Long-term Results of Imatinib Discontinuation in Patients with Chronic Phase Chronic Myeloid Leukemia: National Multicenter Prospective Study

Savaş, E.M. et al: Imatinib Discontinuation in CML

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Abstract

The discovery of imatinib is a milestone for chronic myeloid leukemia (CML) (1). As life expectancy in CML patients has approached that of the general population (2), research has shifted towards improving quality of life and economic considerations. After 2010, it has been shown that some patients could maintain molecular response even after discontinuing imatinib (3). This national multicenter prospective cohort study aimed to observe the long-term consequences of discontinuing imatinib therapy in adult chronic phase CML patients. A total of 41 patients were included. The median follow-up time after imatinib discontinuation was 48 months (minimum-maximum 6-81 months). The rate of molecular relapse-free survival (MRFS) at 48 months was 33.2% (CI: 48.2-18.2%). Twenty-seven of 41 patients lost their major molecular response MMR, treatment was started again, and the molecular response was re-achieved with imatinib in all patients. There was no significant relationship between molecular relapse and clinical factors like duration of treatment or molecular response status. Discontinuing imatinib resulted in approximately 4,392,000 Turkish Liras (TRY) or 245,150 US dollars (USD) in savings. In conclusion, imatinib discontinuation with close molecular monitoring is a safe option and provides important national economic benefits and enhanced quality of life. This approach should be considered for all eligible patients. This is the first tyrosine kinase inhibitor discontinuation study from Turkey.

Öz

 Kronik myeloid lösemi (KML) hastalığının tedavi sürecinde imatininin keşfi bir dönüm noktasıdır. İmatinib sonrası dönemde kronik faz KML hastalarının yaşam beklentisi normal popülasyonla benzer hale gelmiştir (2). Günümüzde bu nedenle kronik faz KML ile ilgili ana araştırma konuları hastaların yaşam kalitesi ve hastalık ile ilgili ekonomik sorunlardır. KML’nin klonal hastalık olması ve aslında imatinib ile eradike edilememesi nedeni ile başlarda tereddütlerle yol açsa da 2010 yılından sonra yapılan çalışmalar uygunsuz hastalarda tirosin kinaz inhibisyonu kesiminde sona bazi hastaların uzun döneminde moleküler remisyonda izlenebildiği gözükmüştür (3). Henüz moleküler remisyon ve relapsa etkili faktörler net olarak bilinmemesine rağmen günümüzde kronik faz KML hastalarının bazıları ilacılı remisyona izlenmeye devam etmektedir. Bu ulusal çok merkezli prospektif kohort çalışması, yeni ve kronik faz KML hastalarında imatinib tedavisinin kesimlerinin uzun vadeli sonuçlarını gözlemleyemi amaçlamıştır. Çalışmaya toplam 41 hasta dahil edilmiştir. İmatinibin kesilmesinden sonraki
Introduction

CML is a hematopoietic stem cell disorder that results in an increase in all three series in the bone marrow (4). It arises from a specific DNA exchange between chromosomes 9 and 22, the Philadelphia chromosome. This alteration results in the creation of the BCR::ABL1 fusion gene by combining the ABL1 and BCR genes, which encode an oncoprotein that dysregulated tyrosine kinase activity (5). Ph chromosome and BCR::ABL1 rearrangement have been demonstrated in multiple lineages of the myeloid series (6). While CML is consistently associated with this cytogenetic alteration, it is also definitively established as a clonal stem cell disorder originating from hematopoietic stem cells. (7) In 2001, imatinib, a tyrosine kinase inhibitor (TKI), was approved by the FDA for use in the treatment of CML, and this revolutionary event started a new era in the treatment of CML (1). With the discovery of imatinib, the outcomes of the disease have changed dramatically. After TKI inhibitors, the life expectancy of chronic phase CML patients has become the same as the general population (2).

Endpoints

At the beginning of the study, the primary endpoint was to observe MRFS rates at 12-month follow-up. However, during this period, with the increasing number of studies suggesting that discontinuing medication is a safe method, our focus shifted to examining MRFS rates at the end of the longer-term follow-up. The secondary endpoint was to assess the factors influencing molecular relapse and calculate the overall national financial savings.

