Suboptimal Responses to Imatinib in Chronic Myelogenous Leukemia: What Are They and How Do They Affect Treatment?

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First-line treatment for chronic myelogenous leukemia (CML) is imatinib, but some patients do not respond or develop resistance to the drug, leading to suboptimal responses. Dasatinib and nilotinib are approved second-line compounds for patients experiencing imatinib failure. In a prospective comparison of dasatinib with high-dose imatinib in patients who did not respond to first-line imatinib, dasatinib was more effective and well tolerated. Nilotinib also is effective, but cross-intolerance does occur in a substantial number of patients. This article explores the importance of suboptimal response to imatinib and the appropriate second-line therapy as well as nursing implications for caring for patients with CML.

Chronic myelogenous leukemia (CML) is a clonal hematopoietic stem cell disorder accounting for approximately 20% of all adult leukemia cases, with an estimated 5,050 new cases per year (American Cancer Society, 2009). The initial chronic phase (CP) can be asymptomatic and, if left untreated, CML progresses to an accelerated phase (AP), then to fatal blast crisis (BC) over the course of three to five years (Sawyers, 1999). In the United States, the age-adjusted incidence rate for CML is 1.5 per 100,000 people per year, and the median age at diagnosis is 66 years (National Cancer Institute, 2007). From 1999-2005, the five-year relative survival rates were 53.3% overall (Leukemia and Lymphoma Society, 2009). With the introduction of imatinib in newly diagnosed patients with CML, survival rates after five years is 89% (Druker et al., 2006). For a more comprehensive review of CML, see D’Antonio (2005).

At the cellular level, the distinguishing feature of CML is the Philadelphia chromosome (Ph), created by the exchange (t[9:22] translocation) of genetic material between chromosomes 9 and 22 (Nowell & Hungerford, 1960; Rowley, 1973). The creation of the Ph chromosome leads to the formation of the Bcr-Abl tyrosine kinase signal transduction protein, which underlies the pathophysiology of CML (Bartram et al., 1983; Groffen et al., 1984; Lugo, Pendergast, Muller, & Witte, 1990).

CML may be cured by bone marrow stem cell transplantation, but few patients can receive the procedure because of the difficulty in finding matched donors and morbidity and mortality concerns, particularly for older adults (National Comprehensive Cancer Network [NCCN], 2009). Furthermore, patient outcomes deteriorate with disease duration (Davies et al., 2001). Therefore, most patients rely on effective drug therapy.

The treatment of CML improved dramatically with the introduction of tyrosine kinase inhibitors (TKIs) directed against Bcr-Abl, thereby specifically targeting the pathophysiology of CML. The first such compound to be introduced as treatment for CML was imatinib in 2001, which has become a paradigm of targeted cancer therapies (Druker et al., 1996). In the key IRIS (International Randomized Study of Interferon and STI571) phase III clinical study, imatinib was associated with significantly longer progression-free survival (PFS) compared with the previous standard, interferon-α plus cytarabine (O’Brien et al., 2003). Estimated rates of overall survival after 54 months of

At a Glance
- Suboptimal responses to first-line imatinib in patients with chronic myelogenous leukemia are associated with poorer patient outcomes.
- High-dose imatinib, a current recommended second-line treatment for patients responding suboptimally to initial imatinib therapy, only benefits a minority of patients temporarily.
- Dasatinib and nilotinib, approved second-line treatments for patients experiencing failure of first-line imatinib therapy, may be used to treat suboptimal responders.

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Imatinib treatment is 89%. As a result, imatinib 400 mg per day was approved by the U.S. Food and Drug Administration (FDA) as a first-line therapy for CP CML and currently remains the only approved first-line treatment for the disease.

Although many patients benefit from imatinib therapy, clinical resistance to the drug has emerged as a significant barrier to successful treatment (O’Brien et al., 2003; Druker et al., 2006). Resistance to imatinib is classified as primary or secondary. Primary (intrinsic) resistance is defined as a lack of response to treatment at initiation of therapy. In the pivotal IRIS study, primary resistance was observed in 24% of patients 18 months after the start of treatment (O’Brien et al.). Secondary (acquired) resistance is defined by loss of a previously achieved response to treatment. Also in the IRIS study, secondary resistance manifested as relapsed disease in approximately 17% of patients and disease progression in an additional 7%, with median follow-up of 60 months (Druker et al., 2006). European LeukemiaNet (2009) and NCCN (2009) have developed precise formal definitions of optimal responses, treatment failure, and criteria for reconsidering treatment prior to imatinib failure (hereafter referred to as suboptimal responses) (Baccarani et al., 2006).

