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Long-term Treatment of Chronic Myeloid Leukemia

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ABSTRACT

Imatinib, a selective tyrosine kinases inhibitor (TKI), has excellent efficacy in the treatment of chronic myeloid leukemia (CML). Imatinib resistance and intolerance opened the way to the development of second generation TKIs against CML, including nilotinib and dasatinib. Because all TKIs are more effective drugs in comparison with previous therapies in CML, the follow-up period is now longer in the TKI era. These compounds are prescribed for prolonged periods, often in patients with comorbidities. Therefore, monitoring of CML should comprise the response to TKIs and long term effects of the TKIs.

Keywords: Chronic myeloid leukemia, Long term treatment, Monitorization

ÖZET

Kronik Myeloid Löseminin Uzun Dönem Tedavisi

Selektif bir tirozin kinaz inhibitörü olan imatinib kronik miyeloid lösemi tedavisinde etkisini kanıtlamıştır. İmatinibe karşı gelişen direnç ve intolerans kronik miyeloid lösemide nilotinib ve dasatinib gibi ikinci jenerasyon tirozin kinaz inhibitörlerinin geliştirilmesine yol açmıştır. Tirozin kinaz inhibitörlerinin hepsi kronik miyeloid lösemide kullanılan ilaçlardan daha üstün oldukları için, hastaların takip süreleri de uzamıştır. Bu ilaçlar komorbiditesi de olan hastalarda uzun süreli olarak kullanılmaktadır. Bu yüzden kronik miyeloid lösemili hastaların monitorizasyonu hem tirozin kinaz inhibitörlerine yanıtı hem de bu ilaçların uzun dönemdeki etkilerini içermelidir.

Anahtar Kelimeler: Kronik miyeloid lösemi, Uzun süreli tedavi, Monitorizasyon

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INTRODUCTION

Chronic myeloid leukemia (CML) is a progressive and often fatal myeloproliferative neoplasm genetically characterized by the presence of the reciprocal translocation t(9;22)(q34;q11) resulting in a bcr-abl fusion gene on the derivative chromosome 22, which is called Philadelphia (Ph) chromosome. The resulting gene product is BCR-ABL and the deregulated tyrosine kinase activity of this oncoprotein is responsible for leukemogenesis.[1-3] The natural history of CML consists of 3 distinct stages: chronic phase (CP), accelerated phase (AP), and a blast phase (BP).[4] Most patients (90%) present with CML in CP.

In CP patients well differentiated leukemic cells are proliferating relatively slowly. CP is followed by AP and white blood cell counts are poorly controlled and the numbers of immature blasts in the peripheral blood are increased.[5] After 1 to 2 years, AP may transit into BP. In this phase cytopenias, infections, bleeding, organ failure, and death can occur. The transition occurs as rapidly as 3 years in the absence of treatment. The median survival for patients with untreated BP CML is 3 to 6 months.[5]

With the advent of tyrosine kinase inhibitors (TKIs) to treatment of CML, the natural history of this disease changed dramatically in the last ten years and extremely longer survivals and longer follow-ups are expected for the CML patients. Thus, the number of CML patients is accumulating and the patients have to be closely monitored, as their TKI therapy continues.

MONITORING RESPONSE IN CML

The goals of CML treatment are to achieve normal blood count values, reduction and elimination of the Ph chromosome, and reduction and elimination of BCR-ABL transcripts. These goals can be monitored with the assessment of hematologic, cytogenetic, and molecular responses, respectively. Prior to the TKI therapy, the response to treatment was assessed with hematologic and cytogenetic measurements. Nowadays, the TKIs commonly achieve deep molecular responses and more sensitive techniques of disease detection are required.

i. Hematologic Response

A complete hematologic response (CHR) is achieved, when white blood cell count is <10.000/mm^3, platelet count is <450.000/mm^3, myelocytes plus metamyelocytes are <5%, blasts and promyelocytes in peripheral blood are absent, and extramedullary involvement is absent.[6,7] European LeukemiaNet (ELN) recommends performing CBCs at diagnosis, then every 15 days until complete hematologic response (CHR) has been achieved and confirmed, then at least every 3 months or as required. According to ELN achievement of CHR within 3 months from the start of therapy is an optimal response and approximately all patients with CML in chronic phase achieve a CHR with TKI therapy.

