Review Article

Chronic myeloid leukaemia: A paradigm shift in management

ALAKANANDA DASGUPTA, LALIT KUMAR

ABSTRACT

In early 2000, a better understanding of the molecular biology of chronic myeloid leukaemia established a central role for enhanced tyrosine kinase activity leading to targeted therapy with imatinib mesylate. This paradigm shift in the management of this disease has improved the median survival from 8–9 years before 2000 to an estimated 25 years. Rapid research in this area along with well-designed multicentric clinical trials have resulted in the development of second- and third-generation tyrosine kinase inhibitors, which are more effective for patients who develop resistance to imatinib. The synergy of haematological, cytogenetic and molecular parameters is the mainstay of monitoring patients with chronic myeloid leukaemia. Early identification of patients likely to have suboptimal response to initial tyrosine kinase inhibitors and when to discontinue therapy in those with an optimal response are areas of active research.


INTRODUCTION

Chronic myeloid leukaemia (CML) is a clonal disorder of a pluripotent stem cell and results from translocation of the ABL gene on chromosome 9 to the region of the BCR gene on chromosome 22 (t(9;22)). This leads to the formation of the BCR–ABL fusion gene which encodes an abnormal chimeric protein (BCR–ABL; p210) with constitutively activated tyrosine kinase activity. The latter is responsible for the activation of signal transduction pathways leading to abnormal bone marrow proliferation and the clinical and laboratory manifestations of CML. The natural history of untreated CML is bi- or triphasic: there is an initial indolent chronic phase (CP) followed by an accelerated phase (AP), a blast phase or blast crisis (BP or BC) or both. In CP, the leukaemic cells are minimally invasive and the proliferation is largely confined to haematopoietic tissues, primarily blood, bone marrow and spleen although the liver may also be infiltrated. In BC, extramedullary tissues, including lymph nodes, skin and soft tissues may show infiltration by blasts.

EPIDEMIOLOGY

CML has a worldwide annual incidence of 1–2 cases per 100 000 population and this incidence is fairly constant in different countries. The disease can occur at any age, but the median age at diagnosis is between the 5th and 6th decades of life with a slight male predominance. In India, from the population-based cancer registry data (covering 7% of population), an age-adjusted incidence of 0.8–2.2 per 100 000 population has been reported. Though from hospital-based data, CML appears to be a common leukaemia among adults with a median age of 38–40 years at diagnosis. The reasons for the younger age at onset are not clear, though different population demographics in India (65% of the population is below 35 years of age) could be a possibility. Other important differences include diagnosis in the asymptomatic stage in <10% of patients (compared with 20%–40%), presence of splenomegaly in >90% of patients (compared with 20%–25%), presence of hepatomegaly and fever in up to one-third of patients and a higher proportion of patients with Sokal poor or high-risk score (see below).

GENETICS AND MOLECULAR BIOLOGY

At diagnosis, 90%–95% of cases of CML have a characteristic translocation, t(9;22)(q34;q11.2) called Philadelphia (Ph) chromosome. Molecular techniques have identified the critical genes involved as v-abl (Abelson murine leukaemia viral oncogene homologue [ABL]) on chromosome 9 and breakpoint cluster region (BCR) on chromosome 22. This translocation fuses sequences of the BCR gene on chromosome 22 with regions of the ABL1 gene from chromosome 9. The remaining cases either have variant translocations that involve a third or even fourth chromosome in addition to chromosome 9 and 22, or may have a cryptic translocation of q9q34 and 22q11.2. Preclinical identification by routine cytogenetic analysis. In such cases, the BCR–ABL1 fusion gene is present and can be detected by reverse transcription polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH) analysis. The Ph-negative, BCR–ABL-positive CML behaves clinically like Ph-positive CML.

