



# JNCCN

Journal of the National Comprehensive Cancer Network

SUPPLEMENT

## Optimizing Patient Care In Chronic Phase Chronic Myelogenous Leukemia: A Multidisciplinary Approach

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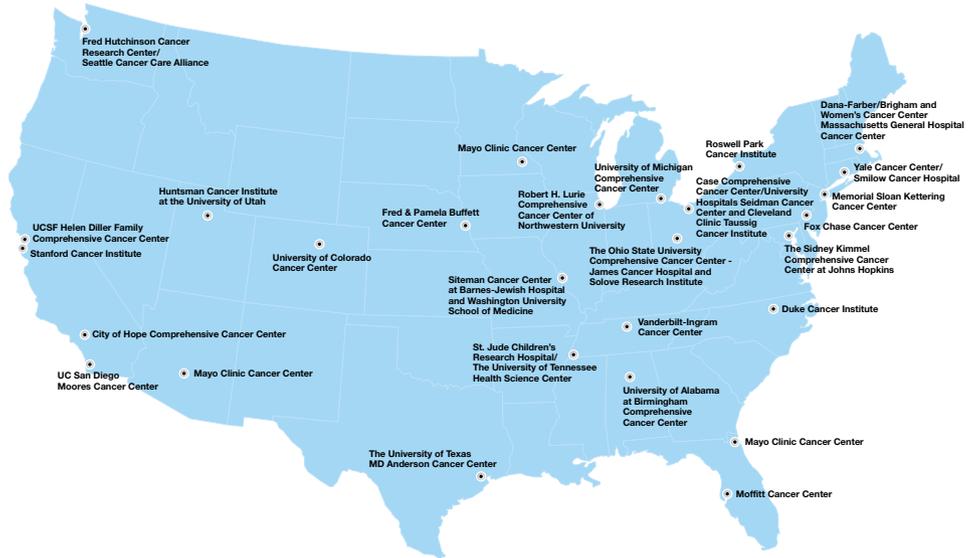


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# Optimizing Patient Care in Chronic Phase Chronic Myelogenous Leukemia: A Multidisciplinary Approach

Hema Sundar, PhD,<sup>a</sup> and Jerald Radich, MD<sup>b</sup>

## Abstract

Chronic myelogenous leukemia (CML) is characterized by the presence of the Philadelphia chromosome arising from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)]. This translocation results in the formation of the *BCR-ABL* fusion gene. The product of this fusion gene, p210, a protein with deregulated tyrosine kinase activity, plays a central role in the pathogenesis of CML. Tyrosine kinase inhibitor (TKI) therapy with small molecule inhibitors of BCR-ABL tyrosine kinase has significantly reduced the annual mortality rate among patients with CML. Although most of these patients respond to first-line TKI therapy, the use of TKIs is complicated by the development of resistance or intolerance in some patients, resulting in a loss of response or discontinuation of treatment. Inadequate response to TKI therapy is associated with poor long-term outcome, and the cases of patients with resistance or intolerance should be carefully evaluated for alternative treatment options. This report discusses the challenges associated with the management of newly diagnosed chronic phase CML in a patient with intolerance to multiple TKI therapies. *J Natl Compr Canc Netw* 2016;14(Suppl1):S1-S6

## Case Report

A 45-year-old woman presented in October 2008 with progressive 7 of 10 abdominal pain, greater on the left side, and a 15-pound weight loss over the past 3 months. On physical examination, her spleen extended

12 cm below the costal margin. Her past medical history was notable for non-insulin dependent (type II) diabetes mellitus, well-controlled with oral hyperglycemic medication, and Factor V Leiden mutation with 2 documented deep vein thromboses (DVTs) within the past 10 years. On her presentation to the hematology/oncology clinic, a complete blood count was performed, which revealed a high white blood count of 221,000/ $\mu$ L, hemoglobin 11.2 g/dL, and a platelet count of 361,000/ $\mu$ L. Peripheral blood differential showed 2% blasts, 2% eosinophils, 2% basophils, 38% neutrophils, 40% bands, 11% metamyelocytes, and 14% myelocytes. Bone marrow aspirate revealed a hypercellular marrow, with blast counts less than 5%. Cytogenetics returned with a classic Philadelphia chromosome involving the reciprocal translocation of chromosomes 9 and 22. She was given the diagnosis of chronic phase chronic myelogenous leukemia (CP-CML), with an intermediate-risk Sokal score but a low-risk Hasford and EUTOS score.

