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Use of Second Generation Tyrosine Kinase Inhibitors for Second-Line Treatment of Chronic Myeloid Leukemia After Imatinib Failure

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ABSTRACT

Invention of imatinib was a great step for much more successful clinical management of chronic myeloid leukemia (CML). Now, two other tyrosine kinase inhibitors (TKIs) are available both for first-line and later treatments of CML. In Turkey, currently 2nd line TKIs are indicated only for imatinib failure. This review will evaluate indications for changing imatinib with dasatinib or nilotinib, success of the 2nd line agents in the second-line treatment and some important properties of these agents.

Keywords: Chronic myeloid leukemia, Targeted therapy, Imatinib, Dasatinib, Nilotinib

ÖZET

İmatinib Başarısızlığı Sonrası İkinci Nesil Tirozin Kinaz İnhibitörlerinin Kronik Miyeloid Lösemi'nin İkinci Basamak Tedavisi İçin Kullanılması

Imatinib'in geliştirilmesi, kronik miyeloid lösemi'nin (KML) çok daha başarılı klinik yönetimi için büyük bir adım olmuştur. Günümüzde KML'nin hem birinci hem de sonraki basamak tedavileri için iki tirozin kinaz inhibitörü (TKİ) daha vardır. Türkiye'de günümüzde ikinci nesil TKİ'ler yalnızca imatinib başarısızlığı için ruhsatlanmış durumdadır. Bu derlemede imatinib'i dasatinib ya da nilotinib ile değiştirme indikasyonları, ikinci basamak tedavide ikinci nesil ajanların başarıları ve bu ajanların bazı önemli özellikleri değerlendirilecektir.

Anahtar Kelimeler: Kronik miyeloid lösemi, Hedeflenmiş tedavi, Imatinib, Dasatinib, Nilotinib

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INTRODUCTION

In chronic phase (CP) chronic myeloid leukemia (CML) patients treated with imatinib as the first-line treatment agent, indications for changing therapy to a second generation tyrosine kinase inhibitor (TKI) should be considered in 3 conditions:[1]

1. Imatinib intolerance
2. Imatinib resistance
3. Suboptimal response to imatinib

Imatinib Intolerance

As cross intolerance is not expected except for hematologic toxicity, any of the second generation TKIs can be selected in patients with imatinib intolerance. Side effects which are mentioned in Table 1 and comorbidities may be considered during drug selection.

Imatinib Resistance and Second-line Treatment

There are many different pathophysiologic mechanisms for imatinib resistance, including BCR-ABL kinase domain mutations preventing imatinib binding, clonal evolution, BCR-ABL amplification/over-expression, and decreased imatinib bioavailability/cell exposure. Mutations (notably T315I, Y253F/H, and E255K/V) and clonal evolution are the most important mechanisms.[2] They are related to each other. BCR-ABL mutations have been reported in 36% to 55.7% of all chronic myeloid leukemia patients failing imatinib therapy.[3-5] Mutation frequency ranged from 27% to 55% in chronic phase, 50% to 59.2% in accelerated phase (AP), and 47.6 to 79.4% in blastic crisis (BC) or BCR-ABL+ acute lymphoblastic leukemia (ALL).[3-7]

Table 1. Important characteristics of the second generation TKIs that may help drug selection (according to FDA and EMEA labels)

