RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2023.2023.0194
Turk J Hematol 2023;40:236-241

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

Kronik Faz Kronik Myeloid Lösemi Hastalarında İmatinib Tedavisinin Kesilmesinin Uzun Dönem Sonuçları: Ulusal Çok Merkezli Prospektif Bir Çalışma

Emine Merve Savaş[1], Seda Yılmaz[2], Ayşe Asena Başer Dikyar[3], Zübeyde Nur Özkurt[1], Ramazan Öcal[4], Ferda Can[5], Sezgin Pepeler[5], Lale Aydın Kaynar[3], Sanem Gökçen[1], Abdulkerim Yıldız[6], Murat Albayrak[7], Sema Karakuş[8], Özcan Çeneli[9], Münci Yağcı[1]

[1]*Gazi University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*
[2]*Konya City Hospital, Department of Hematology, Konya, Türkiye*
[3]*Ankara Etlik City Hospital, Clinic of Hematology, Ankara, Türkiye*
[4]*Liv Hospital, Clinic of Hematology, Ankara, Türkiye*
[5]*Ankara Bilkent City Hospital, Clinic of Hematology, Ankara, Türkiye*
[6]*University of Health Sciences Türkiye, Hitit University Çorum Erol Olçok Training and Research Hospital, Clinic of Hematology, Çorum, Türkiye*
[7]*University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Hematology, Ankara, Türkiye*
[8]*Başkent University Faculty of Medicine, Department of Hematology, Ankara, Türkiye*
[9]*Necmettin Erbakan University Faculty of Medicine, Department of Hematology, Konya, Türkiye*

Abstract

Objective: The discovery of imatinib was a milestone for chronic myeloid leukemia (CML). As the life expectancy of CML patients has approached that of the general population, research has shifted towards improving quality of life and economic considerations. After 2010, it was shown that some patients could maintain molecular response even after discontinuing imatinib. This national multicenter prospective cohort study aimed to observe the long-term consequences of discontinuing imatinib therapy in adult chronic-phase CML patients.

Materials and Methods: We enrolled 41 CML patients from 4 different centers in this non-randomized single-arm trial. Molecular responses of all patients were re-evaluated using real-time polymerase chain reaction at a single center. The median follow-up time after imatinib discontinuation was 48 months (minimum-maximum: 6-81 months).

Results: The rate of molecular relapse-free survival at 48 months was 33.2% (confidence interval: 48.2-18.2). Twenty-seven of 41 patients lost their major molecular response, treatment was started again, and deep molecular response was re-achieved with imatinib in all cases. There was no significant relationship between molecular relapse and clinical factors such as duration of treatment or molecular response

Öz

Amaç: İmatinib'in keşfi, kronik myeloid lösemi (KML) için bir dönemeç olmuştur. KML hastalarının yaşam süresi genel nüfusun yaşam süresine yaklaştıkça, araştırmalar yaşam kalitesini artırmaya ve ekonomik faktörlere odaklanmıştır. 2010'dan sonra, bazı hastaların imatinib'i bıraktıktan sonra bile moleküler yanıtı sürdürebildiği gösterilmiştir. Bu ulusal çok merkezli prospektif kohort çalışması, erişkin kronik faz KML hastalarında imatinib tedavisinin sonlandırılmasının uzun vadeli sonuçlarını gözlemlemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu prospektif, randomize olmayan, çok merkezli çalışmaya dört farklı merkezden 41 kronik faz KML hastası dahil edildi. Tüm hastaların moleküler yanıtları, tek bir merkezde gerçek zamanlı polimeraz zincir reaksiyonu kullanılarak yeniden değerlendirildi. Tedavi kesilmesinden sonraki ortanca takip süresi 48 aydı (minimum-maksimum 6-81 ay).

Bulgular: Kırk sekizinci ayda moleküler relapssız sağkalım oranı %33,2 (güven aralığı: 48,2-18,2) olarak hesaplandı. 41 hastanın 27'si majör moleküler yanıtı kaybetti, tedaviye tekrar başlandı ve tüm hastalarda imatinib ile derin moleküler yanıt sağlandı. Moleküler nüks ile tedavi süresi veya moleküler yanıtın derinliği gibi klinik faktörler arasında ilişki yoktu. Çalışma ile şu ana kadar toplamda yaklaşık 4.392.000 Türk lirası (TRY) veya 245.150 dolar (USD) tasarruf sağlandı.