She was started on imatinib in November 2008 at a dose of 400 mg daily. The importance of monitoring *BCR-ABL1* level and response milestones, adherence to imatinib therapy, and the common adverse effects of imatinib (eg, edema, diarrhea, muscle aches) were discussed with the patient. The patient was also counseled by the nurse practitioner to avoid grapefruit juice while taking imatinib and was also advised about the potential interactions of imatinib with other medications that the patient was taking at the time of therapy.

The patient had experienced complete normalization of blood counts (complete hematologic response) after 2 months of therapy. After 6 months of therapy, the polymerase chain reaction (PCR) *BCR-ABL1* result was 10% on the International Scale (IS).

The patient continued on imatinib 400 mg daily. Her best response to imatinib was in April 2010 (18 months of therapy) with a *BCR-ABL1* level of 1.5%.

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However, in March 2011, she presented with complaints of progressive gastrointestinal toxicity (diarrhea) and severe myalgia that did not improve despite multiple attempts at adverse effect management (diet changes, over-the-counter antidiarrheals, and ibuprofen). The symptoms became significant enough that she often did not take her daily imatinib.

Imatinib was discontinued, and she was started on nilotinib 400 mg twice daily. A baseline electrocardiogram (ECG) was done before the start of nilotinib followed by another one 7 days after initiation. The patient was advised to avoid food 2 hours before and 1 hour after taking nilotinib. In addition, her primary care physician was also asked to monitor the patient's blood glucose levels more closely. Her disease responded well to nilotinib, and *BCR-ABL1* level decreased to 0.025%. However, she was experiencing nausea and headache, both of which could not be managed with appropriate supportive care measures suggested by the nurse practitioner (including anti-nausea medicines and ibuprofen). The patient eventually developed glucose intolerance despite being on multiple oral diabetes medications prescribed by her primary care physician. The medical oncologist recommended that she make a follow-up appointment with her primary care physician to start insulin injections. The patient refused to start insulin injections and it was discovered that she was no longer adhering to the TKI regimen as a reaction to her poorly controlled hyperglycemia.

Nilotinib was therefore discontinued, and she was started on dasatinib 100 mg daily. The patient was asked to stop taking antacids while on dasatinib due to potential drug-drug interactions and was also made aware of the common adverse events associated with dasatinib (eg, peripheral edema and pleural effusion). She was also asked to notify the doctor immediately if she developed cough or shortness of breath, since this could be an obvious complication of pleural effusion. However, although dasatinib was well tolerated and the patient remained adherent to therapy, her *BCR-ABL1* level continued to rise to approximately 12% in May 2014. She remained on dasatinib until June 2014, when a *BCR-ABL1* kinase domain mutational analysis was performed, which showed a 35 nucleotide insertion. As a result of failure to obtain an adequate molecular response (note that a complete cytogenetic response [CCyR]

roughly corresponds to a *BCR-ABL1* level of <1% IS), dasatinib was discontinued.

In June 2014, the patient was started on bosutinib 400 mg daily. She had great difficulty with diarrhea, with up to 8 loose stools per day, and *BCR-ABL1* levels did not improve. Bosutinib was discontinued due to intolerance and lack of molecular response. The patient was not a good candidate for ponatinib due to history of recurrent DVTs and thus was started on a clinical trial while an adequate donor for an allogeneic hematopoietic cell transplant (HCT) was pursued.

## Discussion

In 2015, an estimated 6,660 people were diagnosed with CML in the United States, and the prevalence is increasing each year.<sup>1</sup> CML is diagnosed in the chronic phase in about 85% of patients. Untreated CP-CML will progress to advanced phase in 3 to 5 years.<sup>2</sup> TKI therapy with imatinib, dasatinib, or nilotinib has resulted in remarkable improvement in clinical outcome for patients diagnosed with CP-CML. It is now the standard first-line therapy for patients with newly diagnosed CP-CML. Allogeneic HCT, which was the treatment of choice for CML before the advent of tyrosine kinase inhibitor (TKI) therapy, is now generally reserved for patients with CP-CML resistant to multiple TKIs, patients unable to tolerate TKIs, those who have the *T315I* mutation and who are not suitable for prolonged ponatinib therapy, or for those with CP-CML that evolves into accelerated or blast phase CML.