	Preferable	Contraindications (According to FDA or EMEA lebels)	Condition to be careful (According to FDA or EMEA lebels)	Warnings and precautions (According to FDA or EMEA lebels)	Others
Dasatinib	-Blastic crisis Ph+ acute lymphoblastic leukemia -Nilotinib-resistant mutations: Y253H, E255V, E255K, F359C	-Hypersensitivity to drug constituents	-Antiplatelet or anticoagulant drug therapies -Patients with long QT or at risk for prolongation -Moderate-severe liver dysfunction -CYP3A4 substrates with narrow therapeutic index.	-Periodic CBC analysis required due to myelosupression risk. -Bleeding events that are mostly related to thrombositopenia (and occuring more frequently in accelerated phase/blastic crisis). Severe central nervous system and gastrointestinal hemorrhages, including fatalities, are observed. Gastrointestinal hemorrhage may require treatment interruptions and transfusions. -Sometimes significant fluid retention (ascites, edema, pleural and pericardial effusions). Appropriate precautions should be taken. -Be careful in patients with long QT or at risk for QT prolongation. -Significant cardiac events were reported during treatment (1.6% cardiomyopathy, heart failure, myocardial infarction) -May cause fetal harm when administered to a pregnant women	-Heart disease, hypertension and twice daily use of dasatinib have been found as risk factors for pleural effusion in a retrospective study. -Dasatinib has been found to cause platelet function defects in in vitro tests and animal studies. Clinical importance of these findings are not clear.
Nilotinib	-Dasatinib-resistant mutations F317L and V299L	-Hypokalemia -Hypomagnesemia -Long QT syndrome -Hypersensitivity to drug constituents	-Liver disfunction -History of pancreatitis -Coronary artery disease or risk factors, congestive heart failure, clinically significant bradicardia -Drugs carrying risk of QT prolongation -Patients taking CYP3A4, CYP2C8, CYP2C9, CYP2D6, or UGT1A1 enzyme substrates with narrow therapeutic index -Patients taking Pgp inhibitors	-CBC every 2 weeks for 2 months and then every month. -EKG within one week before treatment and periodically thereafter and at dose modifications due to QT prolongation risk. For similar reason electrolyte monitoring and meticulous correction of hypokalemia/hypomagnesemia are important. Avoid use of QT prolonging agents and CYP3A4 inhibitors. -Sudden death was reported (~0.6% in > 1 study). -Lipase, liver enzymes and bilirubin monitoring due to frequent elevations. -CYP3A4 inhibitors and activators are to be avoided. Nilotinib dose reductions or close QT monitoring are appropriate in patients using CYP3A4 inhibitors. -Food may increase blood levels. Avoid food 2 hours before and 1 hour after the drug. -May cause fetal harm when administered to a pregnant women.	-Considerable risk of hyperglisemia. Importance of this side effect in diabetic patients and those with cardiovascular risks factors is not clear.

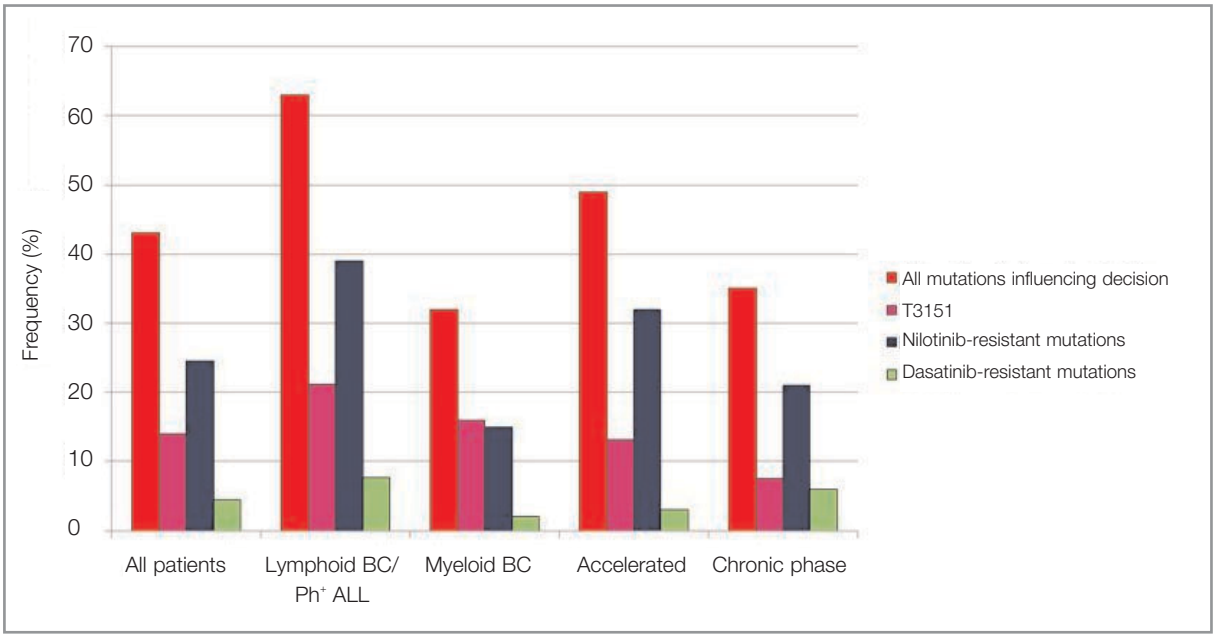

Figure 1. Frequency of imatinib-resistant chronic myeloid leukemia patients with mutations where one or more of their mutations would influence the treatment decision. The frequencies are percentages of all patients with BCR-ABL mutations. Adapted from reference 15 with modifications depending on approximate data presented in this reference.

