Chronic Myeloid Leukemia: Practical Issues in Diagnosis, Treatment and Follow-Up

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ABSTRACT

Chronic myeloid leukemia (CML) is sometimes mentioned as the disease of “firsts”. 1) It is the first disease where the term “leukemia” was used. 2) It is the first neoplastic disorder which was found to be associated with a recurrent chromosomal abnormality. 3) It is the first disease where targeted therapy against a fusion protein was used. Entrance of BCR-ABL tyrosine kinase inhibitors, first imatinib and then dasatinib and nilotinib, into clinical practice within the last decade has fundamentally changed both treatment and follow-up of CML. In this review, practical points about CML have been summarized, with a special emphasis to treatment and follow-up.

Keywords: Chronic myeloid leukemia, Philadelphia chromosome, BCR-ABL, Imatinib, Dasatinib, Nilotinib

ÖZET

Kronik Myeloid Lösemi: Tanı, Tedavi ve İzlem Pratiği

Kronik miyeloid lösemi (KML) “ilk”lerin hastalığı olarak da adlandırılır. Çünkü bir çok yönüyle “ilk”lerin gerçekleştiği bir hastalıktır: 1) Lösemi teriminin ilk kez kullanılanı hastalıktır. 2) Sabit bir kromozom bozukluğu ile ilişkili olduğu gösterilen ilk neoplastik rahatsızlığıdır. 3) Bir füzyon proteinine karşı hedefe odaklı tedavinin ilk olarak uygulandığı hastalıktır. Son 10 yıl içerisinde BCR-ABL tirozin kinase inhibitörlerinin (önce imatinib, daha sonra da dasatinib ve nilotinib) klinik kullanma girmesiyle KML’nin tedavi ve izlemi köken değişmiştir. Bu derlemede KML ile ilgili pratik konular, tedavi ve izlem ağrlıkları olmak üzere ele alınmıştır.

Anahtar Kelimeler: Kronik miyeloid lösemi, Philadelphia kromozomu, BCR-ABL, Imatinib, Dasatinib, Nilotinib
INTRODUCTION

In the last decade, very important developments occurred in clinical management of chronic myeloid leukemia (CML), making this previously fatal disease a chronic controllable disorder in many patients. Introduction of BCR-ABL tyrosine kinase inhibitors to clinical practice has fundamentally changed both treatment and follow-up of CML. In this review, CML is summarized with a special emphasis to practical issues including treatment and follow-up.

1. Incidence

According to the United States Surveillance Epidemiology and End Results data (http://www.seer.cancer.gov) incidence of CML was 1.1 and 2 per 100,000 in men and women, respectively between 2003 and 2007. The median age at diagnosis was 65. Approximately 2.5% were diagnosed under age 20; 7.4% between 20 and 34; 10.1% between 35 and 44; 13.3% between 45 and 54; 15.0% between 55 and 64; 19.0% between 65 and 74; 22.7% between 75 and 84; and 9.9% at 85+ years of age.

2. Pathogenesis

BCR-ABL hybrid gene is an invariable finding in CML patients. It results from a translocation between BCR (chromosome 22) and ABL (chromosome 9) genes in a pluripotent hematopoietic stem cell, either at chromosome level, i.e., the Philadelphia chromosome or a cryptic one at gene level.1,2 BCR-ABL gene is the reason for chronic myeloid leukemiagenesis.3–5 Product of the BCR-ABL is a constitutionally active cytoplasmic tyrosine kinase, leading to uninhibited cell proliferation. Three different fusion proteins may be produced depending on the breakpoints in BCR and ABL genes, p210 BCR-ABL, p190 BCR-ABL, and p230 BCR-ABL.

Acute lymphoblastic leukemia (ALL) and a rare biphenotypic acute leukemia are also pathogenetically associated with the BCR-ABL gene.5,6 The reason of why BCR-ABL fusion gene can cause three different leukemia phenotypes probably depends on the stem cell compartment affected.