### Selection of First-line TKI Therapy

The results of the IRIS trial demonstrated that imatinib induces high durable responses and improves survival in a large proportion of patients with newly diagnosed CP-CML.<sup>3,4</sup> The 5-year follow-up data from the DASISION<sup>5</sup> and ENESTnd<sup>6</sup> studies have shown that dasatinib and nilotinib result in superior cytogenetic and molecular responses as well as lower rates of progression to accelerated or blast phase compared with imatinib in patients with newly diagnosed CP-CML. However, thus far the different TKIs (imatinib, dasatinib, and nilotinib) appear to show no differences in overall survival in the front-line setting. The choice of first-line TKI therapy depends on the risk score (Sokol or Hasford), physician's experience, agent's toxicity profile, patient's age and ability to tolerate therapy, and the presence of comorbid conditions.

Imatinib is still recommended as a reasonable first-line therapy for patients with newly diagnosed CP-CML. Dasatinib or nilotinib may preferentially benefit patients with intermediate- and high-risk scores, because those disease states are associated with higher risk of transformation.<sup>7,8</sup> Because both dasatinib and nilotinib have very good efficacy, differences in their potential toxicity profiles may also be helpful in selecting either of these TKIs over imatinib for first-line therapy. Pleural effusion is an adverse effect of dasatinib. Nilotinib is associated with QT interval prolongation and electrolyte abnormalities (elevations in lipase and bilirubin, hypophosphatemia, and hyperglycemia). Therefore, nilotinib may be preferred for patients with a high blood pressure, history of lung disease, or suspected risk of developing pleural effusions. Alternatively, dasatinib may be appropriate for patients with a history of arrhythmias, cardiovascular disease, pancreatitis, or a severe history of diabetes that is poorly controlled.

### Monitoring Response to TKI Therapy

Cytogenetic response is an important prognostic indicator of long-term survival in patients treated with imatinib.<sup>3,4</sup> Many recent studies have shown that early molecular response (*BCR-ABL1* level of  $\leq 10\%$ ) 3 and 6 months after first-line TKI therapy is associated with superior progression-free survival compared with patients who do not experience that level of molecular response.<sup>5,9-11</sup> Data from prospective studies support considering an alternate TKI if early molecular response is not obtained after first-line imatinib therapy,<sup>9,12</sup> although no clear evidence is currently available suggesting changing therapy early can make a long-term difference in outcome. *BCR-ABL1* level of 10% or lower (IS) at 3 and 6 months after second-line TKI therapy has also been reported to be a predictor of long-term survival.<sup>13,14</sup>

The goal of TKI therapy is to obtain a CCyR within 12 months of TKI therapy. At the molecular level, this corresponds to a *BCR-ABL1* level of 1% or less. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML have included a *BCR-ABL1* level of 10% or lower (IS) or PCyR at 3 and 6 months, CCyR or *BCR-ABL1* level of 1% or lower but greater than 0.1% (IS) at 12 months and beyond as response milestones after first-line TKI therapy (Figure 1). Monitoring response to TKI therapy is therefore crucial for the early identification of patients who would benefit from alternate treatment

options. An IS has been proposed to standardize molecular monitoring with quantitative PCR (QPCR) across different laboratories.<sup>15</sup> Monitoring molecular response (decrease in the amount of *BCR-ABL1* chimeric mRNA) with QPCR (IS) provides important information about the efficacy of TKI therapy and is now recommended every 3 months for all patients after starting TKI therapy.

