Sequential Therapy in Chronic Myelogenous Leukemia: Where Do Emerging Therapies Fit Within Current Treatment Regimens?

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**Abstract:** Chronic myelogenous leukemia (CML) is a slowly progressing malignancy that most often includes a clonal genetic aberration (the Philadelphia chromosome) that results in the BCR-ABL fusion protein, a constitutively activated tyrosine kinase. The management of CML was revolutionized more than a decade ago with the introduction of imatinib, a targeted inhibitor of the BCR-ABL protein. Imatinib has improved outcome and increased survival, but a substantial number of patients will develop resistance or intolerance to therapy. The second-generation tyrosine kinase inhibitors nilotinib and dasatinib are now approved in both the first-line and second-line settings. More recently, ponatinib and bosutinib were approved for resistant or refractory disease. This expansion to the treatment armamentarium has raised questions regarding the best selection and sequencing of agents. Clinical trials are now beginning to address these issues and others. The many treatment options in CML can offer patients improved outcomes, greater quality of life, and increased survival.
Sequential Therapy in Chronic Myelogenous Leukemia: Introduction

Michael J. Mauro, MD

Chronic myelogenous leukemia (CML) is one of the more rare hematologic malignancies, accounting for 15% of all adult leukemias. This myeloproliferative disease is nearly always characterized by the presence of the Philadelphia (Ph) chromosome, a chromosomal translocation that results in the production of the \( BCR-ABL \) oncogene.

Diagnosis of CML is often made serendipitously, when a patient is undergoing medical testing for an unrelated reason. When a patient does present with CML, it is typically owing to the presence of B symptoms, such as abdominal pain or fullness, night sweats, weight loss, and fatigue. Although B symptoms are not specific to CML, their presence should trigger an in-depth investigation. A complete blood count is the first test performed. Patients with CML usually exhibit an extremely high white blood cell count (often in the double or triple digits), which should prompt referral to a hematologist to clarify the diagnosis. Elevated numbers of white blood cells are often accompanied by some degree of anemia and a platelet count that is either elevated or suppressed (as seen in advanced-stage disease).

When CML is suspected, further diagnostic testing is necessary to confirm the diagnosis as well as to fully characterize the patient’s disease. One such test is detection of the Ph chromosome, which is considered the hallmark genetic abnormality in CML. This unique translocation was first described by Nowell and Hungerford in 1960, while in Philadelphia. These investigators noted that all of the CML patients studied showed a shortened chromosome 22. Subsequent studies identified a translocation event between chromosomes 9 and 22; this led to inquiry regarding the genes located within the translocated chromosomal regions. This then led to identification of the \( BCR-ABL \) oncogene fusion, which results in constitutive activation of the \( BCR-ABL \) kinase, established as the causative role in CML pathogenesis.

Bone marrow biopsy and aspirate are typically performed to query for additional morphologic findings, such as fibrosis. The bone marrow aspirate can help to quantify the blast percentage and rule out accelerated-phase disease or blast crisis. It is also a more reliable way to perform high-quality cytogenetic testing, as full karyotypes are not always obtainable from blood samples. A quality karyotype is needed to rule out chromosomal evolutions. CML is associated with classical pathological hallmarks, such as a hypercellular bone marrow. Normal bone marrow is a mixture of space and fat with cellular elements. In CML patients, the bone marrow consists almost entirely of cellular activity. The distinction between chronic-phase and accelerated-phase CML is based primarily on whether these cells have sustained further genetic alteration to the point where they remain in an immature blast form.

The gold standard diagnostic test for CML is a karyotype analysis, which permits visual confirmation of the translocation between chromosomes 9 and 22. Fluorescence in situ hybridization (FISH), while not a substitution for karyotype in assessing response, is a more readily available method because it does not require actively dividing cells. With fluorescent probes, the regions surrounding chromosome 9 and 22 can be tagged and visually assessed.

One of the most important advances in molecular diagnostics for CML is polymerase chain reaction (PCR). PCR for the \( BCR-ABL \) fusion gene permits the detection of very small levels of cellular RNA or DNA encoding the \( BCR-ABL \) transcript. Therefore, this method can be used as a means of very sensitive detection, and it allows identification of patients who are in deep remission or who have significant eradication of disease. In addition to its utility in assessing treatment response, \( BCR-ABL \) PCR can be used at diagnosis to measure baseline levels of disease, and early in treatment to gauge response.

Prevalence and Prognosis

An estimated 5,920 people will be diagnosed with CML in 2013. Between 2003 and 2007, CML-related mortality decreased by 7.2%. With an ever-improving prognosis associated with tyrosine kinase inhibitor therapy, it is expected that the prevalence of CML will continue to rise in the coming years. Overall, the 5-year relative survival for patients diagnosed with CML between 2001 and 2007 was 57.2%; subsequent periods should show further improvement.