The site of the breakpoint in the BCR gene may influence the phenotype of the disease. In CML, the breakpoint almost always is in the major breakpoint cluster region (M-BCR), spanning exons 12–16 (previously known as b1–b5) and an abnormal fusion protein p210 is formed which has enhanced tyrosine kinase activity in excess of the normal 145 kDa ABL product. Rarely, the breakpoint in the BCR gene occurs in the µ-BCR region, spanning exons 17–20 (previously known as c1–c4) and encoding a larger fusion protein, p230. Patients with this fusion may show prominent neutrophilic maturation and/or conspicuous thrombocytosis. Breaks...
in the minor breakpoint region, m-BCR (BCR exons 1–2) lead to a shorter fusion protein (p190) and are associated with Ph-positive acute lymphoblastic leukaemia (ALL). Very small amounts of the p190 transcript can be detected in >90% of patients with classical p210 CML as well, due to the alternative splicing of the BCR gene. p190 may also be seen in rare cases of CML-CP that have increased numbers of monocytes and resemble chronic myelomonocytic leukaemia.1,5,6 The molecular basis of disease transformation is not well established. Progression is usually associated with clonal evolution and, at the time of transformation to AP or BP, 80% of patients show cytogenetic changes in addition to the Ph chromosome, such as extra Ph, +8, +19, or i(17q).1,2

CLINICAL AND LABORATORY FEATURES
These have been reviewed earlier.1 Briefly, 90%–95% of patients are diagnosed in CP which usually has an insidious onset. Nearly 20%–40% of patients are asymptomatic and may be detected incidentally on routine white blood cell (WBC) count. The common findings at presentation include fatigue, weight loss, night sweats, splenomegaly and anaemia. Only 5%–10% of patients may be in AP or BC at initial presentation and infrequently, the presentation may be akin to acute leukaemia—poor performance status, fever and symptoms related to severe anaemia, thrombocytopenia or marked splenomegaly.

Laboratory diagnosis of CML—CP, AP and BC—is generally based on the WHO criteria.1 BP or BC may be diagnosed when (i) blasts >20% of the peripheral blood WBC or the nucleated cells of the bone marrow, or (ii) when there is an extramedullary blast proliferation.2,8,9 Table I lists the investigations to be done at different times in the management of CML.

PROGNOSTIC SCORES
Three prognostic scores—the Sokal relative risk,10 Hasford relative risk,11 and the EUTOS (European Treatment and Outcome Study) score12 have been developed. These provide useful information for prognostication of CML patients at baseline (Table II). There is no indication if one is better than the other. A high score is associated with a higher risk of progression to AP or BC.

### TABLE I. Investigations at diagnosis and during therapy

<table>
<thead>
<tr>
<th>At diagnosis</th>
<th>Full blood count and differential count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calculation of Sokal score</td>
</tr>
<tr>
<td></td>
<td>Bone marrow aspirate with cytogenetic analysis of 30 metaphases</td>
</tr>
<tr>
<td></td>
<td>[FISH for BCR–ABL1 in the absence of a Philadelphia chromosome]</td>
</tr>
<tr>
<td></td>
<td>qRT-PCR for BCR–ABL1 transcripts to characterize the BCR–ABL1 junction [optional]</td>
</tr>
<tr>
<td>Thereafter</td>
<td>Blood counts at intervals of 2 or more weeks</td>
</tr>
<tr>
<td></td>
<td>Liver chemistry</td>
</tr>
<tr>
<td>At 3 months</td>
<td>Blood count</td>
</tr>
<tr>
<td></td>
<td>Bone marrow cytogenetics</td>
</tr>
<tr>
<td></td>
<td>qRT-PCR for BCR–ABL1 transcripts</td>
</tr>
<tr>
<td>At 6 months</td>
<td>Blood count–bone marrow cytogenetics</td>
</tr>
<tr>
<td></td>
<td>qRT-PCR for BCR–ABL1 transcripts</td>
</tr>
<tr>
<td></td>
<td>[Thereafter bone marrow aspirates are only required if complete cytogenetic response has not been achieved]</td>
</tr>
<tr>
<td>At 3-month intervals thereafter</td>
<td>qRT-PCR for BCR–ABL1 transcripts indefinitely</td>
</tr>
</tbody>
</table>

Source: Modified from reference 9

FISH fluorescent in situ hybridization
qRT-PCR quantitative reverse transcription polymerase chain reaction