3. Clinical Presentation and Diagnosis

In contrast to other chronic leukemic disorders, such as chronic lymphocytic leukemia, CML is rarely diagnosed in an asymptomatic person. Constitutional complaints (fatigue, weight loss, and fever), those related to splenomegaly (abdominal fullness, anorexia, abdominal pain, and early satiety) and bleeding tendency (easy bruising or bleeding) are most frequent symptoms. Splenomegaly (≥ 95%), sternal tenderness, hepatomegaly, purpura, and retinal hemorrhage are commonly reported signs at physical exam.

Lab tests typically reveal leukocytosis and presence of immature myeloid cells at peripheral blood. Bone marrow examination at diagnosis shows prominent myeloid hyperplasia.

Conditions causing leukemoid blood picture (i.e., reactive prominent neutrophilia with immature neutrophilic precursors in peripheral blood related to infections, rare inflammatory conditions, malignant diseases, drugs such as corticosteroids, eclampsia, thyroid storm, diabetic ketoacidosis, excessive adrenocorticotropic hormone, severe burns, mercury poisoning, etc.) and some myeloproliferative disorders (polycythemia vera, essential thrombocythemia, primary myelofibrosis, unclassifiable myeloproliferative neoplasm) and myelodysplastic/myeloproliferative disorders (atypical CML, chronic myelomonocytic leukemia, unclassifiable myelodysplastic/myeloproliferative neoplasm) are to be considered in the differential diagnosis of CML. Fortunately, the diagnosis is rarely problematic. It depends on demonstration of the Philadelphia chromosome by cytogenetic analysis or BCR-ABL gene by reverse-transcriptase polymerase chain reaction or floresence in situ hybridization.

4. Natural Course of CML and Prognostic Classifications

CML has a characteristic biphasic clinical course. The initial chronic phase is a relatively indolent disorder which can last for some years. Untreated CML invariably progress to acute myeloid or lymphoblastic leukemia (i.e., blastic crisis, BC). Sometimes an accelerated phase (AP) precedes blastic transformation.
Without effective therapies, median survival of the chronic phase disease, AP disorder and BC cases were 2.5 to 5 years, less than 1.5 years, and 3 to 6 months, respectively. In addition to disease phase, some baseline characteristics also have prognostic implications. These characteristics are formulized in the Sokal and Euro scores.

5. Treatment

Introduction of imatinib (Glivec, Novartis) into clinical practice nearly one decade ago, has dramatically changed treatment and follow-up of CML. Imatinib specifically targets tyrosine kinase activity of the oncogenic protein encoded by BCR/ABL gene. Subsequently, other tyrosine kinase inhibitors (TKIs) were developed. Currently, two other TKIs are available for clinical use, namely dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis). The European LeukemiaNet recommendations for treatment of CML are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1. The European LeukemiaNet recommendations for treatment of chronic myeloid leukemia</th>
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<tbody>
<tr>
<td><strong>CHRONIC PHASE, FIRST LINE</strong></td>
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<tr>
<td>Imatinib 400 mg daily</td>
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<td><strong>CHRONIC PHASE, SECOND LINE</strong></td>
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<tr>
<td>Imatinib intolerant</td>
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<tr>
<td>Continue imatinib therapy for the same duration</td>
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<tr>
<td>Imatinib suboptimal response</td>
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<td>Continue imatinib same dose; or test high dose imatinib,</td>
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<tr>
<td>dasatinib, or nilotinib</td>
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<tr>
<td>Imatinib failure</td>
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<td>Dasatinib or nilotinib</td>
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<tr>
<td>Allogeneic stem cell transplantation in patients who</td>
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<tr>
<td>experienced progression to accelerated phase or</td>
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<td>blast crisis and in cases with T315I mutation</td>
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<td><strong>CHRONIC PHASE, THIRD LINE</strong></td>
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<tr>
<td>Dasatinib or nilotinib suboptimal response</td>
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<tr>
<td>Continue dasatinib or nilotinib, with an option for</td>
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<tr>
<td>allogeneic stem cell transplantation in patients with</td>
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<td>warning features (ie, prior hematologic resistance to</td>
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<tr>
<td>imatinib, mutations) and</td>
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<td>in cases with an EBMT risk score ≤ 2</td>
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<tr>
<td>Dasatinib or nilotinib failure</td>
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<td>Allogeneic stem cell transplantation</td>
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<tr>
<td><strong>ACCELERATED OR BLASTIC PHASE, FIRST LINE (Patients who are</strong></td>
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<tr>
<td>TKI naive**</td>
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<td>Imatinib 600 or 800 mg, dasatinib, or nilotinib (in case of</td>
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<td>mutations poorly sensitive to imatinib) followed by</td>
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<td>allogeneic stem cell transplantation</td>
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<td><strong>ACCELERATED OR BLASTIC PHASE, SECOND LINE (Patients with</strong></td>
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<td>prior treatment of imatinib)</td>
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<tr>
<td>Dasatinib or nilotinib followed by allogeneic stem cell</td>
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<td>transplantation</td>
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First-line Treatment in Chronic Phase Patients