Two scoring systems are generally used in the United States for estimating CML patient prognosis in practice and in clinical trials. The Sokal score incorporates clinical and laboratory variables, including patient age, spleen size, platelet count, and percentage of blasts present in the peripheral blood. The Hasford score uses the same factors, and in addition includes cell counts (eosinophils and basophils) in the peripheral blood. Both scoring sys-
tems classify patients into 3 risk groups. As categorized by the Sokal score, historical median overall survival was 4.5 years in low-risk patients, 3.5 years in intermediate-risk patients, and 2.5 years in high-risk patients. Although these survival times are drawn from the era before the introduction of tyrosine kinase inhibitors, the Sokal score is still relevant in the current era, and it strongly reflects response to tyrosine kinase inhibitors. Both the Sokal and Hasford scores are still used today in clinical trials.

A newer scoring system, the European Treatment and Outcome (EUTOS) score, was developed specifically for the evaluation of patients treated with tyrosine kinase inhibitors. It was designed to be more simple than older scoring systems and to increase prognostic ability. The EUTOS score was validated in a group of 2060 patients enrolled in clinical trials of first-line imatinib-based therapy.

**Challenges in the Management of CML Patients**

The discovery, development, and subsequent approval of imatinib more than a decade ago revolutionized the management of CML, allowing patients to experience long-term survival with minimal to no toxicity. Subsequent drug discovery and development has resulted in the addition of several second- and third-generation tyrosine kinase inhibitors. In 2013, there are now a total of 5 tyrosine kinase inhibitors available for treatment of CML: imatinib, nilotinib, dasatinib, ponatinib (Figure 1), and bosutinib (Figure 2). Although these agents have greatly broadened the choices available for patient management and resulted in improved patient outcomes, there remain several challenges in the management of CML patients. Chief among these challenges is how to choose which tyrosine kinase inhibitor to use in the first-line, second-line, third-line, and subsequent settings. There are many questions regarding how best to sequence therapy. Other questions surround the toxicity profiles of each of these drugs, an especially important concept considering the long-term nature of therapy.

Overall, there has now been a paradigm shift in the management of CML, whereby patients are managed using a chronic maintenance approach, with the goal of achieving very deep remissions with little or no clinical signs of disease. That stated, there is clearly a functional cure on the horizon, as we are beginning to observe treatment-free remission in some clinical trial patients.

**Acknowledgment**

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**References**

First-Line and Second-Line Management of Chronic Myelogenous Leukemia

Moshe Talpaz, MD

First-Line Therapy: Which to Choose

Until a few years ago, deciding on the first-line treatment of a CML patient was simple, as there was only 1 tyrosine kinase inhibitor. Imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, was initially approved in 2001 for the treatment of advanced-stage CML. This approval was subsequently broadened in 2002 for the first-line treatment of CML patients. However, the selection of first-line therapy was made more complicated in recent years with the US Food and Drug Administration (FDA) approval of 2 second-generation tyrosine kinase inhibitors. Both nilotinib and dasatinib received FDA approval in 2010 for first-line CML treatment. (They had been previously approved for treatment of imatinib-resistant or imatinib-intolerant CML.) Although the introduction of these agents added depth to the treatment arsenal for newly diagnosed CML, it also has raised many questions regarding which treatment should be chosen as first-line therapy. When considering these options, it is important to understand the potential benefits and limitations of each.

With more than a decade of experience and knowledge regarding imatinib, it is now well established that the majority of newly diagnosed CML patients respond remarkably well to this agent, with robust and durable responses. However, it is also clear that a certain proportion of patients will progress even with treatment. Primary hematologic resistance (defined as the inability to achieve hematologic remission within 3 to 6 months of beginning treatment) is relatively uncommon among newly diagnosed patients. In contrast, primary cytogenetic resistance (the inability to achieve any level of cytogenetic response by 6 months, a major cytogenetic response by 12 months, or a complete cytogenetic response by 18 months) may occur in 15% to 25% of patients.²

The IRIS (International Randomized Study of Interferon vs STI571) trial demonstrated that the majority of patients who experienced disease progression on imatinib did so within the first 3 years of therapy.² Disease-related events (including the loss of a complete hematologic response, loss of a major cytogenetic response, progression to accelerated-phase or blast-crisis disease, or death during treatment) occurred most frequently during the first 3 years after study randomization (3.3% during year 1, 7.5% during year 2, and 4.8% during year 3). Afterward, the rate of disease-related events fell dramatically (1.5% during year 4, 0.8% during year 5, and 0.4% during year 6); there were no new cases of disease progression reported during the sixth year of study treatment. Together, these findings suggest that this 3-year marker represents an important period for CML patients.