The consequences of imatinib resistance are treatment failure and suboptimal responses. Treatment failure indicates that imatinib treatment at the current schedule is no longer appropriate for a patient and a change in therapy is indicated. Suboptimal responses indicate that although patients may continue to receive a benefit from imatinib treatment at the current dose, long-term outcome may be better with an alternative strategy (Baccarani et al., 2006). This article discusses the evidence surrounding appropriate treatment for patients with suboptimal responses to first-line imatinib therapy.

### Treatment Response Landmarks

Monitoring response to treatment is essential for effective patient care in CML. Frequent disease assessment that follows defined standards ensures that a patient’s disease is monitored appropriately and that prompt decisions can be made if and when a treatment should be changed. Different techniques are used to monitor the disease as the number of leukemia cells decreases during treatment. Each technique is associated with specific response landmarks (see Table 1).

The first test for patients receiving treatment for CML is hematologic testing, and the desired corresponding landmark is complete hematologic response (CHR). CHR is measured by complete blood count and defined as a normal complete blood count and physical examination. Conventional cytogenetic testing is the second step and can be evaluated from bone marrow aspirate. It is more sensitive and allows the level of disease to be monitored even after CHR has been achieved. The three levels of response are minor, major (MCyR), and complete (CCyR) cytogenetic responses.

Sixty-nine percent of patients receiving imatinib will achieve CCyR by 12 months and 87% by 60 months (Druker et al., 2006); therefore, techniques to detect very low levels of cells carrying the BCR-ABL gene have been developed. The landmark response of such molecular monitoring is the major molecular response (MMR), evaluated with peripheral blood or bone marrow for fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR). Complete molecular response (i.e., 0% CML cells detected) is the best and deepest achievable response for patients but does not represent disease eradication because cancerous cells may still be present elsewhere in the body. The small group of cancerous cells could remain undetected despite repeated sampling; expansion of the population could lead to disease relapse.

NCCN (2009) outlined recommended intervals for response monitoring. At initiation of treatment, bone marrow cytogenetics and molecular assessments should be conducted. If the patient appears to be responding during treatment, cytogenetic testing is recommended at 6 and 12 months after the start of therapy. Another cytogenetic evaluation should be conducted at 18 months if CCyR has not been achieved by 12 months. When CCyR is achieved, cytogenetic testing may be considered every 12–18 months. Molecular testing also is recommended every three months in responding patients, particularly when CCyR is achieved. If a molecular test reveals a rise in Bcr-Abl levels (by 1-log), the result should be confirmed with another assessment after one month. If confirmed, the frequency of molecular monitoring should be increased to once a month and the patient should be tested for BCR-ABL mutations (NCCN). Treatment continues; however, if an increase in PCRs persists, a bone marrow biopsy would be required and mutation analysis obtained. A second-line tyrosine kinase inhibitor also would be initiated.

### Optimal Responses to First-Line Imatinib Treatment in Newly Diagnosed Patients With Chronic-Phase Chronic Myeloid Leukemia

The NCCN (2009) guidelines defined an optimal response to first-line imatinib as achieving CHR by three months and CyR by six months. The time-based parameters are supported...

### Table 1. Definitions of Landmark Responses to Imatinib Therapy

<table>
<thead>
<tr>
<th>TECHNIQUE</th>
<th>RESPONSE</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>Hematologic</td>
<td>Complete</td>
<td>White blood cell counts less than 1 x 10^9/L with normal differential; platelet count less than 450 x 10^9/L; nonpalpable spleen</td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>Minor</td>
<td>Ph+ metaphases = 36%–95%</td>
</tr>
<tr>
<td></td>
<td>Major</td>
<td>Ph+ metaphases = 0%–35%</td>
</tr>
<tr>
<td></td>
<td>Complete</td>
<td>Ph+ metaphases = 0%</td>
</tr>
<tr>
<td>Molecular</td>
<td>Major</td>
<td>Bcr-Abl/Abl ratio less than 0.1% or greater than three-log reduction from baseline</td>
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by IRIS follow-up data, correlating early responses with improved long-term outcomes. Achieving a hematologic response is necessary for a patient to subsequently achieve CyRs and long-term survival (Hughes, 2006). Therefore, CHR within three months is a key early component of the optimum response. Further evidence supports that CyR at six months is associated with subsequent survival or CCyR (Baccarani et al., 2006; Kantarjian et al., 2002) and MCyR (defined as less than 35% Ph+ metaphases) at 12 months is significantly (p < 0.001) associated with survival at 42 months (Roy et al., 2006). In addition, CCyR at 18 months results in PFS at five years in 98%–100% of patients. For those patients who do not experience CCyR at 18 months, the five-year PFS rate is 87% (Druker et al., 2006).

