twice monthly for the next 2 months, monthly during months 4-6, and at 3-month intervals thereafter if signs, symptoms, or laboratory evidence of disease progression were absent. FISH analysis for Ph positivity or RT-PCR analysis for BCR/ABL transcription levels was performed at 3-month intervals during the first year, then twice yearly. Response definition and treatment rearrangements were adopted from the National Comprehensive Cancer Networks (NCCN) clinical practice guidelines (9).

Complete hematologic response was defined as a white blood cell count lower than $10 \times 10^9/L$ without immature granulocytes, with $<5\%$ basophils, and a platelet count lower than $450 \times 10^9/L$. Cytogenetic response was evaluated according to FISH analysis and categorized as complete (absence of Ph-positive cells), partial (1%-35% Ph-positive cells), minor (36%-65% Ph-positive cells), minimal (66%-95% Ph-positive cells), or no response ($>95\%$ Ph-positive cells). Molecular response was categorized as complete (negative BCR/ABL transcripts by

quantitative RT-PCR) or major (reduction in BCR/ABL transcript levels by 33_{\log} (0.1%)) compared with the baseline (100%).

Adverse events

Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (10) and managed according to the NCCN clinical practice guidelines (9).

Imatinib dosage was reduced if it was considered intolerable because of adverse events, and imatinib therapy was discontinued if the patient developed grade 3 or 4 toxicity. Therapy was resumed at 300 mg/day when the toxicity had subsided.

Statistical analysis

The statistical significance of differences between groups was evaluated with the Mann-Whitney U-test. Correlations between grades of hematologic, cytogenetic, and molecular response rates were evaluated with the Pearson test. Progression-free survival was calculated from the first day of imatinib administration to the date of death, the date of accelerated-phase or blastic crisis development, or the date of the last follow-up. Maintenance of responses was analyzed according to the Kaplan-Meier method. The level of significance was set at 0.05.

Results

In all, 31 patients with chronic-phase CML were treated in our facility over the course of 44 months. Of these, 20 (65%) received imatinib as first-line therapy within 6 months after CML diagnosis (early-chronic-phase group), with the remaining 11 patients (35%) receiving imatinib either as second-line therapy ($n = 5$) or for longer than 6 months after diagnosis ($n = 6$, late-chronic-phase group). More than half of the patients were women, and the average age was 48.9 years (Table 1).

Imatinib (400 mg daily by mouth) was the initial treatment for all of the early-chronic-phase patients. Of the late-chronic-phase patients, 5 had been previously treated with either interferon α or hydroxyurea before receiving imatinib. The overall follow-up was a mean 40.9 ± 29.3 months, and the follow-up under imatinib therapy was a mean $27.9 \pm$

Table 1. Baseline characteristics of the study cohort.

Characteristic	(n = 31)
Female sex, n (%)	19 (61.9%)
Age (years)	48.9 (18-75)
White blood cells ($\times 10^9/L$)	141.23 (13-437)
Hematocrit (%)	34.32 (23-49)
Platelets ($\times 10^9/L$)	513.9 (134-1571)
Splenomegaly (cm)	5.87 (0-20)
Hepatomegaly (cm)	1.87 (0-16)
Fluorescent in situ hybridization-positive (%)	67.4 (20-98)
Eosinophilia (%)	3.05 (1-8)
Basophilia (%)	2.8 (0-9)
Lactate dehydrogenate (IU/L)	1054.4 (247-3133)
Uric acid (mg/dL)	6.2 (2.3-11.9)

13.1 months. None of the patients progressed to an accelerated phase or blastic crisis during follow-up.

All patients achieved complete hematologic response within 3 months after beginning imatinib therapy; 25 (80.6%) achieved this response by the end of the first month, and the other 6 (19.4%) by the end of the second. Failure of hematologic response was observed in 2 of 21 patients (9.5%) who reached 24 months of follow-up. The imatinib dose for these 2 patients was then changed to 600 mg/day. Both patients regained complete hematologic response within 1 month after the dose change; however, 1 of these patients required an increase to 800 mg/day because of repeat hematologic failure at 30 months of therapy. This patient was switched to a second-generation tyrosine kinase inhibitor (TKI) at 36 months because of a lack of molecular response.