Address for Correspondence/Yazışma Adresi: Emine Merve Savaş, M.D., Gazi University Faculty of Medicine, Department of Hematology, Ankara, Türkiye
Phone : +90 507 741 78 81
E-mail : merve-tombul@hotmail.com ORCID: orcid.org/0000-0001-8295-9431

Received/Geliş tarihi: May 11, 2023
Accepted/Kabul tarihi: October 25, 2023

status. Discontinuing imatinib resulted in savings of approximately 4,392,000 Turkish lira or 245,150 US dollars.

Conclusion: Tyrosine kinase inhibitor discontinuation with close molecular monitoring is a safe option and provides important national economic benefits for chronic phase CML patients. This approach should be considered for all eligible patients. This is the first tyrosine kinase inhibitor discontinuation study from Türkiye.

Keywords: Chronic myeloid leukemia, Tyrosine kinase inhibitor, Treatment-free survival, Molecular relapse-free survival

Sonuç: Kronik faz KML hastalarında yakın moleküler izlem ile tirozin kinaz inhibitörü kesimi güvenli bir seçenektir ve önemli ulusal ekonomik faydalar sağlar. Bu yaklaşım, tüm uygun hastalar için düşünülmelidir. Bu çalışma Türkiye'de yapılan ilk tirozin kinaz inhibitörü kesilme çalışmasıdır.

Anahtar Sözcükler: Kronik myeloid lösemi, Tirozin kinaz inhibitörü, Tedavisiz sağkalım, Moleküler relapssız sağkalım

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder that results in an increase in all three series in the bone marrow [1]. 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 dysregulates tyrosine kinase activity [2]. The Ph chromosome and *BCR::ABL1* rearrangement have been demonstrated in multiple lineages of myeloid series [3]. 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 [4]. In 2001, imatinib, a tyrosine kinase inhibitor (TKI), was approved by the US Food and Drug Administration for use in the treatment of CML, and this revolutionary event started a new era in the treatment of CML [5]. With the discovery of imatinib, the outcomes of the disease have changed dramatically. After the introduction of TKIs, the life expectancy of chronic-phase CML patients became the same as that of the general population [6]. Therefore, one of the main topics of research in CML over the last decade has been improving the quality of life and reducing economic burdens. In the past, there were significant concerns about discontinuing TKIs due to CML being a clonal disease and TKIs not being able to eliminate CML stem cells [7]. However, in 2010, the Stop Imatinib study revealed that about 41% of patients maintained a deep molecular response without treatment for more than 2 years after stopping imatinib [8]. After this milestone study reached its endpoint, numerous similar studies were conducted, and it was observed that some patients continued to have TKI-free remission after stopping their TKIs. Nevertheless, it remains uncertain which patients have experienced relapse or attained molecular response [9,10,11,12]. In this study, we aimed to investigate whether TKI usage after achieving a prolonged deep molecular response is a safe long-term approach in chronic-phase CML patients within the Turkish population. Additionally, we aimed to identify the effective factors for long-term molecular relapse-free survival (MRFS) in patients whose imatinib treatment was discontinued.

Materials and Methods

For this prospective non-randomized single-arm trial, we enrolled CML patients from 4 different centers. All patients were 18 years or older, diagnosed with chronic-phase CML, and receiving imatinib treatment. The minimum duration of treatment with imatinib was required to be 3 years and the minimum time interval for deep molecular response (MR4 or MR4.5) to discontinuation was 2 years. All patients included in the study were followed for at least 2 years after TKI discontinuation. Molecular responses of all patients were re-evaluated using real-time polymerase chain reaction (rt-PCR) at a single center and reported as the ratio of *BCR::ABL1* to *ABL1* on an international scale. Molecular response was evaluated monthly in the first year, once every 2 months during the second year, and then every 3 months. Demographic data, physical examination results, and Sokal risk scores of all patients were recorded at the beginning of the study.

Molecular relapse was confirmed by two *BCR::ABL1* PCR tests. If a patient experienced molecular relapse as defined in the definitions section below, drug-free observation was terminated and imatinib treatment was started again.