ii. Cytogenetic Response

Cytogenetic analysis is the gold standard for response monitoring in CML.[8] In conventional cytogenetics >20 metaphases from the bone marrow is required and the presence of the Ph chromosome is evaluated. Categories of cytogenetic response are the followings: minimal cytogenetic response (66% to 95% Ph$^+$ metaphases), minor cytogenetic response (%36-65 Ph+ metaphases), partial cytogenetic response, (1% to 35% Ph+ metaphases), major cytogenetic response (0% to 35% Ph$^+$ metaphases), and complete cytogenetic response (0% Ph$^+$ metaphases). The association between cytogenetic response and positive outcomes has been established well.[9]

Fluorescent in situ hybridization (FISH) is an alternative technique for evaluating cytogenetic response. Approximately 200 interphase cells are analyzed from peripheral blood samples instead of bone marrow samples. Due to technical restrictions clinicians should be aware of the possibility of low-level false-FISH positivity in making a decision for treatment failure. Current data are based on conventional cytogenetics so FISH is only recommended prior to treatment to identify cases of Ph$^-$, BCR-ABL+ CML, and those with variant Ph translocations, Ph amplification, or del9q+.[1,7]

According to the ELN recommendations conventional cytogenetics should be done at diagnosis, at 3 months, and at 6 months; then every 6 months until a CCyR (complete cytogenetic response) has been

achieved and confirmed, then every 12 months if regular molecular monitoring can not be assured; always for occurrences of treatment failure and for occurrences of unexplained cytopenias. The achievement of CCyR at 12 months is considered as an optimal response to imatinib treatment.[7]

iii. Molecular Responses

The majority of patients with CML treated with TKI therapy achieve a complete cytogenetic response. Molecular monitoring is applied for detecting deeper responses. In this method the presence of BCR-ABL mRNA using real-time quantitative polymerase chain reaction (QPCR) is evaluated.[10] This analysis can be performed on peripheral blood samples and is more convenient than bone marrow aspiration for the patient and clinician.[11,12] The amount of reduction in BCR-ABL transcripts compared to a standardized baseline is assessed.[7] Individual laboratories can report BCR-ABL transcript levels on an international scale with the introduction of a conversion factor, which is specific for the individual laboratory. Thus, a comparison between the values of different laboratories is possible.

A major molecular response is defined as a 3-log reduction of the BCR-ABL transcript in comparison to the standardized baseline or a BCR-ABL (international scale) 0.1%.[12] There is a good correlation between the BCR-ABL (international scale) levels in the peripheral blood and the bone marrow cytogenetical findings. A 1-log reduction or BCR-ABL (international scale) 10% is equivalent to a major cytogenetic response and a 2-log reduction or a BCR-ABL (international scale) 1% is equivalent to a complete cytogenetic response. Elimination of the leukemic stem cell is the ultimate goal of treatment and the only potential for a CML cure.

Complete molecular response is defined as undetectable BCR-ABL mRNA transcripts by RQ-PCR and/or nested PCR in 2 consecutive high-quality samples (sensitivity $>10^4$).[10] However, the ultimate goal of treatment, elimination of the leukemic stem cells and cure, can not be shown with all these methods.

If conventional cytogenetics of the bone marrow is performed, there is additional information about bone marrow morphology by bone marrow smears and about additional chromosomal changes. The molecular monitoring lacks this advantages.[13]

ELN recommends performing molecular BCR-ABL RQ-PCR-analysis at diagnosis, every 3 months until MMR has been achieved and confirmed, then at least every 6 months. Regular molecular monitoring over the course of disease can help making treatment decisions for example in patients who are responding slowly to treatment or are not using the drug adherently.[14] A rise in BCR-ABL transcript levels detected during TKI treatment is a warning sign and a confirmative RQ-PCR analysis should be performed.[15]

Achievement of major molecular response at 18 months is an optimal response to imatinib treatment. Several studies have demonstrated that achievement of a major molecular response is associated with prolonged durations of complete cytogenetic response in comparison to the patients who did not have the same depth of BCR-ABL levels.[16,17]

The degree of molecular response at early time points may predict later achievement and sustain of major molecular response and improved rates of progression free and event free survival.[18]

Minor changes in BCR-ABL should not necessitate a treatment change. If there is an increase of 5-10 fold or greater, confirmation of the test and additional assessments such as cytogenetic analysis and mutation analysis should be done.[7,19]

The National Comprehensive Cancer Network (NCCN) published evidence-based clinical practice guidelines for CML and proposed indications for cytogenetics and PCR for BCR-ABL quantification, and indications for bcr-abl domain mutation analysis.[15]