According to NCCN (2009) guidelines, patients on standard-dose imatinib who do not reach time-based milestones are considered to have primary resistance and should be switched to alternate therapies. In addition, for patients who did reach those milestones, loss of CHR or CCyR or the development of BCR-ABL mutations with a high insensitivity to imatinib constitute secondary resistance and also justify a change in treatment (NCCN).

Suboptimal Responses

Suboptimal response in patients with newly diagnosed CP CML is formally defined as the inability to reach response landmarks within given time limits but with less stringent parameters than those for treatment failure (NCCN, 2009) (see Table 2). The NCCN and European LeukemiaNet guidelines both include definitions of suboptimal response but vary slightly in their classifications (Baccarani et al., 2006). The European LeukemiaNet guidelines stated that no CHR at three months is a marker of suboptimal response rather than treatment failure, as defined by NCCN. The European LeukemiaNet six-month landmark also differs slightly in that a suboptimal response is classified as no cytogenetic response (Ph+ 90% or more), compared to no MCyR in the NCCN guidelines. No CCyR by 12 months is defined as a suboptimal response in both guidelines. The European LeukemiaNet guidelines include no MMR at 18 months to be a criterion for suboptimal response. In addition, the European LeukemiaNet guidelines stated that loss of MMR or the detection of BCR-ABL mutations or secondary clonal abnormalities are markers of suboptimal response (Baccarani et al.; NCCN), whereas the NCCN guidelines list BCR-ABL mutation to be a criterion of treatment failure.

Rates of suboptimal response may be estimated using data from the key IRIS trial (Druker et al., 2006) in which increasing percentages of patients had suboptimal responses to imatinib, from approximately 10% at three months to almost 40% at 18 months of therapy, respectively. According to European LeukemiaNet criteria, the only clinical study to date to focus on the consequences of suboptimal responses to imatinib, patients responding suboptimally at six months had outcomes identical to those experiencing treatment failure (i.e., no patient achieved a CCyR or MMR at 24 months) (Alvarado et al., 2007). In the same study, significantly more patients achieved CCyRs after 24 months of treatment if they responded optimally as opposed to suboptimally at 12 (94% versus 56%) or 18 (98% versus 93%) months (p = 0.01).

Data from the key IRIS trial support the view that suboptimal responses predict negative patient outcomes. In the study, the probability of attaining a CCyR within two years was markedly greater if a partial cytogenetic response (PCyR), 1%–35% Ph+ metaphases detected) was experienced at six months (more than 80%) compared to at 12 months (50%) (Baccarani et al., 2006). Also, achievement of CCyR at 12 months was significantly (p < 0.001) associated with improved survival (Roy et al., 2006). Therefore, not achieving CCyR within 12 months is associated with poorer patient outcomes.

Molecular response in the IRIS study also was associated with better long-term outcome. Achievement of MMRs plus CCyRs at 18 months correlated with a PFS rate of 100%, compared with 98% for patients who did not achieve those landmarks (p < 0.001) and 85% for patients who did not achieve CCyR (p = 0.013) (Druker et al., 2006).

Table 2. Definitions of Suboptimal Response or Treatment Failure During Imatinib Therapy for Newly Diagnosed Chronic-Phase Chronic Myelogenous Leukemia

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>TIME OF ASSESSMENT (MONTHS)</th>
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<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>–</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>No CHR or hematologic relapse</td>
</tr>
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CCyR—complete cytogenetic response; CHR—complete hematologic response; MCyR—major cytogenetic response; Ph+—Philadelphia chromosome positive