We calculated the financial savings by multiplying the number of months without imatinib by its monthly cost and then subtracting the combined monthly expenses for molecular and patient monitoring. This allowed us to determine the overall financial gain.

All patients were included in the study after giving written informed consent in line with the Declaration of Helsinki. Approval of the study protocols was obtained from the Central Ethics Committee of the Ministry of Health (no: 188, date: 14.04.2014).

This trial was sponsored by the Turkish Society of Hematology. This is the first TKI discontinuation study from Türkiye.

Endpoints

At the beginning of the study, the primary endpoint was to observe MRFS rates at 12 months of follow-up. However, during this period, with increasing numbers of studies suggesting

that discontinuing this 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% was categorized as major molecular response (MMR). When the *BCR::ABL1* transcript level reached ≤0.01%, it was defined as molecular response 4 (MR4). Achieving a *BCR::ABL1* transcript level of ≤0.0032% was 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 was taken to evaluate the loss of response from the initial measurement.

MRFS was 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 was determined by the date of the first MMR after restarting treatment.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 25.0 for Windows (IBM Corp., Armonk, NY, USA). For descriptive data, categorical variables were presented as numbers and percentages, while continuous variables were presented as means ± standard deviations for normally distributed data and medians (ranges) 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. Values of $p<0.05$ were considered to indicate statistical significance.

Results

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 between 2015 and 2020 were included in the study. Of the 41 patients, 30 (73%) were female and 11 (27%) were male. The median age at diagnosis was 49±14.6 years, while it was 56±14 at the time of discontinuation of imatinib. The Sokal score was low for 27 patients (70.7%), intermediate for 8 (19.5%) patients, and high for 4 (9.7%) patients. Prior to imatinib treatment, 19 patients received hydroxycarbamide, but none received interferon treatment. The median time from diagnosis to imatinib discontinuation was 83.2 (55.7-123) months, and the duration of imatinib treatment was 82.5 (54.5-121) months. The time to reach DMR after starting imatinib treatment was a median of 6 (6-8.7) months. The median follow-up with DMR before imatinib discontinuation was 75.6 (47.8-106.4) months (Table 1).

MRFS Rates at 6, 12, 24, and 48 Months

The median follow-up time after imatinib discontinuation was 48 (6-81) months. At the end of the follow-up period, the MRFS rate was 26.6% [mean: 25.4 months, 95% confidence interval (CI): 16.5-34.2]. 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. Out 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 the MRFS rates on the Kaplan-Meier curve during follow-up for imatinib discontinuation.

During the follow-up, 27 of 41 patients lost their MMR. Imatinib treatment was started again for all these patients. All patients re-achieved MMR within a median of 2.9 (1.7-3.5) months and reached DMR after re-treatment within a median of 4.5 (2.5-6.3) months. Figure 2 shows the rate of re-achieving MMR after re-treatment with imatinib. None of the patients developed resistance to imatinib or required second-generation therapy. No patients died.

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

	Patients (n=41)
Age, years, mean ± standard deviation At time of diagnosis At TKI discontinuation	 49±14.6 56±14
Sex, n (%) Female Male	 30 (73%) 11 (27%)
Sokal score at time of diagnosis, n (%) Low Intermediate High	 29 (70.7%) 8 (19.5%) 4 (9.7%)
Treatment before TKI, n (%) Yes (hydroxycarbamide) No	 19 (46.3%) 22 (53.6%)
Molecular remission status, n (%) MR4 MR4.5	 14 (34.1%) 27 (65.9%)
Duration of imatinib treatment, months, median (range)	82.5 (54.5-121)
Time to achieve DMR, months, median (range)	6 (6-8.7)
Duration of DMR, months, median (range)	75.6 (47.8-106.4)
Time from diagnosis to imatinib discontinuation, months, median (range)	83.2 (55.7-123)

TKI: Tyrosine kinase inhibitor, MR: molecular remission; DMR: deep molecular response.

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 low Sokal scores (with low and intermediate taken as the same group) (Figure 3), but this difference did not reach statistical significance (p=0.066). Age, sex, imatinib treatment duration, MMR duration, time to reach MMR, and molecular response status (MR4 or 4.5) were examined with the log-rank test and Cox proportional hazard test, and there was no relationship between molecular relapse and those parameters (p>0.05).