### TABLE II. Prognostic scores

<table>
<thead>
<tr>
<th>Risk</th>
<th>Sokal score10</th>
<th>Hasford score11</th>
<th>EUTOS score12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>–Exp[0.0116 (age–43.4 years)+0.0345 (spleen size–7.51)+0.188 [(platelets/700)2–0.563]+0.0887 (blasts–2.1)]</td>
<td>–(0.6666 × age [0 when age &lt;50 years; otherwise 1]) + 0.042 × spleen size [0 when basophils &lt;3% at baseline; otherwise 1]) + 1.0956 × platelet count [0 when platelets &lt;1500 per μL; otherwise 1]) × 1000</td>
<td>(7 × basophils)+ (4 × spleen size) where spleen is measured in cm below the costal margin and basophils as a percentage at baseline</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;0.8</td>
<td>&lt;780</td>
<td>&lt;87</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.8–1.2</td>
<td>780–1480</td>
<td>–</td>
</tr>
<tr>
<td>High</td>
<td>&gt;1.2</td>
<td>&gt;1480</td>
<td>&gt;87</td>
</tr>
</tbody>
</table>

EUTOS European treatment and outcome study
increased gastrointestinal side-effects and myelosuppression. A multicentre trial from India evaluated the safety and efficacy of indigenous recombinant interferon-alpha-2b in CML and found the toxicity profile to be similar to other preparations. 

TYROSINE KINASE INHIBITOR (TKI) THERAPY

Imatinib mesylate (STI 571, Gleevec, Glivec) was introduced in 2001 and led to a paradigm shift in the management of CML. Imatinib is a potent and a specific inhibitor of BCR–ABL, the tyrosine kinase central to the pathogenesis of CML. Imatinib functions through competitive inhibition at the ATP-binding site of BCR–ABL, leading to the inhibition of tyrosine phosphorylation of proteins. In the first prospective, multicentre, open-label, phase 3, randomized study (IRIS: International Randomized Study of Interferon and STI 571), the combination of recombinant interferon-alpha and low-dose cytarabine (n=553) was compared with imatinib (n=553). In terms of haematological and cytogenetic responses, tolerability and the likelihood of progression to AP or BC CML, imatinib was superior to interferon-alpha with low-dose cytarabine as first-line therapy in newly diagnosed CP CML. At 8 years of follow-up, patients randomized to the imatinib arm continued to show durable haematological and cytogenetic responses, low progression rates to AP or BC, and excellent survival outcomes. This trial established imatinib as a strong predictor for outcome of patients treated with front-line TKIs (Table V).

MONITORING THE RESPONSE

Routine cytogenetic analysis is still considered the gold standard for evaluating response in CML (Table I). It has been assumed that increased accuracy might be better at predicting outcome. A single measurement of BCR–ABL transcripts performed at 3 months is the best way to identify patients destined to fare poorly, thereby allowing early clinical intervention. The assessment of cytogenetic or molecular response at 3 months has been defined as a strong predictor for outcome of patients treated with frontline TKIs (Table V).

FAILURE TO RESPOND TO IMATINIB

A number of factors could be responsible for poor or suboptimal response to imatinib. Failure to achieve adequate plasma trough levels is associated with an inferior response. Poor compliance

Response criteria

The excellent response following imatinib therapy led to the need for response criteria. European LeukaemiaNet (ELN) and NCCN (National Comprehensive Cancer Network) have defined response criteria and these are widely used (Table III).

Experience from India

Many studies from India have found the toxicity profile of imatinib to be similar to that reported elsewhere in the world (Table IV).

MONITORING THE RESPONSE

Routine cytogenetic analysis is still considered the gold standard for evaluating response in CML (Table I). It has been assumed that increased accuracy might be better at predicting outcome. A single measurement of BCR–ABL transcripts performed at 3 months is the best way to identify patients destined to fare poorly, thereby allowing early clinical intervention. The assessment of cytogenetic or molecular response at 3 months has been defined as a strong predictor for outcome of patients treated with frontline TKIs (Table V).