A phase I study of imatinib in interferon-alpha resistant, intolerant or refractory CML patients was started at 1998. Subsequently, a phase II study was conducted in similar patients. Chronic phase patients showed 95% and 60% complete hematologic (CHR) and cytogenetic (CCyR) responses, respectively. Estimated progression-free survival (PFS) and overall survival (OS) rates at 6 years were 61% and 76%, respectively. In AP/BC patients, response rates were also satisfactory. However, early relapses which generally occurred within one year of treatment were quite common. These results led to an accelerated FDA approval of imatinib at 2001.

The IRIS study was started at 2000. It was a randomized-controlled international multicenter study including more than 1000 untreated chronic phase CML cases. The patients were randomized to 400 mg/day imatinib or interferon alpha plus cytarabine. At 18 months, imatinib arm showed better cumulative CHR (95.3% vs. 55.5%) and CCyR (73.8% vs. 38.6%).
vs. 8.5%) rates. Imatinib was also better considering rates of freedom from progression to AP/BC (96.7% vs. 91.5%) at 18 months and drug discontinuation due to intolerance (12% vs. 33%).

Because a very large proportion of cases in the combination arm crossed over to imatinib due to interferon plus cytarabine failure or intolerance, OS benefit of imatinib could not be observed within the IRIS study. This advantage has been seen when results of the IRIS study were compared with historical 91 CML interferon plus cytarabine data.

Last follow-up results of the IRIS study were published in abstract form at the 51st Congress of the American Society of Hematology. Eight-year follow-up showed that 55% patients remained on imatinib, while 45% had discontinued treatment due to adverse events (6%), unsatisfactory response (16%), stem cell transplantation (3%), death (3%) or other reasons (17%). Estimated event-free survival (EFS) and freedom from progression to AP/BC were 81% and 92%, respectively. Estimated OS was 85% and 93% when only CML-related deaths and those prior to stem cell transplantation were considered. Only 3% of patients (15 cases) who achieved CCyR progressed to AP/BC, all but 1 within 2 year of achieving CCyR. Minor cytogenetic response at 3, partial cytogenetic response at 6 and 12, and CCyR at 18 months were associated with stable CCyR during the observation period.

Studies on first-line use of the second generation TKIs dasatinib and nilotinib have been ongoing. First results of the ENESTnd study comparing the efficacy and safety of 300 or 400 mg bid nilotinib with 400 mg qd imatinib in patients with newly diagnosed chronic phase CML showed superior efficacy in nilotinib arms.

Rates of major molecular response (MMR) at 12 months were superior in nilotinib 300 mg (44%) arm compared to imatinib (22%) and also for nilotinib 400 mg (43%) arms in comparison to imatinib arms. Rates of CCyR at 12 months were 55.7% in all chronic myeloid leukemia patients failing imatinib therapy. 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. Mutations (notably T315I, Y253F/H, and E255K/V) and clonal evolution are the most important mechanisms.

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. 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. Mutations (notably T315I, Y253F/H, and E255K/V) and clonal evolution are the most important mechanisms.

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 gradually lose their initially good response. Therefore, for patients who fail imatinib, changing treatment to a second-generation TKI is a better option (Table 2). If a patient is relatively young and has a suitable HLA-matched donor, then allogeneic stem cell transplantation should also be considered.