At the end of the first year of imatinib treatment, 71% of the patients had achieved complete cytogenetic response, and by 18 months, 88% had achieved this response (Table 2). Complete or partial cytogenetic response was achieved in 25 of 28 patients at 1 year. In 2 of the 3 patients who did not have complete or partial cytogenetic response at 1 year, the imatinib dose was escalated to 600 mg/day. Of these patients, 1 still lacked complete or partial cytogenetic response

Table 2. Cytogenetic response to imatinib therapy in the study cohort.

Month of follow-up	n	Cytogenetic response, n (%)		
		None or minimal	Partial or complete	Complete
3	31	24 (78)	6 (19)	1 (3)
6	30	10 (34)	20 (66)	14 (46)
12	28	3 (12)	25 (88)	20 (71)
18	25	3 (12)	22 (88)	22 (88)

at 18 months, so the dose was increased again, to 800 mg/day. At 24 months, this patient was switched to a second-generation TKI because of a lack of major molecular response. The second patient was only at month 12 of follow-up when the study was finished. For the third patient, although he had not reached complete or partial cytogenetic response at 1 year, the imatinib dose was not increased because he showed complete hematologic response. At 18 months, he did achieve complete cytogenetic response.

At the end of 18 months, 25 patients remained in the study. Of these, 22 (88%) had a complete or partial cytogenetic response. In the case of 1 previously mentioned patient, we switched to a second-generation TKI. The imatinib dose of 1 other patient was escalated to 600 mg/day, and the patient achieved major molecular response at 24 months and complete molecular response at 36 months, with no change in the imatinib dose.

Complete or major molecular response was attained in 40% of the patients at 12 months, in 72% at 18 months, and in 85% at 24 months (Table 3).

Of the 7 patients who had not achieved complete or major molecular response at 18 months, 5 did not receive an imatinib dosage change because they had achieved early and stable complete hematologic and cytogenetic response by that point. These 5 patients achieved complete molecular response at 24 months. One of the remaining 2 patients who did not achieve complete or major molecular response at 18 months was among those mentioned above who was switched to a second-generation TKI at 24 months. The other had the imatinib dose escalated to 600 mg/day. This patient achieved complete molecular response at 24 months. Of the patients with a complete molecular response at 18 months, 2 had relapsed by 24 months. The imatinib dose was increased to 600 mg/day for both of these patients, 1 of whom regained complete molecular response at 30 months. The other patient had his imatinib dose increased at 30 months to 800 mg/day, and he was switched to a second-generation TKI at 36 months.

The rates of complete or major molecular response differed significantly by disease duration

Table 3. Molecular response to imatinib therapy.

Month of follow-up	n	Major or complete molecular response, n (%)	Complete molecular response, n (%)
12	28	10 (40)	10 (40)
18	25	18 (72)	14 (56)
24	21	18 (85)	18 (85)
30	14	11 (78)	10 (71)
36	11	9 (81)	9 (81)

before imatinib therapy. At 18 months, 91% of the early-chronic-phase CML patients had achieved this response, compared with only 50% of the late-chronic-phase CML patients ($P = 0.03$) (Figure 1).

In general, imatinib was well tolerated. Of the 31 patients, 10 (32.3%) had no adverse event. There were no grade 3 or 4 toxicities, and no patient required interruption of imatinib therapy because of an adverse event. The most commonly observed adverse event was edema (38.7%), which manifested mostly as facial edema. Other adverse events included musculoskeletal pain (29%), gastrointestinal symptoms (19.4%), fatigue (6.5%), and rash (3.2%). We observed no cases of elevated transaminase or creatinine levels, drug- or disease-related anemia, or thrombocytopenia during the study.

At 23 months of treatment, 1 patient with long-standing chronic obstructive pulmonary disease died due to severe pneumonia-related pulmonary failure. The estimated 5-year overall survival rate was 96.7% (Figure 2).

Discussion

The discovery of imatinib has caused a revolution in the treatment of CML. The responses of our patients at 24 and 36 months are similar to those seen in the International Randomized Study of Interferon and STI571 (IRIS), which showed the superior safety and efficacy of imatinib compared with standard interferon a plus cytarabine therapy at 18 and 60 months in selected late-chronic-phase CML patients (11,12). The 5-year rates of complete hematologic and cytogenetic response in the imatinib arm were 96% and 82%, respectively. The response rates in the interferon a group were not reported because few were still receiving that therapy; most of them had either switched to imatinib (65%) or withdrawn from the study. The last reported daily dose of imatinib was 400 mg in 82% of patients. The major molecular response rate to imatinib at 5 years was 80% (11). Only 15 of 456 patients still receiving imatinib after 7 years (3%) had progressed to the accelerated phase or blastic crisis (13).