Treatment Options for Patients Experiencing Suboptimal Responses

High-Dose Imatinib

NCCN (2009) guidelines recommended that patients with suboptimal responses receive imatinib dose escalation from 400 mg per day to 600–800 mg per day (as tolerated) for suboptimal responses. Preliminary data from the only specific studies in patients with suboptimal hematologic or cytogenetic responses to initial imatinib therapy (European LeukemiaNet criteria) do respond to high-dose imatinib. In the studies, CCyRs were experienced by 50%–100% of patients after 6–20 months of follow-up, although patients with mutated BCR-ABL did not achieve MCyRs (Kim et al., 2007; Rea et al., 2007). Outcomes are worse for patients with suboptimal molecular responses to first-line imatinib; only 45% of the patients achieved subsequent MMRs (Rea et al.). The authors concluded that alternative treatment should be sought for such patients. Further follow-up is needed.
Until more data become available on the efficacy of imatinib-dose escalations in suboptimally responding patients, guidance also should be sought from evidence in patients with primary resistance. Current evidence suggests that dose escalation does not induce CCyRs in most patients with primary resistance. In clinical studies, dose escalation was associated with CCyR and MCyR rates of 11%–39% and 26%–52% in patients with primary resistance, respectively (Jabbour et al., 2007; Kantarjian et al., 2003; Kantarjian, Pasquini, et al., 2007; Marin, Goldman, Olavarria, & Apperley, 2003; Zonder, Pemberton, Brandt, Mohamed, & Schiffer, 2003). In addition, 93% of patients who did not achieve any cytogenetic response on standard-dose imatinib did not subsequently benefit from high-dose imatinib (Kantarjian et al., 2003; Kantarjian, Pasquini, et al., 2007).

Some early studies of high-dose imatinib in primary resistance show that best attained cytogenetic responses were lost by 43%–50% of patients (Cortes & Kantarjian, 2003; Marin et al., 2003; Zonder et al., 2003). However, preliminary data from a recent study suggest that CCyRs were maintained in 82% of patients receiving high-dose imatinib after a median follow-up of 50 months (Jabbour et al., 2007). A retrospective analysis of data from the IRIS study also demonstrated a 90%, three-year PFS rate in patients receiving high-dose imatinib who were primary resistant or had suboptimal response (Kantarjian, Druker, et al., 2007). The contradictory data highlight the need for further investigation in this area.

Although imatinib dose escalation may increase the therapeutic effect of the drug in some patients, toxicity may become a major barrier. Studies have shown that imatinib discontinuation or dose interruption or reduction was necessary in 31%–63% of patients following dose escalation, mostly because of grade 3–4 hematologic adverse events (24%–31%) (Kantarjian et al., 2003; Kantarjian, Pasquini, et al., 2007; Zonder et al., 2003). Other adverse events causing a change in treatment included abdominal pain, diarrhea, vomiting, fatigue, pain, joint effusion, rash, bone ache, dizziness, and blister (Kantarjian et al., 2003; Kantarjian, Pasquini, et al., 2007). Finally, unlike in Europe, imatinib 800 mg per day has not been approved in the United States for patients with CP CML.

**Dasatinib**

Dasatinib has activity against BCR-ABL (Lombardo et al., 2004). The current approved doses are 100 mg once daily in CP CML and 70 mg twice daily in AP or BC CML. As a result of a series of open-label, multicenter, phase II clinical studies in patients who were resistant of or intolerant to imatinib, dasatinib was approved initially by the FDA in June 2006 as second-line treatment across all phases of CML at a dosage of 70 mg twice daily and then for the 100 mg once daily dose (Cortes, Rousselot, et al., 2007; Guilhot et al., 2007; Hochhaus et al., 2007).

A prospective comparison of dasatinib 70 mg twice daily and high-dose imatinib (800 mg per day) in patients who did not respond to first-line imatinib demonstrated that dasatinib has greater efficacy (Kantarjian, Pasquini, et al., 2007). After a median follow-up of 15 months, dasatinib was superior to high-dose imatinib for rates of MCyR (52% versus 33%, p = 0.02), CCyR (40% versus 16%, p = 0.004), and MMR (16% versus 4%, p = 0.04) (Kantarjian, Rousselot, et al., 2007). In patients with no prior cytogenetic response to imatinib, MCyR rates were 49% versus 7% (p = 0.04). Moreover, responses achieved with dasatinib were highly durable: PFS was substantially longer in patients receiving dasatinib compared with high-dose imatinib (hazard ratio = 0.14, p < 0.0001). Duration of PFS in dasatinib is 5.6 months and data continues. The discontinuation rate also was significantly lower in the dasatinib arm than in the high-dose imatinib arm (82% versus 28%, p < 0.0001) because of the intolerance or lack of response in the high-dose imatinib arm (Kantarjian, Pasquini, et al., 2007).

Recently, the approved dose of dasatinib for patients with CP CML was changed to 100 mg once daily based on a phase III trial that evaluated dasatinib over four dose regimens: 70 mg twice daily, 140 mg once daily, 50 mg twice daily, and 100 mg once daily (Shah et al., 2007). Similar response rates were observed across all four dasatinib arms (CHRs in 88%–93% of patients, MCyRs in 58%–64%, and CCyRs in 46%–50%). Importantly, a significantly lower incidence was observed of grade 3–4 thrombocytopenia in the 100 mg once daily arm compared with the other three arms combined (22% versus 34%–40%; p = 0.005); similar findings were observed with pleural effusions (all grades: 10% versus 18%).