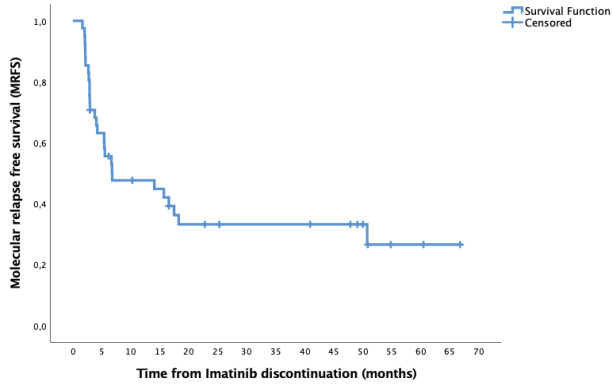

Figure 1. Molecular relapse-free survival rates after imatinib discontinuation.

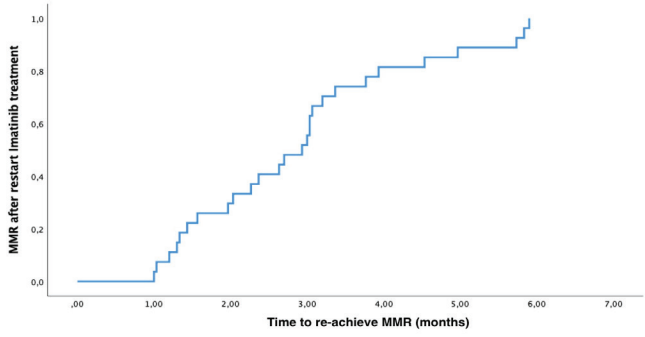

Figure 2. Time to re-achieve major molecular response (MMR) after restarting imatinib treatment.

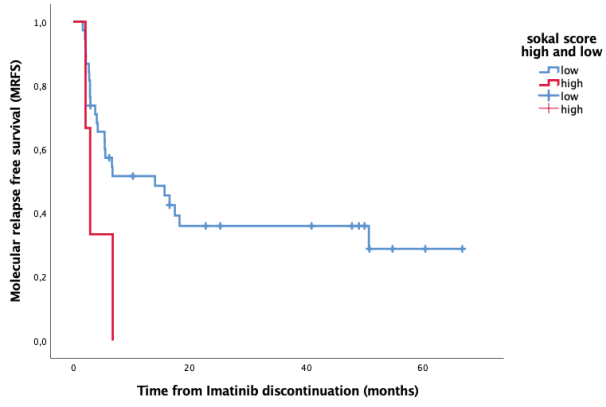

Figure 3. Comparison of molecular relapse-free survival rates between Sokal score groups (high vs. low-intermediate).

Financial Savings

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 evaluations. During the median 48 months, a total of 4,392,000 Turkish lira (245,150 US dollars) was saved. If the annual drug cost of a patient is approximately 72,000 lira per year (4019 US dollars), a total of 1,008,000 Turkish lira (56,294 US dollars) will be saved each year as a result of the 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 [8]. In the TWISTER study, which included 40 chronic-phase CML patients, the treatment-free remission (TFR) rate was found to be 4.1% at the 24th month [9]. According to the National Comprehensive Cancer Network, discontinuation of therapy can be attempted in chronic-phase CML patients who were approved for TKI therapy for at least 3 years and have had stable molecular response for at least 2 years [14]. Moreover, European LeukemiaNet guidelines suggest that TKI discontinuation may be considered for patients who have received TKI therapy for at least 5 years (>4 years for second-generation TKIs) with molecular response duration for more than 3 years (>2 years for MR4.5) [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 these 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 STIM1 study, the estimated MRFS was 41% (29-52%) at 12 months and 38% (27-50%) at 24 months, and most patients experienced molecular relapse within 6 months. The latest relapse was observed at 22 months. In EURO SKI, the largest TKI discontinuation study to date, the TFR rate at 36 months was 49%. In that study, 12 patients lost MR after 36 months [8]. The MRFS rates in our study are similar to those of other studies. This suggests that treatment discontinuation may be a safe option and may be considered appropriate for chronic-phase CML patients in the Turkish population.