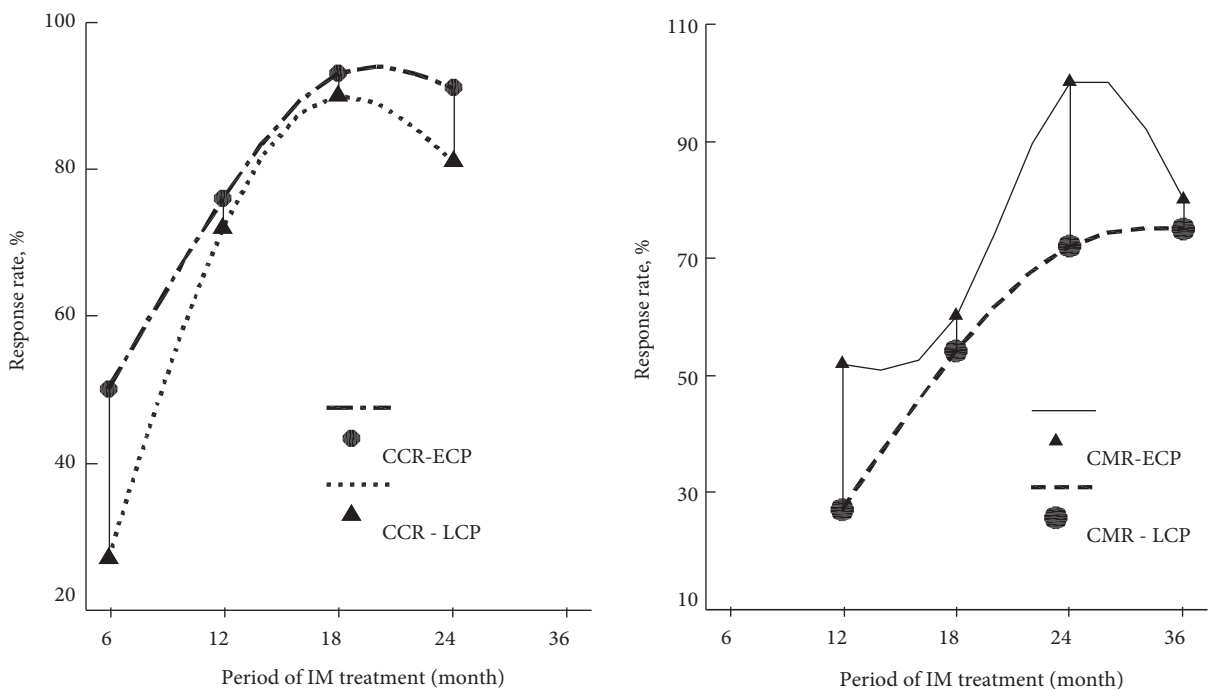


Figure 1. a) Complete cytogenetic response (CCR) and b) complete molecular response (CMR) rates of patients in the early chronic phase (ECP) and late chronic phase (LCP) of chronic myeloid leukemia treated with imatinib (IM).

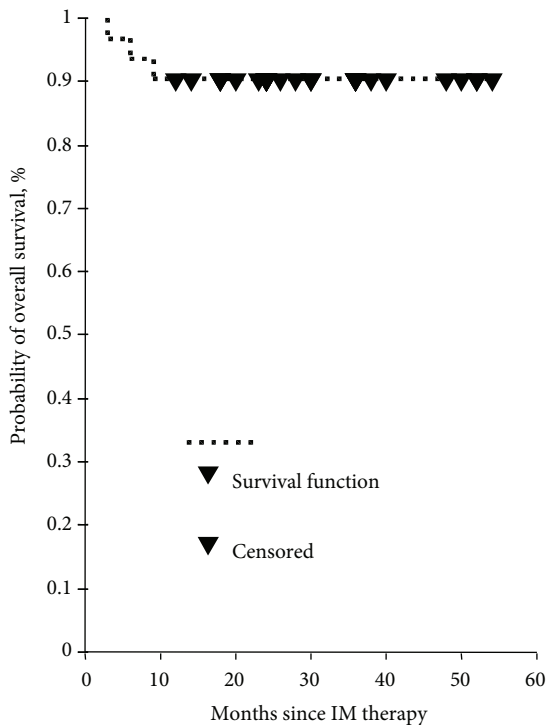


Figure 2. Overall survival of patients with chronic myeloid leukemia treated with imatinib (IM).