Imatinib dose escalation, second generation TKIs and allogeneic stem cell transplantation are treatment options for imatinib-resistant cases. Many patients do not achieve a worthwhile response to higher doses of imatinib and the majority of responders will gradually lose their initially good response. Therefore, for patients who fail imatinib, changing treatment to a second-generation TKI is the best option.[8-13] If a patient is relatively young and has a suitable HLA-matched donor, then allogeneic stem cell transplantation should also be considered.[14] Resistance to second generation TKIs and BCR-ABL T315I mutation are absolute indications for the transplantation. In a transplant-eligible patient with good response to second generation TKI treatment, whether to continue with pharmacotherapy or to transplant is a clinical dilemma.

When selecting a second generation TKI, BCR-ABL kinase domain mutations and patient co-morbidities may be considered. Table 1 summarizes clinically important properties of the second generation TKIs which may be useful during drug selection.

In a large series, 43% of imatinib resistant/BCR-ABL-mutated patients had one or more second generation inhibitor clinically relevant mutations, i.e., mutations insensitive to nilotinib and/or dasatinib.[15] Rates of the patients with clinically relevant mutations were 35% in chronic phase, 49% in AP, 32% in myeloid BC, and 63% in lymphoid BC/BCR-ABL+ ALL. Frequencies of those with nilotinib-resistant mutations (Y253H, E255K/V, and F359V/C) were ~21%, ~32%, ~15%, and ~39% in chronic phase, AP, myeloid BC, and lymphoid BC/BCR-ABL+ ALL, respectively. V299L occurred rarely. Patients harboring the other dasatinib-resistant mutation, F317L, were 6%, ≤ 5%, ≤ 5%, and 7.7%. T315I was carried by 7.5%, 13.2%, 16%, and 21.2% of imatinib resistant/BCR-ABL-mutated patients in CP, AP, myeloid BC, and lymphoid BC/BCR-ABL+ ALL, respectively (Figure 1).

Depending on the presented data, an algorithm for selection of second generation TKIs is presented in Figure 2.

Suboptimal Response to Imatinib

Clinical studies evaluating suboptimal responders showed relatively unfavourable prognosis. Hammersmith data revealed worse complete remission, stable complete remission, overall survival (OS) or progression-free survival (PFS) results in subopti-