In our study, molecular response was obtained by all patients who developed molecular relapse within 6 months after restarting imatinib. No patient developed progression or drug resistance and no patients died. Similar results were also seen in the STIM1, TWISTER, and other TKI discontinuation studies [8,9,11]. This is additional 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 high Sokal risk scores may be associated with low MRFS rates. However, this difference did not achieve statistical significance. We think this might be because we had a small number of patients. Similarly, the association between high Sokal scores and low MRFS rates was reported in the DOMEST study [10]. We evaluated the effects of age, sex, imatinib treatment duration, MMR duration, time to reach DMR, and depth of molecular response (MR4 vs. MR4.5) on MRFS rates and we observed that these clinical parameters had no effects. 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 was 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 was 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 TKI-like environment. Irani et al. [15] reported that patients who achieved TFR had increased natural killer cell count and activity, while FoxP3+ regulatory T-cell and monocytic myeloid-derived suppressor cells were reduced. 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 in chronic-phase CML patient management. According to a health practice communique from the Turkish Social Security Institution, imatinib is the only choice for the treatment of chronic-phase CML in the first line, and the one-year treatment cost is approximately 72,000 Turkish liras ($4019). A total of approximately 4,392,000 Turkish lira ($245,150) has been saved since the beginning of this study and annual national income of 1,008,000 lira ($56,294) is provided as a result of 14 TFR patients. There are similar studies investigating the financial effects 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. [19] reported a total savings of $3,065,376 in their study, which included 29 patients and achieved treatment-free molecular remission in 16 patients. According to the report of the updated results of the STIM1, study, a total of 5.5 million euro was saved by 100 patients followed in TFR at a median follow-up of 54 months [8].

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 a quality-of-life scale was established at the beginning of the study, no conclusive results could be obtained due to the low number of patients.

Conclusion

The data obtained in this study 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 CML. 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 very important national economic savings; therefore, every chronic-phase CML patient should be evaluated in terms of whether they are suitable for drug discontinuation in daily clinical practice.

Ethics

Ethics Committee Approval: Approval of the study protocols was obtained from the Central Ethics Committee of the Ministry of Health (no: 188, date: 14.04.2014).

Informed Consent: All patients were included in the study after giving written informed consent in line with the Declaration of Helsinki.

Authorship Contributions

Surgical and Medical Practices: M.Y., R.Ö., F.C., L.A.K., A.A.B.D., S.Y.; Concept: M.Y., Z.N.Ö., M.A., S.Y.; Design: M.Y.; Data Collection or Processing: R.Ö., S.P., L.A.K., F.C., S.Y., A.A.B.D., M.Y., Z.N.Ö., S.K., M.A., Ö.Ç., A.Y.; Analysis or Interpretation: S.G., M.Y., E.M.S., Z.N.Ö., R.Ö.F.C., A.A.B.D.; Literature Search: M.Y., E.M.S., Z.N.Ö., A.A.B.D.; Writing: E.M.S., M.Y., Z.N.Ö.

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

Financial Disclosure: This trial was sponsored by the Turkish Society of Hematology.