Definitions

A BCR::ABL1 transcript level equal to or less than 0.1% is categorized as the “major molecular response” (MMR). When the BCR::ABL1 transcript level reaches ≤0.01%, it is defined as molecular response 4 (MR4).
Achieving a BCR::ABL1 transcript level of ≤0.0032% is classified as molecular response 4.5 (MR4.5). These levels, MR4 and MR4.5, are referred to as “deep molecular response” (DMR) in the context of CML treatment with TKIs (13).

The term “molecular relapse” refers to the loss of MMR during treatment-free follow-up. A second measurement is taken to evaluate the loss of response in the initial measurement.

MRFS is defined as the time period from the discontinuation of imatinib until the development of molecular relapse. For patients who experienced molecular relapse, imatinib treatment was restarted. The MMR re-achievement date is determined by the date of the first MMR after restart treatment.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). In the descriptive data, categorical variables are presented as numbers and percentages, while continuous variables are presented as mean ± standard deviation for normally distributed data and median (range) for non-normally distributed data. The conformity of continuous variables to normal distribution was evaluated using histograms and the Kolmogorov-Smirnov/Shapiro-Wilk tests. MRFS rates were estimated using the Kaplan-Meier method. Cox regression analyses were performed to examine the factors affecting molecular relapse. The p-value of <0.05 was considered to indicate statistical significance.

Results

Between 2015 and 2020, forty-one patients with chronic phase CML, who had been treated with imatinib for at least 3 years and monitored for at least 2 years for DMR were included in the study. Out of the 41 patients, 30 (73%) were female and 11 (27%) were male. The median age at diagnosis was 49 (range 14-61), while it was 56 ±14 at the time of discontinuation of imatinib. The Sokal score was low in 27 patients (70.7%), intermediate in 8 (19.5%) patients and high in 4 (9.7%) patients. Prior to imatinib treatment, 19 patients received hydroxyurea, but none received interferon treatment. The median time from diagnosis to imatinib discontinuation was 83.2 months (55.7-123), and the duration of imatinib treatment was 82.5 months (54.5-121).

The time to reach DMR after starting imatinib treatment was a median of 6 months (6-8.7). The median follow-up with DMR before imatinib discontinuation was 75.6 (47.8-106.4) months.

MRFS Rates at 6, 12, 24 and 48 Months

The median follow-up time after imatinib discontinuation was 48 months (minimum-maximum 6-81 months). At the end of the follow-up time, the MRFS rate was 28.6% (mean 25.4 months, 95% CI: 16.3-34.2). MRFS rates at 6, 12, 24 and 48 months were 55.6% (CI:70.8-40.4), 47.6% (CI:63-32.2), 33.2% (CI:48.2-18.2) and 33.2% (CI:48.2-18.2) respectively.

Of 14 patients experiencing a molecular relapse, 13 patients (92.8%) had it within the first 24 months, while only 1 patient (7.1%) had a late relapse (at 51 months). Figure 1 shows MRFS rates on the Kaplan Meier curve during the follow-up from imatinib discontinuation.

During the follow-up, 27 of 41 patients lost the MMR. Imatinib treatment was started again in all these patients. All patients re-achieved MMR within a median of 2.9 months (1.7-3.5) and reached DMR after re-treatment within a median of 4.5 months (2.3-6.3). Figure 2 shows the re-achieving MMR rate after re-treatment with imatinib. None of the patients developed resistance imatinib or required second-generation therapy. Any patient who has not died.

We evaluated the risk factors for relapse after discontinuation of imatinib. Based on the log-rank test, it was observed that a high Sokal score was associated with low MRFS rates compared to a low Sokal score (low-intermediate as the same group) (Figure 3), but this difference did not reach statistical significance (p=0.066).

Age, gender, imatinib treatment duration, MMR duration, time to reach MMR and molecular response status (MR4 or 4.5) were examined with log-rank test and Cox proportional hazard test and there was no relationship between molecular relapse and these parameters (p=0.05).