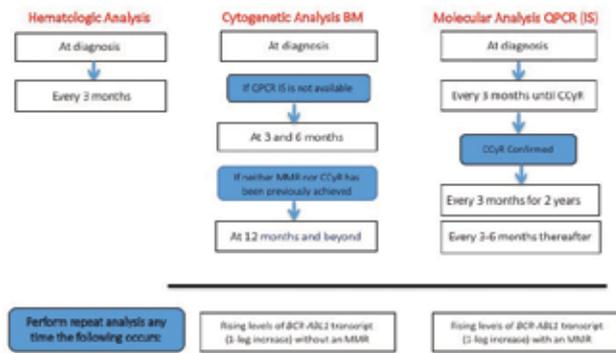
### Management of Intolerance to TKI Therapy

Intolerance to TKI therapy due to adverse events can lead to interruption or discontinuation of treatment and is also a potential barrier to adherence to therapy.<sup>16</sup> In the IRIS trial, diarrhea, nausea, and musculoskeletal pain were reported in 45%, 50%, and 47% of patients, respectively.<sup>3</sup> At 8 years follow-up, 6% of patients discontinued imatinib due to intolerance of adverse events.<sup>4</sup> Chronic fatigue (mostly correlated with musculoskeletal pain and muscular cramps) has been identified as a major factor limiting health-related quality of life in patients with CML treated with imatinib.<sup>17</sup>

Different TKIs demonstrate “cross intolerance,” meaning that patients who need to discontinue one TKI for toxicity will not likely have the same problem with a different TKI (but may have new toxicities). In patients with CP-CML treated with nilotinib after imatinib resistance or intolerance, grade 3 or 4 lipase elevation (18%), hypophosphatemia (17%), and hyperglycemia (12%) were the most common electrolyte abnormalities.<sup>18</sup> Discontinuations were primarily due to disease progression (30%) or adverse events (21%).<sup>13</sup> In patients treated with dasatinib after imatinib failure in CP-CML, infection (6%) and pleural effusion (5%) were the most common grade 3 or 4 adverse events.<sup>14</sup> The occurrence of pleural effusion was significantly minimized with dasatinib 100 mg once daily compared with 70 mg twice daily.<sup>19</sup> Diarrhea (83%), nausea (48%), and vomiting (48%) were the most common nonhematologic grade 1 or 2 adverse events associated with bosutinib.<sup>20</sup> Hepatotoxicity and arterial and venous thrombotic events are the serious nonhematologic toxicities reported with ponatinib. Serious arterial and venous thrombotic events were seen in 14% and 3% of patients, respectively.<sup>21</sup>

Close monitoring and timely intervention are necessary for patients at risk of developing pleural effusion during dasatinib therapy. Electrolyte abnormalities should be corrected before the start of treat-

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**Figure 1** NCCN recommendations for monitoring response to treatment in chronic myelogenous leukemia (CML). From the NCCN Clinical Practice Guidelines in Oncology for Chronic Myelogenous Leukemia. Version 1.2016. (Available at NCCN.org.) Abbreviations: BM, bone marrow; CCyR, complete cytogenetic response; IS, international scale; MMR, major molecular response; QPCR, quantitative polymerase chain reaction.

ment with nilotinib and should be monitored periodically. ECG should be obtained to monitor the QT interval at baseline, 7 days after initiation of nilotinib, and periodically thereafter. Increased bioavailability of nilotinib (after food consumption) may have an adverse effect on QT interval prolongation. Drugs that prolong QT interval should be avoided. Patients receiving ponatinib should be monitored for evidence of thromboembolism and vascular occlusion. Cardiovascular risk factors should be identified and controlled before starting ponatinib. Patients with cardiovascular risk factors should be referred to a cardiologist. Drugs that induce or inhibit CYP3A4 or CYP3A5 enzymes may alter the therapeutic effect of TKIs.<sup>22</sup> These drugs should be used with caution, and appropriate alternatives should be explored to minimize drug interactions with TKIs.

Poor adherence to imatinib is associated with undesirable clinical outcomes.<sup>23-25</sup> Nonadherence to imatinib has been identified as the only independent predictor for poor molecular response to imatinib.<sup>24</sup> Therefore, it is important to communicate with patients concerning some of the predictable and potentially treatable adverse effects of TKIs. Careful monitoring and adequate and appropriate management of adverse events improves adherence for most patients.<sup>26</sup> Frequent monitoring of *BCR-ABL1* level in peripheral blood can potentially identify nonadherence to TKI therapy, as a rise in *BCR-ABL1* is either resistance or nonadherence.