References

1. Dameshek W. Some speculations on the myeloproliferative syndromes [editorial]. Blood. 1951;6(4):372-375. Blood 2016;127:663.
2. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-293.
3. Whang J, Frei E 3rd, Tjio JH, Carbone PP, Brecher G. The distribution of the Philadelphia chromosome in patients with chronic myelogenous leukemia. Blood. 1963;22(6):664-673. Blood 2016;127:3295.
4. Sloma I, Jiang X, Eaves AC, Eaves CJ. Insights into the stem cells of chronic myeloid leukemia. Leukemia 2010;24:1823-1833.
5. Capdeville R, Buchdunger E, Zimmermann J, Matter A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nat Rev Drug Discov 2002;1:493-502.
6. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016;34:2851-2857.
7. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saußele S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013;122:872-884.
8. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, Legros L, Charbonnier A, Guerci A, Varet B, Etienne G, Reiffers J, Rousselot P; Intergroupe Français des Leucémies Myéloïdes Chroniques. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11:1029-1035.
9. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Yeung DT, Dang P, Goyne JM, Slader C, Filshie RJ, Mills AK, Melo JV, White DL, Grigg AP, Hughes TP. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood 2013;122:515-522.
10. Fujisawa S, Ueda Y, Usuki K, Kobayashi H, Kondo E, Doki N, Nakao T, Kanda Y, Kosugi N, Kosugi H, Kumagai T, Harada H, Shikami M, Maeda Y, Sakura T, Inokuchi K, Saito A, Nawa Y, Ogasawara M, Nishida J, Kondo T, Yoshida C, Kuroda H, Tabe Y, Maeda Y, Imajo K, Kojima K, Morita S, Komukai S, Kawaguchi A, Sakamoto J, Kimura S. Feasibility of the imatinib stop study in the Japanese clinical setting: Delightedly Overcome CML Expert Stop TKI Trial (DOMEST Trial). Int J Clin Oncol 2019;24:445-453.
11. Mahon FX, Richter J, Guilhot J, Muller MC, Dietz C, Porkka K, Hjorth-Hansen H, Gruber F, Panagoitidis P, Ossenkoppele GJ, Mayer J, Almeida A, Machova Polakova K, Ehrencrona H, Kairisto V, Berger MG, Olsson Stromberg U, Mustjoki S, Hochhaus A, Pfirrmann M, Saussele S. Interim analysis of a pan European stop tyrosine kinase inhibitor trial in chronic myeloid leukemia: the EURO-SKI study. Blood 2014;124:151.
12. Takahashi N, Tauchi T, Kitamura K, Miyamura K, Saburi Y, Hatta Y, Miyata Y, Kobayashi S, Usuki K, Matsumura I, Minami Y, Usui N, Fukuda T, Takada S, Ishikawa M, Fujimaki K, Gomyo H, Sasaki O, Ohishi K, Miyake T, Imai K, Suzushima H, Mitsui H, Togitani K, Kiguchi T, Atsuta Y, Ohtake S, Ohnishi K, Kobayashi Y, Kiyoi H, Miyazaki Y, Naoe T; Japan Adult Leukemia Study Group. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. Int J Hematol 2018;107:185-193.
13. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, Clark RE, Cortes JE, Deininger MW, Guilhot F, Hjorth-Hansen H, Hughes TP, Janssen JJWM, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Mayer J, Nicolini F, Niederwieser D, Pane F, Radich JP, Rea D, Richter J, Rosti G, Rousselot P, Saglio G, Saußele S, Soverini S, Steegmann JL, Turkina A, Zaritskey A, Hehlmann R. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-984.
14. Deininger MW, Shah NP, Altman JK, Berman E, Bhatia R, Bhatnagar B, DeAngelo DJ, Gotlib J, Hobbs G, Maness L, Mead M, Metheny L, Mohan S, Moore JO, Naqvi K, Oehler V, Pallera AM, Patnaik M, Pratz K, Pusic I, Rose MG, Smith BD, Snyder DS, Sweet KL, Talpaz M, Thompson J, Yang DT, Gregory KM, Sundar H. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020;18:1385-1415.
15. Irani YD, Hughes A, Clarson 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 immune suppressors and increased natural killer cells. Br J Haematol 2020;191:433-441.
16. Irani YD, Hughes A, Kok CH, Clarson J, Yeung DT, Ross DM, Branford S, Hughes TP, Yong ASM. Immune modulation in chronic myeloid leukaemia patients treated with nilotinib and interferon-alpha. Br J Haematol 2023;202:1127-1136.
17. Jun K, Ya-Zhen Q, Xiao-Su Z, Hong-Xia S, Yue-Yun L, Kai-Yan L, Xiao-Jun H, Hao J. Interferon-α may help prevent molecular relapse of chronic myeloid leukemia after the discontinuation of tyrosine kinase inhibitors. Ther Adv Hematol 2021;12:2040620720986643.
18. Burchert A, Müller MC, Kostrewa P, Erben P, Bostel T, Liebler S, Hehlmann R, Neubauer A, Hochhaus A. Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. J Clin Oncol 2010;28:1429-1435.
19. McCloskey JK, Koprivnikar JL, Goldberg SL, Nyirenda TL, Stanislaus G, Howlett C, Faderl S. A Single Institution Respective Study of Tyrosine Kinase Inhibitor Cessation in Patients with Chronic Phase CML in MMR. Blood 2015;126:5168.