When selecting a second generation TKI, BCR-ABL kinase domain mutations and patient co-morbidities may be considered. Table 3 summarizes cli-
nically 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. Rates of the patients with clinically relevant mutations were 35% in chronic phase, 49% in AP, 32% in myeloid BC, and 59% in lymphoid BC. 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 chronic phase, AP, myeloid BC, and lymphoid BC/BCR-ABL+ ALL, respectively.

**Suboptimal Response to Imatinib**

Clinical studies evaluating suboptimal responders showed relatively unfavourable prognosis. Hammersmith data revealed worse complete remission, stable complete remission, OS or PFS results in suboptimal response cases depending on the time period when this response occurred. Similar results were also observed in a GIMEMA study. In this study, suboptimal responders at 6th or 12th months attained worse ultimate CCyR, MMR and 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. 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 parti-

| Table 2. Results of dasatinib and nilotinib following imatinib failure due to resistance or intolerance (adapted from 36). |
|---|---|---|---|---|---|---|
| Dasatinib Chronic (n = 387) | Dasatinib AP (n = 174) | Dasatinib Myeloid BC (n = 109) | Dasatinib Lymphoid BC (n = 48) | Nilotinib Chronic (n = 321) | Nilotinib AP (n = 136) |
| Treatment duration, mo | CHR | MCR | CCyR | MMR | Overall survival |
| Not reported (≥ 24 mo of follow-up) | Not reported | 50% | 62% | 53% | 24 mo: 94% |
| 13.5 (treatment duration) | 26% | 40% | 33% | 24 mo: 93% | 12 mo: 83% |
| 3.4 (treatment duration) | 29% | 34% | 27% | 24 mo: 72% | 24 mo: 38% |
| 13 (treatment exposure) | 26% | 52% | 46% | median 11.8 mo | median 5.3 mo |
| 6.9 (treatment exposure) | 77% (patients not in CHR at baseline) | 57% | 41% | 12 mo: 95% | 12 mo: 81% |
| 2.8 (treatment exposure) | 26% | 31% | 19% | 18 mo: 91% | |
al cytogenetic response cases, respectively. There are M.D. Anderson Cancer Center results supporting these data, too.\textsuperscript{42} In this study, results of the patients with suboptimal response at 6th month were especially striking. These cases had a very low possibility (30\%) of ultimate CCyR and EFS and transformation-free survival rates similar to 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 manage this modification is not clear. Imatinib dose escalation or switching to se-

### Table 3. Important characteristics of the 2nd generation TKIs that may help drug selection (according to FDA and EMEA labels).

<table>
<thead>
<tr>
<th>Preferable</th>
<th>Contraindications (According to FDA or EMEA labels)</th>
<th>Conditions To Be Careful (According to FDA or EMEA labels)</th>
<th>Warnings and Precautions (According to FDA or EMEA labels)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dasatinib</strong></td>
<td>• Blastic crisis • Ph+ acute lymphoblastic leukemia • Nilotinib-resistant mutations: Y253H, E255V, E255K, F359C</td>
<td>• Hypersensitivity to drug constituents</td>
<td>• Antiplatelet or anticoagulant drug therapies • Patients with long QT or at risk for prolongation • Moderate-severe liver dysfunction • CYP3A4 substrates with narrow therapeutic index</td>
<td>• Periodic CBC analysis required due to myelosupression risk. • Bleeding events that are mostly related to thrombocytopenia (and occurring 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. • May cause fetal harm when administered to a pregnant woman.</td>
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<tr>
<td><strong>Nilotinib</strong></td>
<td>• Dasatinib-resistant mutations: F317L, v299L • Hypokalemia • Hypomagnesemia • Long QT syndrome • Hypersensitivity to drug constituents</td>
<td>• Liver dysfunction • History of pancreatitis • Coronary artery disease or risk factors, congestive heart failure, clinically significant bradycardia • Drugs carrying risk of QT prolongation • Patients taking CYP3A4, CYP2C8, CYP2C9, CYP2D6 or UGT1A1 enzyme substrates with narrow therapeutic index • Patients taking Pgp inhibitors</td>
<td>• 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 is reported. • 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 woman.</td>
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<tr>
<td><strong>Others</strong></td>
<td></td>
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<td></td>
<td>• May interact with antacids, H2 receptor antagonists and proton pump inhibitors. • 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.</td>
</tr>
</tbody>
</table>