TABLE III. Response criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological complete</td>
<td>Leucocyte count &lt;10x10^9/L; platelet count &lt;450x10^9/L; no immature granulocytes; basophils &lt;5%; non-palpable spleen</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic complete</td>
<td>No Ph+ metaphases</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>1%–35% Ph+ metaphases</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>Complete + partial</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>36%–65% Ph+ metaphases</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>66%–95% Ph+ metaphases</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>&gt;95% Ph+ metaphases</td>
<td></td>
</tr>
<tr>
<td>Molecular complete</td>
<td>Undetectable BCR–ABL by qRT-PCR in two consecutive samples</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>Ratio of BCR–ABL to ABL ≤0.1% on the International scale</td>
<td></td>
</tr>
</tbody>
</table>

*Mmodified from references 20 and 21

qRT-PCR quantitative reverse transcription polymerase chain reaction

TABLE IV. Studies from India on the use of imatinib mesylate for chronic myeloid leukaemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Medhi et al. (2010), AIIMS, New Delhi</th>
<th>Rajappa et al. (2008), NIMS, Hyderabad</th>
<th>Ganesan et al. (2011), CIA, Chennai</th>
<th>Deshmukh et al. (2005), TMH, Mumbai</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>400</td>
<td>201</td>
<td>516</td>
<td>174</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median 35</td>
<td>32</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Range</td>
<td>7–75</td>
<td>18–72</td>
<td>6–70</td>
<td>4–79</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Men 66.3</td>
<td>69.2</td>
<td>66.5</td>
<td>70.1</td>
</tr>
<tr>
<td>Phase (%)</td>
<td>Chronic 90.7</td>
<td>100</td>
<td>100</td>
<td>55.8</td>
</tr>
<tr>
<td>Accelerated</td>
<td>6.5</td>
<td>–</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Blast crisis</td>
<td>2.7</td>
<td>–</td>
<td>–</td>
<td>17.2</td>
</tr>
<tr>
<td>Haematological response (%)</td>
<td>Complete + partial 286/400*</td>
<td>97</td>
<td>91.1</td>
<td>72.4</td>
</tr>
<tr>
<td>Cytogenetic response (%)</td>
<td>Complete 53</td>
<td>56</td>
<td>23.2</td>
<td>41.7, 27.3*</td>
</tr>
<tr>
<td>Partial</td>
<td>19</td>
<td>23</td>
<td>58</td>
<td>–</td>
</tr>
<tr>
<td>Major</td>
<td>12</td>
<td>72</td>
<td>81.2</td>
<td>–</td>
</tr>
<tr>
<td>Minor</td>
<td>19</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No response</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*at last follow-up †early and late chronic phase

A number of factors could be responsible for poor or suboptimal response to imatinib. Failure to achieve adequate plasma trough levels is associated with an inferior response. Poor compliance

TABLE V. Time-points for responses to tyrosine kinase inhibitors (imatinib)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Optimal response</th>
<th>Suboptimal response</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CHR</td>
<td>&lt;CHR</td>
<td>No HR</td>
</tr>
<tr>
<td>6</td>
<td>PCyR</td>
<td>Minor CyR</td>
<td>No CyR</td>
</tr>
<tr>
<td>12</td>
<td>CCyR</td>
<td>PCyR</td>
<td>&lt;PCyR</td>
</tr>
<tr>
<td>18</td>
<td>MMR</td>
<td>&lt;MMR</td>
<td>&lt;CCyR</td>
</tr>
<tr>
<td>Anytime</td>
<td>Stable CCyR and MMR</td>
<td>Loss of MMR mutations,</td>
<td>HR, Loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACA in Ph+ cells</td>
</tr>
</tbody>
</table>

Source: European LeukaemiaNet [ELN] criteria, adapted from reference 21

CHR complete haematological response
PCyR partial cytogenetic response
CCyR complete cytogenetic response
MMR major molecular response
ACA additional cytogenetic abnormalities
or non-compliance to imatinib (use of ≤85% or 90% of prescribed dose) has been reported in up to one-third of patients and is associated with poor cytogenetic response or increased probability of losing cytogenetic response. Poor compliance was associated with inferior event-free survival in a study from Chennai; 76.7% in compliant compared with 59.8% in non-compliant patients. The most common reason for non-compliance was forgetting to take the drug or to minimize side-effects. Patients who fail to respond to imatinib are changed to a second-line TKI (nilotinib or dasatinib). Higher doses of imatinib (600–800 mg daily) may yield response in some patients especially those with suboptimal responses, i.e. less than CCyR or loss of CCyR. Patients with loss of complete haematological response (CHR) or non-achievement of CHR are less likely to benefit from higher doses of imatinib.