Furthermore, the 100 mg once daily dose was associated with a lower incidence of treatment interruption and discontinuation (p < 0.005), with only 6% of patients discontinuing because of toxicity.

In general, most adverse events emerging in response to dasatinib therapy are hematologic and mild to moderate (grades 1–2) in severity. Imatinib intolerance is not associated with recurrence of adverse events (e.g., hepatic function abnormalities, rash) (Hochhaus et al., 2007). Dasatinib, however, is associated with favorable rates of treatment adherence and toxicity-related withdrawal; it is better tolerated than higher doses of imatinib and had lower rates of grade 3 and 4 nonhematologic toxicities, less gastrointestinal symptoms, muscle cramps, and rash (Cortes, Rousselot, et al., 2007; Guilhot et al., 2007; Hochhaus et al., 2007).

**Nilotinib**

The phenylaminopyrimidine derivative nilotinib is an imatinib analog with greater potency against BCR-ABL than imatinib. Nilotinib was FDA approved in October 2007 for the treatment of CP and AP CML in a regimen of 400 mg twice daily with a fasting requirement.

Nilotinib 800 mg per day was approved by the FDA on the basis of an open-label phase II study in patients with CP or AP CML who did not respond to or who were intolerant to imatinib therapy (Kantarjian, Giles, et al., 2007; Novartis Pharmaceuticals, 2007). After at least six months of follow-up in patients with CP CML, rates of MCyR and CCyR were 56% and 40%, respectively (Kantarjian, Hochhaus, et al., 2007). Responses also were durable (median duration of MCyR not reached) (Kantarjian, Hochhaus, et al., 2007). In total, 16% of patients discontinued treatment for disease progression.

In a similar manner to dasatinib treatment, adverse events emerging in response to nilotinib therapy predominantly are mild to moderate in severity and generally may be managed with dose reduction or interruption and appropriate supportive care (NCCN, 2009; Novartis Pharmaceuticals, 2007).
However, cross-intolerance with imatinib with the reoccurrence of a grade 3−4 adverse events during nilotinib treatment that caused the discontinuation of imatinib can occur. In patients with hematologic intolerance to imatinib, almost half (49%) exhibited cross-intolerance to nilotinib, mostly a result of re-emergent thrombocytopenia. In patients with nonhematologic intolerance to imatinib, 3% experienced nilotinib cross-intolerance (Cortes, Jabbour, et al., 2007). In total, 16% of patients discontinued treatment as a result of adverse events (Kantarjian, Hochhaus, et al., 2007).

Notably, the prescribing information for nilotinib carries a black-box warning regarding the risk of QTc prolongation and sudden death. Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, and long QTc syndrome. Potassium and magnesium levels can be corrected in patients prior to starting nilotinib and monitored very closely. Patients need to avoid drugs that can cause QT interval prolongation and strong CYP3A4 inhibitors. Electrocardiograms should be obtained prior to starting nilotinib, then one week after initiation and periodically as clinically indicated. Five sudden deaths were reported in patients receiving nilotinib in an ongoing study (N = 867, 0.6%) (Novartis Pharmaceuticals, 2007). Prolongation of the QT interval can result in a type of ventricular tachycardia called torsades de pointes, which may result in seizure, syncope, and death. As food may increase the bioavailability of nilotinib and increase the risk of adverse events, no food should be consumed at least two hours before and one hour after administration (Novartis Pharmaceuticals).

Conclusion

Accumulating evidence suggests that suboptimal responses to first-line imatinib therapy have an adverse effect on patient outcomes. NCCN (2009) guidelines suggested dose escalation of imatinib in such circumstances, but increased toxicity is a barrier in many patients and most evidence suggests that any benefit achieved is temporary. Clearly, further research evaluating the role of high-dose imatinib is needed.

In the only prospective comparison of second-line treatments for CML, dasatinib was superior to high-dose imatinib in terms of efficacy and patient discontinuation. Nilotinib is a further second-line option, although cross-intolerance with imatinib may prove problematic. Also, nilotinib remains the only therapy approved for CML that has a black-box warning for sudden death. The availability of dasatinib and nilotinib provides options for patients who do not respond to or have suboptimal responses to first-line imatinib treatment.

Nurses play an important role in monitoring patients with CML. Nurses should be aware of the concomitant medications patients may be taking and familiar with possible drug interactions of these medications. Electrocardiograms need to be obtained prior to starting patients on nilotinib. Side effects of the medications should be monitored closely and reported to physicians. The side effects easily can be controlled if reported early. Nurses are an intricate part of patient care.

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