Financial Saving

After discontinuing imatinib, 27 patients who experienced molecular relapse were observed for 165 months without imatinib before restarting treatment. Additionally, 14 patients who did not experience molecular relapse were observed for a total of 567 months without imatinib until their most recent evaluation. During the median 48 months of 4,392,000 Turkish liras (TRY) (245.150 USD) was saved. While the annual drug cost of a patient is approximately 72,000 TRY/year (4019 USD), a total of 1,008,000 TRY (56,294 USD) will be saved each year from 14 patients who continue to be followed in molecular response.

Discussion

Although there was great hesitation about discontinuing TKI treatment due to concerns about clonal stem cells, the STIM1 study showed that MRFS continues in approximately 41% of patients after TKI discontinuation (3).

In the TWISTER study, which involved 40 chronic phase CML patients, the TFR rate was found to be 4.1% at the 24th month (9). According to the NCCN, discontinuation of therapy can be attempted in chronic phase CML patients who approved TKI therapy for at least 3 years and have a stable molecular response for at least 2 years (14). Moreover, ELN guidelines suggested that TKI discontinuation may be considered in patients who have received TKI therapy for at least five years (>4 years for second-generation TKI) and molecular response duration for more than 3 years (>2 years in MR 4.5) (13).
In this prospective multicenter study, we evaluated the outcomes of treatment-free follow-up results of chronic phase CML patients after imatinib discontinuation. We observed that 30% of patients maintained MMR for a median of 48 months during the follow-up period. The MRFS rates were 55.6% at 6 months, 47.2% at 12 months, and 33.2% at 24 months. Nineteen (%70.3) of 27 relapses occurred within the first 6 months after stopping imatinib and only one relapse was seen after 18 months. In the STIM study, the estimated MRFS was 41% (29–52) at 12 months and 38% (27–50) at 24 months, most patients experienced molecular relapse within 6 months. The latest relapse was observed at 22 months. In the largest TKI discontinuation study EURO SKI the TFR rate at 36 months was 49%. In this study, 12 patients lost MR after 36 months (3). The MRFS rates in our study are similar to those in other studies. This suggests that treatment discontinuation may be a safe option and may be considered appropriate for chronic phase CML patients within the Turkish population.

In our study, molecular response was obtained in all patients who developed molecular relapse within 6 months after restarting imatinib. No patient developed progression, or drug resistance and any patient died. Similar results are also seen in STIM, TWISTER and other TKI discontinuation studies (3,9,11). This is also another important evidence that TKI discontinuation is a safe option in CML patients.

In our study, the factors causing molecular relapse after discontinuation of imatinib were examined. It was observed that a high Sokal risk score may be associated with low MRFS. This difference did not achieve statistical significance. This might be because we had a small number of patients. Similarly, the association between high Sokal score and low MRFS was reported in the DOMEST study (10). We evaluated the effects of age, gender, imatinib treatment duration, MMR duration, time to reach DMR, and the depth of molecular response (MR4 vs. MR4.5) on MRFS rates and we observed that these clinical parameters had no effect. Another important result of this study is that the probability of remaining in molecular response cannot be explained solely by clinical factors. There are conflicting results in the literature on this subject. In the Euro SKI study, the duration of molecular response is associated with relapse-free survival. However, there was no significant difference in relapse rates based on the depth of molecular response (MR4 vs. MR4.5 vs. MR5) (11). On the other hand, the JALSG-STIM213 study showed that there is no association between a loss of MMR and duration of imatinib or time to achieve MR (12). We think that the immune system’s effector and suppressor components may play a role in the continuation of the tyrosine kinase inhibitor-like environment. Irani et al reported that patients who achieved TFR had increased natural killer cell count and activity, while FoxP3+ regulatory T cells and monocytic myeloid-derived suppressor cells were reduced (15). Another study demonstrated that interferon-α increased NK cell receptor numbers, resulting in a faster achievement of DMR in CML patients (16). Likewise, studies about TKI discontinuation have also demonstrated a relationship between interferon-α therapy and higher MRFS rates (17-18). These findings suggest a potential relationship between NK cells and MRFS following TKI discontinuation. Further research is needed to understand the molecular and immune factors influencing long-term TFR and to develop biomarkers for safe treatment discontinuation.