HIGH-DOSE IMATINIB

To improve cytogenetic and molecular response rates to imatinib, a number of studies have attempted higher doses of imatinib (800 mg daily upfront compared to the standard daily dose of 400 mg). It was found that high-dose imatinib is effective in inducing rapid cytogenetic and molecular responses in patients with intermediate Sokal risk. However, randomized studies have failed to show a clear advantage of higher dose imatinib on progression-free and overall survival. A higher frequency of myelosuppression leading to frequent interruptions preclude the routine use of high-dose imatinib as a first-line therapy in CP CML.

IMATINIB RESISTANCE

Primary haematological resistance (defined as failure to obtain a CHR at 3 months, Table V) occurs in about 5% of patients. About 15% of patients have primary cytogenetic resistance (defined as failure to achieve either a major cytogenetic response (<35% Ph-positive marrow metaphases) after 6 months of therapy, or a CCyR after 12 months of therapy). Secondary or ‘acquired’ haematological and cytogenetic resistance refers to loss of a previously established response. Development of resistance to imatinib mesylate in patients with CML is often accompanied by selection of point mutations in the kinase domain (KD) of the BCR–ABL oncoprotein, where imatinib binds. To date, more than 70 different BCR–ABL KD mutations, encoding for over 50 different amino acid substitutions, have been described. Nilotinib and dasatinib (second-generation TKIs) are active against the majority of imatinib-resistant mutations, but some confer clinical resistance to nilotinib (Y253H, E255K, E255V, F359V and F359C), dasatinib (V299L, T315A, F317L, F317I, F317V and F317C) or both (T315I). Other mutations have decreased in vitro sensitivity to dasatinib, such as E255K and E255V. The BCR–ABL T315I mutation is resistant to imatinib, nilotinib and dasatinib in CML. For such patients the available options are ponatinib, omacetaxine and allogeneic stem cell transplant.

Studies from India have identified BCR–ABL mutations in 45%–50% of patients who are resistant to imatinib. These mutations may be higher in patients with more advanced disease. Sharma et al. found point mutations to be the major mechanism for primary cytogenetic resistance. Patients with mutations had inferior progression-free survival (PFS) compared to those without mutations. Similar results have been reported in a study from southern India. A study by Kagita et al. reported 15 exonic mutations in 46% of patients; among them, 7 patients had multiple mutations. The KD mutation profile plays little, if any, role in selecting an initial TKI, but becomes relevant in patients who relapse.

SECOND-GENERATION TKIs

The understanding of the mechanism of resistance to imatinib led to the rapid development of new drugs to circumvent resistance. Dasatinib

Dasatinib (Table VI) is structurally unrelated to imatinib and is approximately 325-fold more potent than imatinib. In a randomized study, dasatinib (100 mg daily, n=259) was compared with imatinib (400 mg daily, n=260) in treatment-naive CML-CP patients. Patients in the dasatinib arm had higher rates of CCyR (83% v. 72%) and major molecular response (46% v. 28%) at 12 months, and an acceptable safety and tolerability profile. In a 2-year follow-up of this study, first-line dasatinib resulted in faster and deeper cytogenetic and molecular responses compared with imatinib. This led to better 2-year PFS and overall survival. Studies have shown the benefit of dasatinib 70 mg twice daily in patients with AP CML, who are intolerant or resistant to imatinib. Once-daily treatment was associated with an improved safety profile.

Nilotinib

Akin to imatinib, nilotinib functions through competitive inhibition at the ATP-binding site of BCR–ABL, leading to the inhibition of tyrosine phosphorylation of proteins. Nilotinib (300 mg twice a day and 400 mg twice a day) was compared with imatinib in a phase 3, randomized, open-label, multicentre study, in newly diagnosed patients with CP CML. At 12 months, the major molecular response rate was 44% for the 300 mg dose and 43% for the 400 mg dose compared to 22% for the imatinib arm. The rates of CCyR at 12 months were higher for nilotinib (80% for 300 mg dose and 78% for 400 mg dose) compared with 65% for imatinib. Although dasatinib has been shown to be 16-fold more potent...
than nilotinib at inhibiting unmutated BCR–ABL in vitro, no direct comparisons between these agents in patients with CML have been reported.