SAFETY PROFILES OF THE VARIOUS TKIs

The safety profiles of the various TKIs differ from each other, because there are differences in the targeted tyrosine kinases of these compounds. In the pivotal phase III International Randomized Study of Interferon and STI571 (IRIS) trial over 8 years of follow-up 5.4% of patients had discontinued treatment because of adverse events.[20] The most common grade 3/4 hematologic adverse events among imatinib-treated patients in IRIS were neutropenia, thrombocytopenia, and anemia.[21] Adverse events

occurred mostly in the first two years and decreased to less than 2% after 4 years of imatinib therapy.[22] Imatinib had a favorable long term safety profile after 5 year results of IRIS.[23]

There has not been a trial comparing second-generation TKIs to one another, but there have been studies for each where they have been compared with imatinib. Nilotinib was rationally designed based on the structure of imatinib, but its safety profile is very different from that of imatinib. Nilotinib does not cause fluid retention as frequently as imatinib, but is associated with higher rates of asymptomatic pancreatic lipase elevation.[24,25] Dasatinib produces more myelosuppression compared to imatinib. Bleeding and pleural effusions are the non-desired effects of dasatinib.[24] Grade I-II cytopenias and biochemical abnormalities usually recover after withholding the drug. Dasatinib 100 mg once daily instead of 70 mg twice daily minimized the occurrence of pleural effusions.[26] If the pleural effusion does not resolve with interruption of dasatinib treatment, diuretics and corticosteroids can be added to the treatment. If the pleural effusion reoccurs, dose reduction is needed.[26]

LONG TERM EFFECTS OF TKIs

Discontinuation of TKIs in CML patients is associated with a high risk of relapse. Therefore tyrosine kinase inhibitors should be given during the lifespan of the patient. TKIs impact multiple targets for long period of time, which can induce late side effects. The extent and nature of potential late effects are important for physicians to consider. These effects could be either harmful, or beneficial.

Cardiac Effects of TKIs

All of the clinically available TKI inhibitors contain the information of the potential for cardiotoxicity in their respective package inserts. Severe congestive heart failure and left ventricular dysfunction have been reported rarely with especially high dose imatinib treatment. The general consensus is that the majority of patients who develop cardiotoxicity, heart failure, and/or myocardial infarction are older (>65 years old) and have pre-existing cardiac risk factors or existing cardiac disease.[27,28] Cardiac failure is also very uncommon in CML patients on nilotinib and dasatinib therapy. Prolongation of the QTc interval is relatively uncommon with both nilotinib[29] and dasatinib.[30] FDA maintains a warning for nilotinib regarding QTc prolongation. If the QTc is > 480 msec, therapy should be withheld and serum potassium and magnesium levels corrected, if below normal. Concomitant medication that can prolong QTc should also be checked. Treatment should be resumed at the previous dose in < 2 weeks if the QTc returns to < 450msec and < 20 msec of baseline. Neither nilotinib nor dasatinib should be administered to patients with long QT syndrome and with drugs known to prolong QTc.[15]

Immune System

In addition to BCR-ABL, TKIs inhibit other proteins, some of which play a role in the immune system. Imatinib therapy induces hypogammaglobulinemia[31] and impairs the T-cell response[32] directly. Indirectly, inhibition of the dendritic cell function can also affect T-cell function.[33] Thus, imatinib use can help to improve graft versus host disease (GVHD).[34] Nilotinib reduces proliferation and function of CD 8+ T-lymphocytes.[35] Dasatinib seems to be a more potent immuno-modulating agent. Dasatinib suppresses T-cell function and causes an expansion of the natural killer cell compartment, while suppressing NK cytotoxicity.[36,37] Large, granular lymphocytosis[38] is observed in patients on dasatinib treatment. This fact might be associated with improved response in CML.

Bone

The phosphate metabolism can be affected by the use of TKIs and decreased serum phosphate levels are seen occasionally in patients with CML using TKIs.[39] Furthermore, inhibition of PDGFR signalling by imatinib in osteoblasts activates osteoblast differentiation and inhibits proliferation.[40] Imatinib inhibits osteoclastogenesis by both stromal cell-dependent and direct effects on osteoclast precursors.[41] Taking together, the effects of imatinib on bone metabolism potentially have useful clinical effects, where the bone mass is protected and preserved.