### References

1. [Reference not provided]

2. [Reference not provided]

3. [Reference not provided]

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6. [Reference not provided]
cond generation TKIs are possible options. If dose escalation is to be preferred, testing for plasma imatinib level and BCR-ABL kinase domain mutations may give clues for the success of treatment. A low level and absence of imatinib-resistant mutations may indicate a relatively higher possibility of response. European LeukemiaNet recommendations for the suboptimal response patients include continuation of imatinib at same dose, or testing of high dose imatinib, dasatinib, or nilotinib.11

Advanced Disease (Accelerated Phase or Blastic Crisis)

AP patients should be converted to chronic phase via a TKI or chemotherapy and thereafter allogeneic stem cell transplantation should be aimed. In a historic control AP CML study, imatinib provided a survival advantage compared with control patients who received treatment with interferon-alpha or with other modalities.43 In imatinib-refractory cases, dasatinib or nilotinib are suitable options.34,44-46 Probably, multiagent chemotherapy should be reserved for TKI-refractory patients.

In BC, imatinib, dasatinib or multiagent chemotherapy are used for converting to chronic phase. As drug therapy is not curative, allogeneic stem cell transplantation should be definitively aimed. In TKI-naïve BC CML cases, imatinib was found less toxic and more successful regarding response rate and survival in comparison to chemotherapy.43 Dasatinib also has been proven to be effective in imatinib-intolerant or -resistant myeloid or lymphoid BC CML cases.45 If imatinib and dasatinib are not available or felt unsuitable nilotinib or chemotherapy may be alternative options.34 The chemotherapy should be acute myeloid or lymphoblastic leukemia-type depending on type of transformation. As cerebrospinal fluid diffusion of TKIs may not be optimal, central nervous system prophylaxis should also accompany TKIs in BC CML.

In AP imatinib, dasatinib and nilotinib are used at 600 mg qd, 140 mg qd and 400 mg bid doses, respectively. In BC, imatinib and dasatinib doses are 600 mg qd and 140 mg bid, respectively. Dasatinib 140 mg qd is as much effective and safer than the previously licensed dose 70 mg bid.49,50

Follow-up

The European LeukemiaNet expert panel has released very clear recommendations for follow-up of CML patients in TKI era (Tables 4-6).11 These recommendations are currently accepted as gold standards and adopted worldwide. Optimal response to first-line imatinib treatment in early chronic phase CML needs CHR and at least minor cytogenetic response (Ph+ ≤ 65%) at 3 months, at least partial cytogenetic response (Ph+ ≤ 35%) at 6 months, CCyR at 12 months, MMR at 18 months and stable or improving MMR at any time (Table 5). Imatinib failure is diagnosed if any one of the following conditions occurs: less than CHR at 3 months, no cytogenetic response (Ph+ > 95%) at 6 months, less than partial cytogenetic response (Ph+ > %35) at 12 months, less than CCyR at 18 months, loss of CHR or CCyR, emergence of imatinib-insensitive mutations, or occurrence of other clonal chromosome abnormalities in Ph+ cells at any time (Table 5).

During second-line treatment of imatinib-resistant chronic phase CML patients, failure of second generation TKIs should be considered and consequently alternative therapies should be investigated in case of no cytogenetic response at 3 month, minimal or worse cytogenetic responses at 6 month or less than partial cytogenetic response at 12 months (Table 6).