**Bosutinib**

Bosutinib (SKI-606) is an oral, dual SRC/ABL TKI with clinical activity in Ph-positive leukaemia. A phase 3 trial compared the efficacy and safety of bosutinib in newly diagnosed patients of CML. A total of 502 patients were randomized to receive bosutinib 500 mg per day or imatinib 400 mg per day. The CCyR rate at 12 months was similar—bosutinib (70%) versus imatinib (68%). The major molecular response rate at 12 months was higher with bosutinib (41%) compared with imatinib (27%). Time to CCyR and major molecular response was faster with bosutinib.57

**THIRD-GENERATION TKIs**

**Ponatinib**

Ponatinib (AP24534), a novel TKI agent is a pan-BCR–ABL inhibitor with substantial and durable clinical activity in patients with Ph-positive leukaemias with resistance to TKI. Ponatinib blocks native and mutated BCR–ABL, including the gatekeeper mutant T315I, which is uniformly resistant to TKI.58 Studies suggest that a high proportion of patients resistant to two or more TKIs achieve excellent response. The common adverse events are rash, myelosuppression and constitutional symptoms.59

**Homoharringtonine/omacetaxine mepesuccinate**

Omacetaxine mepesuccinate is a reversible protein translation inhibitor. The drug is derived from the bark of species of the Chinese plum yew, cephalotaxus. The drug is not dependent on BCR–ABL binding for its activity; instead it binds to the A-site cleft of ribosomes, resulting in a profound but transient inhibition of protein synthesis.60 Currently, the drug is approved for treatment of patients with CP or AP CML whose disease has progressed during treatment with at least two TKIs. The adverse effects are: grade 3/4 neutropenia (48%), anaemia (33%). Non-haematological adverse events are predominantly grade 1/2 and include diarrhea (44%), nausea (30%), fatigue (24%), pyrexia (20%), headache (20%) and asthenia (20%).61,62

**MOLECULAR MONITORING OF CML**

Serial analysis of BCR–ABL mRNA levels by qRT-PCR is the most sensitive tool for monitoring. qRT-PCR can reliably detect residual disease to a sensitivity of 0.01% and often to 0.001%. The present method uses specific primers to detect transcripts arising from BCR–ABL1 and compares these with the numbers of transcripts from a control gene (typically BCR, ABL1, and beta-glucuronidase [GUSB]); ABL is currently the most widely used control gene. The results are expressed as a ratio of BCR–ABL1 transcripts to the control transcripts, multiplied by 100 to give the result as a percentage, where 10%, 1%, 0.1%, 0.01% and 0.001% correspond to a reduction in tumour load of 1, 2, 3, 4 and 5 logs.

Peripheral blood is suitable for analysis of BCR–ABL transcripts. A minimum of 5 ml (preferably 10 ml) should be collected. EDTA anticoagulant is appropriate for PCR analysis. To prevent significant degradation of transcripts, samples should be processed within 36 hours of collection (ideally within 24 hours).63,64

**DURATION OF THERAPY**

Current guidelines such as ELN recommend continuing TKI therapy indefinitely in all patients who respond to treatment, even those with undetectable minimal residual disease (MRD).21,27 Major molecular response (i.e. a >3-log reduction in BCR–ABL1 transcript levels, BCR–ABL ratio 0.1%) is used in current treatment guidelines to assess prognosis. Deeper molecular responses MR4, correspond to a BCR–ABL ratio <0.01%, MR4.5, to a ratio <0.0032% and undetectable molecular disease, correspond to 5-log reduction or <0.001%.31,64,65