Gynecomastia

KIT and PDGFR are expressed in the male testis. Imatinib can decrease testosterone production by the inhibition of these receptors.[42] Long-term imatinib exposure can cause secondary inhibition of KIT and PDGFR, which can decrease testosterone production over time. In one study hormone levels and clinical evidence of gynecomastia were evaluated in 38 patients at baseline and on treatment with imatinib.[42] In the majority of patients studied, imatinib was associated with a decrease in the production of testicular hormones, and in 7 patients gynecomastia was noted.

Hypothyroidism

Imatinib has no direct effect on hypothyroidism in patients with CML. But it can affect patients treated with levothyroxine for hypothyroidism. In a cohort of 11 patients (10 with medullary thyroid carcinoma and 1 with GIST) treated with imatinib and levothyroxine concurrently.[43] Symptomatic hypothyroidism occurred in all patients, in which thyroid gland was removed surgically. Hypothyroidism was not present in those who did not undergo surgery. Patients with surgery had markedly elevated thyroid-stimulating hormone (TSH) levels and required an increase of levothyroxine during imatinib treatment.[43] At present it can be suggested to monitor TSH levels more frequently in imatinib-treated patients on thyroid hormone replacement.

Long Term Cutaneous Toxicity

Rush, dry skin, pruritus, and photosensitivity are early dermatologic adverse events but may persist throughout therapy.[44] Other form of cutaneous toxicity associated with imatinib is skin hyper/hypo pigmentation, which can persist even after imatinib is stopped.[45] Hypopigmentation is related to the inhibition of KIT and is more prevalent in ethnically pigmented patients. In a group of 133 patients repigmentation of gray hair has been reported.[46]

Secondary Malignancies

During the course of CML treated with imatinib alone or in combination with other agents occasionally other chromosomal abnormalities in the Ph-negative metaphases can arise. This may be the initiator of development of myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML). In a study comprising 1701 patients 3 patients treated with imatinib for CML developed AML (n= 1) and high-risk MDS (n= 2).[47] In a further series of patients with newly diagnosed CML treated with first-line imatinib chromosomal abnormalities in Ph-negative metaphases occurred in 9% of patients.[48] A patient with monosomy 7 developed AML, but the other patients had no signs of myelodysplasia or acute leukemia. These chromosomal changes can occur in patient with CML treated with alternative drugs, including interferon, nilotinib and dasatinib.[49-52] Thus, it is useful to monitor patients on TKIs with bone marrow aspirations and cytogenetic analysis if a secondary clonal evolution is suspected.

ADHERENCE TO TREATMENT

Continuous and adequate imatinib dosing is essential to achieve therapeutic outcomes.[53] The healthcare provider's recommendations should be agreed and kept by the patients in order to achieve better responses. This is reflected by the adherence of the patient to treatment.[54] Although mainly it is a problem of the patient, adherence behavior is influenced also by the clinician and the healthcare system, the disease and its treatment, and economic and social factors. The ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study suggested that nonadherence is more prevalent than patients, physicians, and third persons such as spouses and family members believe it is, and is related to poorer response rates to imatinib.[55]

Among the others, the dosing schedule of the drug is very important for the patients to adhere to treatment. One would expect that once daily dosing regimens would be more convenient for patients with CML, who are in good medical condition and go to work or perform their daily activities like normal people.

Can we Stop TKIs?

The stop imatinib (STIM) trial enrolled 100 patients who discontinued imatinib after achieving and maintaining CMR for 2 years or more. Sixty-nine

patients were followed up at least 12 months (median 24 months), and in 42 (61%) BCR-ABL transcripts re-emerged. In the remaining patients CMR sustained. All but one of these molecular recurrences occurred within 7 months of stopping imatinib, and all patients with recurrent disease responded again to imatinib treatment.

The authors estimate that 10% of patients with CML may be eligible for an attempt of imatinib discontinuation.[56] With a 40% rate of sustained CMR, 4% of CML patients may be 'cured' with imatinib. However, this data are preliminary and observation time is too short. Occasional relapses have been reported almost two decades after allogeneic stem cell transplant.[57] Thus, a longer follow-up time will be needed before making a definite decision.

CONCLUSION

In conclusion, TKIs have revolutionized the treatment of CML and changed the natural history of the disease. The efficacy and safety of imatinib, dasatinib and nilotinib have been confirmed by substantial long-term outcome and response durability data. To optimize therapeutic benefit, clinicians should monitor the patients using TKIs closely and be aware of long-term undesired effects of TKIs.

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