Switching to an alternate TKI should be considered for patients with persistent or recurrent nonhema-

### Patient Centered Approach

- Educating the patient about their disease, response milestones, and treatment, supportive care
  - In terms they can understand
- Multidisciplinary TEAM of care
  - Medical oncologist, advanced nurse practitioner, pharmacist, social worker, resource specialist, patient and family
  - Educators, treatment liaisons, support coordinators, emotional allies
- Maintain life-long treatment, monitoring response, adverse effect management, and adherence

**Figure 2** Facets of a patient-centered approach to care in chronic myelogenous leukemia.

tologic toxicities or those with resistant disease. Long-term data from prospective studies have demonstrated the safety and efficacy of dasatinib and nilotinib in patients with CP-CML intolerant to imatinib or those with resistant disease.<sup>13,14</sup> Limited data are available on the use of nilotinib or dasatinib after failure of 2 prior TKIs.<sup>27,28</sup> Bosutinib is an effective treatment option for patients pretreated with more than one TKI (imatinib followed by dasatinib and/or nilotinib).<sup>20</sup> Ponatinib is indicated for the treatment of CML in patients with intolerance or those with disease resistant to multiple TKI therapies.<sup>21</sup> Omacetaxine is an option for patients with intolerance or for those with disease resistant to 2 or more TKIs.<sup>29,30</sup> Evaluation of patient adherence and potential drug interactions with TKIs are recommended before changing therapy.

In addition to the medical oncologist, other members of the multidisciplinary team also need to communicate key clinical management points to the patient (Figure 2). Nurse practitioners should be able to effectively monitor and manage potential side effects. They should also educate patients about the importance of taking TKIs as prescribed and reporting adverse effects. The involvement of an oncology pharmacist is essential to understand the complete medication profile of an individual patient, discuss potential drug interactions and work with patients to maximize the benefits of TKI therapy.

### Management of Resistance to TKI Therapy

Point mutations in the *BCR-ABL1* kinase domain are the most frequent mechanism of resistance to

TKI therapy, with *T315I* mutation conferring the highest resistance to all of the currently approved TKIs except ponatinib. Insertion of nucleotides in *BCR-ABL1* kinase domain (*BCR-ABL35INS*) is sometimes associated with resistance to imatinib but not with dasatinib or nilotinib.<sup>31,32</sup> Several other *BCR-ABL1* mutations resistant to dasatinib (F317 and V299) and nilotinib (Y253H, E255, and F359) have been identified.<sup>33</sup> Bosutinib and ponatinib are active against *BCR-ABL1* mutations resistant to imatinib, dasatinib, or nilotinib.<sup>20,34</sup>

Rising *BCR-ABL1* levels are associated with an increased likelihood of detecting *BCR-ABL1* mutations.<sup>35,36</sup> Mutational analysis is recommended if *BCR-ABL1* levels rise and major molecular response is lost. In patients with identifiable mutations, the relative effectiveness of a TKI against *BCR-ABL1* mutations will contribute to the selection of alternate TKI therapy. In patients without identifiable mutations, differences in the toxicity profiles of TKIs and the patient's comorbid conditions should be considered in the selection of alternate TKI therapy. The use of alternate TKIs after treatment failure with 2 previous TKIs may induce responses in some patients; however, these responses are not durable except in a few patients in chronic phase. Investigational therapies or allogeneic HCT should be considered for this group of patients. Evaluation for allogeneic HCT (a discussion with a transplant specialist, which might include starting human leukocyte antigen [HLA] typing) is recommended. Treatment with a course of an alternate TKI (not received before) will be beneficial as a "bridge" to allogeneic HCT.

## Conclusions

In most patients responding to TKI therapy, CML is managed like a chronic disease requiring long-term treatment. Regular monitoring of *BCR-ABL1* level, effective management of toxicities, and patient education on adherence to TKI therapy are essential to provide optimal treatment. This case report illustrates the importance of a multidisciplinary team (oncologists, hematologists, advanced nurse practitioners, oncology pharmacists, and case managers) approach for the successful long-term management of CML. In this case, a patient-centered approach was consistently used to educate the patient about the key clinical aspects of CML management (moni-

toring molecular response and the significance of response milestones, adverse event management, and the importance of adherence) in terms that the patient could understand throughout the disease course.

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## Editors' note:

A new tool for health care professionals to communicate with patients regarding patient-centered care in the treatment of CML is available. See "[Patient Education Tool](#)" at right.

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