**TREATMENT-FREE REMISSION**

This has recently emerged as a new goal of treatment in CML. Molecular remission is sustained in around 30% of imatinib-treated patients who stop treatment after ≥2 years with undetectable molecular disease by conventional RT-PCR method.66-69 An additional 20%–30% of patients will lose undetectable molecular disease, but remain in stable major molecular remission off treatment. Results from a German study indicate that patients in deep remissions (MR >4.5) have more stable remissions with lower probabilities of progression, and may be considered for discontinuation of therapy.66 Recent evidence suggests that deeper molecular responses (>4-log reductions in BCR–ABL1 transcript levels), particularly when attained early during treatment, may have even better event-free, progression-free and overall survival and a low risk of progression and disease relapse and also seem less likely to lose major molecular response. Factors associated with a higher probability of treatment-free remission include low-risk Sokal score, prior interferon treatment, longer total duration of imatinib treatment and higher number of natural killer cells at the time of discontinuation of imatinib.67 Independent predictors of stable, undetectable BCR–ABL1 during first-line imatinib therapy were female sex and <10% BCR–ABL1 transcripts at 3 months.68 Studies by the French CML Intergroup (STIM-stop imatinib) in 100 patients indicate that imatinib can be safely discontinued in patients with a complete molecular remission of at least 2 years’ duration.69 Similar results have been reported by the Australasian Leukaemia and Lymphoma Group.70 The most recent study from the French CML Intergroup, STIM2, enrolled 124 imatinib-only patients between April 2011 and June 2013. Using the original definition of molecular remission, 61% of patients were in treatment-free remission at the time of the interim analysis (median follow-up 12 months).71 The studies outlined above have generally included patients in CP only, with no history of BCR–ABL1 kinase domain mutations.71 Thus, achieving a sustained deep molecular response is a requirement for consideration of discontinuation of therapy.65,72

**ALLOGENEIC STEM CELL TRANSPLANT: CURRENT INDICATIONS**

Following introduction of imatinib, the number of patients undergoing allogeneic stem cell transplants has reduced considerably.73 The present indications for transplant include patients in AP or BC, patients with T315I mutation and patients after failure or intolerance of second-generation TKI, and children with CML who fail to achieve major cytogenetic response or a BCR–ABL transcripts level <10% at 6 months despite receiving second-generation TKIs.19,73 The decision involves careful balancing of the risks for transplantation against the risks of disease progression in each patient.74

**PREGNANCY**

The treatment of CML during pregnancy remains a clinical
challenge. Exposure to imatinib during pregnancy might result in an increased risk of serious foetal abnormalities or spontaneous abortion. For men, there may be effects on spermatogenesis. The choice for women who are receiving imatinib and want to become pregnant is difficult. Many reports have suggested successful pregnancies among patients receiving imatinib. However, the risk for teratogenicity remains. Women who wish to become pregnant should be advised to stop imatinib 1–2 months before stopping contraception. However, they should be counselled about the risk of suboptimal response or relapse even if they have achieved a complete molecular remission.

ECONOMIC CONSIDERATIONS

In the past few years a number of TKIs have been introduced for the treatment of CML. However, the cost of these drugs is high (Table VII) and beyond the reach of most people who do not have an insurance cover. High prices of drugs may be the single most common reason for poor compliance and discontinuation of the drug, and the reason for different treatment recommendations in different countries. Support programmes such as the Glivec International Patient Assistance Program (GIPAP), a joint effort of Novartis and The Max Foundation, provides access to about 80% of the patients with CML in India. A recent study from a tertiary care centre in India reported that the outcomes with generic and innovator imatinib were comparable—CCyR 72% for Glivec v. 75% for the generic drug.

CONCLUSION

The outcome for patients with CP CML has changed remarkably in the past 15 years. The initial choice of TKI is between imatinib, nilotinib and dasatinib. The choice should be based upon the availability, risk profile of CML, long-term goals and patient’s comorbid conditions. The availability of second- and third-line TKIs has expanded the treatment options. Regular monitoring of BCR-ABL transcript has helped to identify poor responders and consider changes in therapy. The addition of low-dose interferon-alpha or pegylated interferon along with imatinib has resulted in a deeper molecular response. Excellent response and improved survival following TKI therapy has led to ‘treatment-free remission’ as a new goal. The role of immunotherapy in patients who achieve durable complete molecular remission is another potential area for future research.

REFERENCES


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