The economic burden is also very important for chronic phase CML patient management. According to the Turkey Social Security Institution Health Practice Communique; imatinib is the only choice for the treatment of chronic phase CML in the first line, and the one-year treatment cost is approximately 72 thousand Turkish liras ($4019). A total of approximately 4,392,000 TRY ($245,150) has been saved since the beginning of this study and annually 1,008,000 TRY ($56,294) national income is provided from 14 TFR patients. There are similar studies investigating the budget effect of stopping TKI treatment and all of them have shown that drug-free follow-up comes with significant economic results and savings. McCloskey et al. reported a total savings of $3,065,376 in their study, which included 29 patients and achieved treatment-free molecular remission in 16 patients (15). According to the report of the updated results of the STIM1 study, a total of 5.5 million Euros was saved from 100 patients followed in TFR at a median follow-up of 54 months STIM1 trial (3). This is the first study to demonstrate that TFR is a safe option in chronic phase CML patients in the Turkish population. However, it also has some limitations. The small sample size is the most important limitation of our study. Still, we had enough participants for proper statistical analysis. The other limitation is the absence of quality-of-life assessment. Although the quality-of-life scale was established at the beginning of the study, no conclusive results could be obtained due to low patient participation.

In conclusion, all these data show that discontinuation of imatinib treatment, following an initial period of DMR monitoring is a safe and viable treatment strategy for patients with chronic phase chronic myeloid leukemia. This approach should be considered for all eligible patients. However, in this process, providing close molecular monitoring in an adequate laboratory (preferably the same one) is essential and should continue for a long time to detect any late relapses. Although a high Sokal score is seen as an important factor for molecular relapse, further investigations are needed on factors affecting relapse, especially molecular factors. TFR provides a very important national economic saving, therefore every chronic phase CML patient should be questioned whether they are suitable for drug discontinuation in daily clinical practice.

**Conflict of Interest:** The authors have no conflict of interest.

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References


15. Irani YD, Hughes A, Clarkson J, Kok CH, Shanmuganathan N, White DL, Yeung DT, Ross DM, Hughes TP, Yong ASM. Successful treatment-free remission in chronic myeloid leukaemia and its association with reduced


Table 1. Demographic and clinical characteristics of patients at the time of diagnosis and TKI discontinuation

<table>
<thead>
<tr>
<th>Patients (n=41)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Age (year) [mean ± std deviation]</td>
<td>49±14.6</td>
</tr>
<tr>
<td>Time of diagnosis</td>
<td>56±14</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30 (73%)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>Sokal score at the time of diagnosis [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>29 (70.7%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8 (19.5%)</td>
</tr>
<tr>
<td>High</td>
<td>4 (9.7%)</td>
</tr>
<tr>
<td>Treatment before TKI [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Yes (hydroxycarbamide)</td>
<td>19 (46.3%)</td>
</tr>
<tr>
<td>No</td>
<td>22 (53.6%)</td>
</tr>
<tr>
<td>Molecular remission status [n (%)]</td>
<td></td>
</tr>
<tr>
<td>MR4</td>
<td>14 (34.1%)</td>
</tr>
<tr>
<td>MR 4.5</td>
<td>27 (65.9%)</td>
</tr>
<tr>
<td>Duration of imatinib treatment (mo)-[median (range)]</td>
<td>82.5 (54.5-121)</td>
</tr>
<tr>
<td>Time to achieve DMR (mo)-[median (range)]</td>
<td>6 (6-8.7)</td>
</tr>
<tr>
<td>Duration of DMR (mo)-[median (range)]</td>
<td>75.6 (47.8-106.4)</td>
</tr>
<tr>
<td>Time from diagnosis to imatinib discontinuation (mo)-[median (range)]</td>
<td>83.2 (55.7-123)</td>
</tr>
<tr>
<td>TKI: Tyrosine kinase inhibitor, DMR: Deep molecular response, Mo: Month</td>
<td></td>
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</tbody>
</table>
**Figure 1.** Molecular relapse-free survival rates after imatinib discontinuation

**Figure 2.** Time to re-achieve MMR after restart imatinib treatment
Figure 3. Comparison of MRFS rates between Sokal score groups (high vs. low-intermediate)