The most common event reported in IRIS was edema (60%, including peripheral and periorbital swelling), which was also true in our study, although at a lower incidence (38.7%) (12). Rates of other adverse events, including gastrointestinal symptoms, fatigue, and rash, were also substantially lower than those observed in IRIS. Furthermore, no patient in our study had grade 3 or 4 toxicity or an event that led to interruption of imatinib treatment, unlike in IRIS. This difference may simply be a reflection of the smaller size of our population, or it may reflect other differences in the study populations.

Zhao et al. retrospectively investigated 116 Chinese patients with chronic-phase CML who had been treated with imatinib (14). The complete hematologic response rate was 94.1%; the complete cytogenetic response rate, 69.6%; and the complete molecular response rate, 54.9%. The complete cytogenetic response rate was 78.4% for early-chronic-phase patients versus only 35.7% for late-chronic-phase patients, similar to the pattern for complete or major molecular response observed in our study (91% versus 50%, respectively). The most

commonly reported adverse event in this study was hypopigmentation. Again, rates of grade 3 or 4 hematologic toxicities (anemia, neutropenia, and thrombocytopenia) were much higher than in our study.

Palandri et al. likewise noted a greater molecular response to imatinib among early-chronic-phase CML patients compared with late-chronic-phase CML patients (15). In their study of 54 early-chronic-phase and 115 late-chronic-phase CML patients, the early-chronic-phase patients achieved earlier and higher rates of major molecular response that were also more durable, being sustained in 92% of these patients versus only 61% of the late-chronic-phase patients (15). Although our sample size is inadequate to compare the results of early- versus late-chronic-phase patients, we also observed higher rates of complete or major molecular response in the former group.

Nannya et al. studied 17 male and 18 female Japanese patients with CML (16), 29 of whom were in the early chronic phase. The complete cytogenetic and molecular response rates to imatinib treatment were 93% and 50%, respectively, at 2 years. They observed higher rates of adverse events, similar to those noted by Zhao et al. (14). They concluded that the higher incidence of adverse events noted with imatinib treatment in Asian patients might reflect differential pharmacokinetics in this group. The rate of complete molecular response in our study was 85% at 2 years. The higher response rate in our study could be explained by the lack of interruption in imatinib treatment because of grade 3 or 4 adverse events, which were common in the Asian patients.

A study by Sugita et al. strengthens the theory of different pharmacokinetics of imatinib in Asian populations (17). They retrospectively investigated the response and adverse event rates with imatinib therapy in 213 Japanese patients with CML. At the end of the study, 42 of the patients were receiving a daily imatinib dose of 300-400 mg, 44 were receiving 200-300 mg/day, and 22 were receiving <200 mg/day because of a grade 3 or 4 hematologic adverse event with standard (400 mg/day) therapy (17). They concluded that interruptions in imatinib therapy because of adverse events led to relapses of gained responses. This concept is supported by other studies

showing that interruption or cessation of imatinib therapy results in disease progression and loss of previously gained cytogenetic, hematologic, and molecular responses, to varying degrees (18).

Although no recommendations exist regarding cessation of imatinib treatment in patients with stable CML, there is evidence favoring continued or increased therapy (19-21). Escalation of the imatinib dose, up to 800 mg/day, provokes a response in up to 40% of patients with chronic-phase CML who do not respond to standard-dose imatinib therapy (22,23). Some researchers have also noted a higher response rate with higher initial imatinib dosing (800 mg/day) (24). Recent analysis indicates that increasing the imatinib dose is more effective in cases of cytogenetic failure than in cases of hematologic failure (25). In

our study, we escalated the daily dose of imatinib in cases of inability to achieve relapse in molecular, cytogenetic, and hematologic responses. Similar to previous studies, we observed that higher doses of daily imatinib treatment were associated with higher response rates. Patients who respond to higher daily doses of imatinib might be investigated for the presence of additional genetic mutations (26-28).

In conclusion, our response rates with imatinib treatment of patients with chronic-phase CML were similar to those reported in other countries, although our patients had substantially fewer adverse events, and particularly fewer hematologic effects. Imatinib mesylate was an effective therapeutic choice in the management of CML with tolerable side and adverse effects.

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