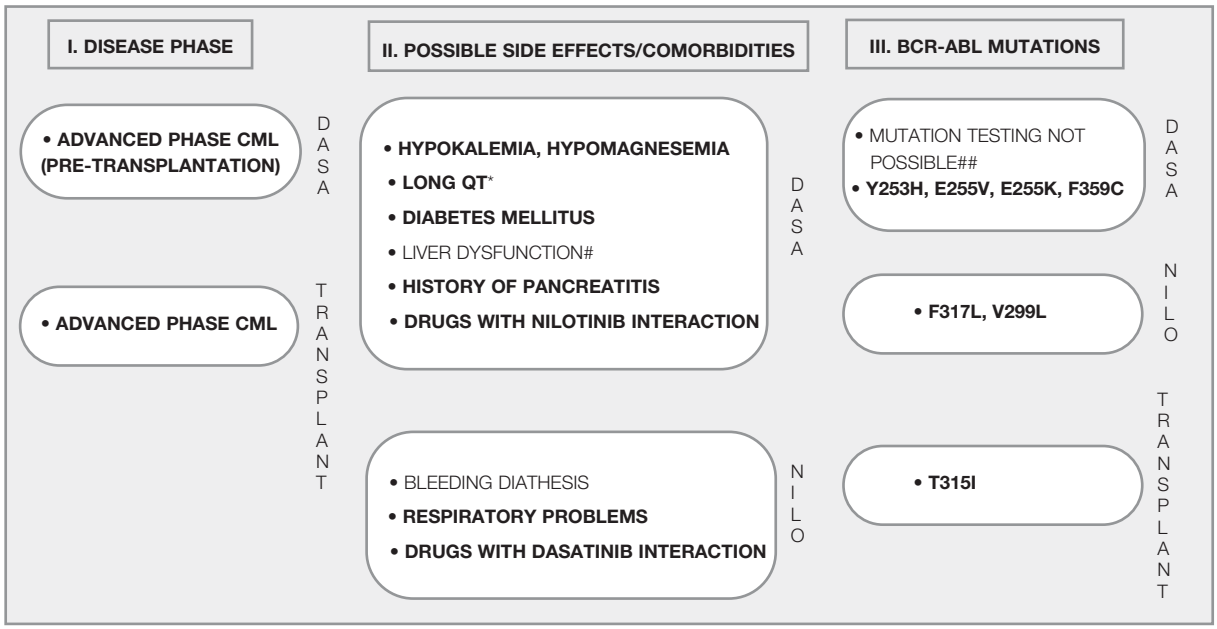

Figure 2. Evaluations during second generation tyrosine kinase inhibitor selection in a chronic myeloid leukemia (CML) patient with imatinib failure. This algorithm depends on contraindications, warnings and frequent side effects indicated in drug labels. Conditions constituting risks for both drugs (e.g. heart failure) are not demonstrated. Side effect (e.g. pleural effusion) prediction studies depending on retrospective data of low evidence level are not considered. Bold letters indicate conditions where one of the drugs is clearly more suitable. The drug of choice is shown beside the boxes.

* Both of the drugs may cause QT prolongation.

Moderate-severe liver dysfunction and heart disorders are conditions to be careful also for dasatinib.

Mutation screening is very important for second-line treatment planning in imatinib-resistant cases. Omitting of mutation analysis may be harmful.

mal response cases depending on the time period when this response occurred.[16] Similar results were also observed in a GIMEMA study.[17] In this study, suboptimal responders at 6th or 12th months attained worse ultimate complete cytogenetic response (CCyR), major molecular response (MMR) and event-free survival (EFS) compared to optimal response patients. Prognosis of the 6th month suboptimal responders (i.e., patients showing minor or minimal cytogenetic responses at this time) was also evaluated in the IRIS study.[18] EFS rate was lower (58%) in suboptimal response patients in comparison to those having optimal response (85-91%). Survival rates without AP/BC transformation at 6th year were 85% and 94-97%, respectively. The chances of attaining CCyR were 54% and 87% in suboptimal and partial cytogenetic response cases, respectively. There are MD Anderson Cancer Center results supporting these data, too.[19] In that study, the results of suboptimal responders - at 6th month were especially striking. Those cases had a very low possibility of ultimate CCyR (30%), and EFS and transformation-free survival rates similar with imatinib failure patients. The transformation risk was 30%.

Consequently, treatment modification should be preferred in these cases due to relatively unfavorable cumulative prognosis and uncertainty in which patient will finally reach to optimal response level. However, how to do this modification is not clear. Imatinib dose escalation or switch to second generation TKIs are possible alternatives. Although not confirmed with randomized clinical studies, second generation TKIs are probably a better option in this situation. European LeukemiaNet recommendations for the suboptimal response patients include continuation of imatinib at same dose, or testing of high dose imatinib, dasatinib, or nilotinib.[1]

During second-line treatment of imatinib-resistant CP CML patients, provisional definitions of responses to second-generation TKIs are presented in Table 2.

Table 2. Provisional definition of the response to second-generation TKIs, dasatinib and nilotinib, as second-line therapy of patients with imatinib-resistant chronic myeloid leukemia in chronic phase according to the European LeukemiaNet

Time of Evaluation (months)	Suboptimal Response	Failure	Warnings
Baseline	Not applicable	Not applicable	Hematologic resistance to imatinib; clonal chromosome abnormalities in Ph^+ cells; mutations*
3	Minor cytogenetic response (Ph^+ 36-65%)	No cytogenetic response (Ph^+ > 95%); new mutations*	Minimal cytogenetic response (Ph^+ 66-95%)
6	Partial cytogenetic response (Ph^+ 1-35%)	Minimal cytogenetic response (Ph^+ 66-95%); new mutations*	Minor cytogenetic response (Ph^+ 36-65%)
12	Less than major molecular response**	Less than partial cytogenetic response (Ph^+ > 35%); new mutations*	

* TKI-insensitive BCR-ABL1 kinase domain mutations.

** Ratio of BCR-ABL to ABL (or other housekeeping genes) ≤ 0.1% on the international scale

Hematological toxicity and related complications may occur more frequently with the second generation TKIs due to higher drug potency. Some important characteristics of these agents (including important side effects) are summarized in Table 1. Pleural effusion under dasatinib and biochemical abnormalities, including hyperglycemia, bilirubin, liver enzyme, lipase, and amylase elevations under nilotinib are not infrequent. Dasatinib 100 mg QD instead of 70 mg BID for CP CML and 140 mg QD instead of 70 BID for advanced phases were found to cause significantly less pleural effusion and hematologic toxicities without impairing efficacy. [20-23]

CONCLUSION

TKIs made treatment of CML easier and more successful. However, there are still many things to be done for more effective use of the modern armamentarium for the management of CML.

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