Assessment for BCR-ABL tyrosine kinase domain mutations is recommended in advanced phases and imatinib-resistant cases.11 Y253F/H (imatinib and nilotinib resistance), E255K/V (imatinib and nilotinib resistance), F359V/C (nilotinib resistance), F317L (dasatinib resistance), V299L (dasatinib resistance) and T315I (resistance to all current TKIs) are the most important clinically relevant mutations.38

Side Effects of the Tyrosine Kinase Inhibitors

Although generally well tolerated, imatinib is not without side effects. The most frequently reported adverse effects in the IRIS study were neutropenia (60%), thrombocytopenia (56%), edema, including local periorbital swelling (55%), anemia (44%), nausea (43%), elevated liver enzymes (43%), muscle cramps (38%), musculoskeletal pain (36%), rash,
fatigue, headache, and abdominal pain. NCI grade 3 or 4 neutropenia, thrombocytopenia, anemia and liver enzyme elevations occurred in 14%, 7%, 3%, and 5%, respectively.18

Hematologic toxicities of the TKI inhibitors are related to suppression of BCR-ABL-positive malignant hematopoiesis. They are very rare in imatinib-treated gastrointestinal stromal tumor patients, even with higher imatinib doses. Hematological toxicity and related complications 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 3. 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 chronic phase 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.49-52

| Definitions | Platelet < 450,000 /µL, White blood cell < 10,000 /µL, No immature granulocytes, Basophils < 5%, Spleen non palpable |
| Complete: 0% Ph i metaphases Partial: 1-35% Minor: 36-65% Minimal: 66-95% No: > 95% |
| Assessment | At diagnosis, every 2 weeks until attaining and confirmation of complete response. Thereafter every 3 months or as required. At diagnosis, 3rd and 6th months. Then at least every 6 months until attaining and confirmation of complete response. Thereafter at least every 12 months if regular molecular assessment cannot be assured. Every time in case of treatment failure (primary or secondary resistance), unexplained anemia, leukopenia or thrombocytopenia. |
| Complete molecular response: Undetectable BCR-ABL mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10^-7) Major molecular response: Ratio of BCR-ABL to ABL (or other housekeeping genes) ≤ 0.1% on the international scale |
| Every 3 months until major molecular response achieved and confirmed. Thereafter at least every 6 months. |
| In case of suboptimal response or failure; always before switching to other TKIs or therapies |

Table 4. Response definitions and assessment in chronic myeloid leukemia as recommended by the European LeukemiaNet.

* Cytogenetics should be evaluated in bone marrow cell metaphases by chromosome banding analysis until complete response is attained and confirmed. Interphase fluorescent in situ hybridization should not be used to evaluate any response worse than the complete cytogenetic response. But, it can be used to define complete cytogenetic response if bone marrow metaphases can not be obtained or evaluated by chromosome banding. Interphase fluorescent in situ hybridization should be performed with BCR-ABL1 extrasignal, dual color, dual fusion, or in situ hybridization probes and that at least 200 nuclei are scored. In many studies, partial and complete cytogenetic responses are counted together and reported as major cytogenetic response.** For a standardized assessment of the molecular response, the conversion of each laboratory data to the international scale is recommended, to correct for the variability of the assays in different laboratories. To allow for intralaboratory variations, a fluctuation of less than one log requires confirmation.
6. Unresolved Clinical Questions

Could it be possible to discontinue TKI in a patient who achieved molecular remission? Is there any role for interferon-alpha in initial treatment of CML or maintenance of molecular remission? Probably, these still unresolved questions are the most clinically relevant ones in clinical management of CML.

In a preliminary study, 12 patients who had been in molecular remission for 2 or more years and dis-
continued imatinib for various reasons were described. Six of them did not relapse after a considerably long time period. In a more recent study, half of 70 patients who stopped imatinib in similar conditions maintained their molecular remissions. Relapses were generally seen within 6 months of drug discontinuation and they were rare at later times. Relapsed patients responded well to re-institution of imatinib.

In a recent study, imatinib was discontinued in 20 patients who had concomitantly been receiving interferon for a median of 2.4 years. The number of cases with complete molecular response increased from 2 at baseline to 5 under interferon maintenance. With a median time of 2.4 years (range, 0.5-4 years) after imatinib withdrawal 15 (75%) patients remained in remission. Relapses occurred within 2 to 10 months, and were sensitive to imatinib rescue.

REFERENCES

45. Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib:


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