Accordingly, the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients) trial directly compared nilotinib with imatinib for first-line therapy of newly diagnosed CML patients.² ENESTnd was a phase 3, multicenter, open-label study that randomized patients to receive either 300 mg of nilotinib twice daily, 400 mg of nilotinib twice daily, or 400 mg of imatinib once daily. The initial 2-year follow-up showed that a significantly greater proportion of patients had achieved a major molecular response with nilotinib compared with imatinib (71% and 67% in the 300-mg and 400-mg nilotinib arms, respectively, vs 44% in the imatinib arm; P<.0001 for both comparisons). The rates of complete molecular response showed the same increase with nilotinib compared with imatinib (26% and 21% in the 300-mg and 400-mg nilotinib arms, respectively, vs 10% in the imatinib arm; P<.0001 for the first comparison and P=.0004 for the second comparison).

Follow-up analysis of this study showed that at 3 years, the rate of progression to accelerated-phase or blast-crisis CML was significantly lower in the nilotinib-treated arms compared with the imatinib-treated arm (0.7% and 1.1% in the 300 mg and 400 mg nilotinib arms, respectively, vs 4.2% in the imatinib arm; hazard ratio, 0.16 and P=.0059 for the first comparison and hazard ratio, 0.25 and P=.0185 for the second comparison; Table 1).³ When clonal evolution was considered as a criteria for progression to accelerated-phase CML, the rates of progression increased slightly (0.7% and 1.8% in the 300-mg and 400-mg nilotinib arms, respectively, vs 6.0% in the imatinib arm, hazard ratio, 0.11 and P=.0003 for the first comparison and hazard ratio, 0.28 and P=.0085 for the second comparison). Importantly, nilotinib also showed a benefit of approximately 20% compared with imatinib in the 3-year rate of major molecular response (73% and 70% in the 300-mg and 400-mg nilotinib arms, respectively, vs 53% in the imatinib arm; P<.0001 for both comparisons). This benefit was also...
Table 1. The ENESTnd Trial: 3-Year Follow-Up

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>HR (95% CI)</td>
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<td>0.28 (0.09–0.85)</td>
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<td>P value (considering only CML-related deaths)</td>
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AP/BC, accelerated phase/blast crisis; CML, chronic myeloid leukemia; EFS, event-free survival; ENESTnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

*Estimated by Kaplan-Meier analysis. †On study includes an event occurring in core or extension treatment or during the follow-up period after discontinuation of core or extension treatment.

apparent in the 3-year rate of complete molecular response (32% and 28% in the 300-mg and 400-mg nilotinib arms, respectively, vs 15% in the imatinib arm; P<.0001 for the first comparison and P=.0003 for the second comparison). At this follow-up, there was not a significant difference in the estimated 3-year overall survival rate between the nilotinib (95.1% and 97.0% for the 300-mg and 400-mg arms, respectively) and imatinib (94.0%) groups. Overall, based on the 3-year follow-up results from the ENESTnd trial, nilotinib appears to be associated with a significantly decreased risk of progression compared with imatinib, as well as a significantly higher likelihood of achieving a deep remission, when used as first-line therapy.

Based on its lower risk of progression as well as its advantage in achieving greater responses, nilotinib appears to be a better choice in first-line therapy of newly diagnosed CML patients. This benefit clearly justifies the choice of nilotinib over imatinib in this setting, especially in the current era in which both drugs are relatively similar in cost. However, this issue will likely be revisited when imatinib becomes available as a generic formulation, which may result in a substantial cost differential. (It should be noted that these data were not drawn from the intent-to-treat analysis.)

The second-generation tyrosine kinase inhibitor dasatinib was also directly compared with imatinib in a clinical trial. The DASISION (Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients) trial is a multinational, open-label, phase 3 trial that randomized newly diagnosed chronic-phase CML patients to treatment with either 100 mg of dasatinib once daily or 400 mg of imatinib once daily.7 In the initial analysis, dasatinib was superior to imatinib in several endpoints, including the rate of confirmed complete cytogenetic response (77% vs 66%; P=.007). At a 2-year analysis, the rate of major molecular response was higher with dasatinib than imatinib (64% vs 46%; P<.0001; Figure 3). Also at 2 years, patients in the dasatinib arm showed half the rate of progression to accelerated-phase or blast-crisis CML compared with the imatinib arm (2.3% vs 5.0%).6

In a 3-year follow-up analysis of the DASISION study, the statistically significant benefit associated with dasatinib compared with imatinib continued.7 Patients in the dasatinib arm were 1.6-fold more likely to achieve a major molecular response compared with patients in the imatinib arm (hazard ratio, 1.62; 95% CI, 1.30-2.02; P<.0001). The 3-year major molecular response rate was 68% with dasatinib vs 55% with imatinib. There was no substantial difference between the 2 groups in terms of risk of progression or death. However, dasatinib was associated with a higher rate of deeper molecular responses compared with imatinib, including in patients with BCR-ABL at or less than 0.01% (35% vs 22%; P=.0063) and BCR-ABL at or less than 0.0032% (22% vs 12%; P=.00069).

Figure 3. In the DASISION trial, dasatinib was associated with a higher rate of MMR than imatinib. DASISION, Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients; MMR, major molecular response. Adapted from Kantarjian HM et al. Blood. 2012;119(5):1123-1129.6

Another important topic when considering the first-line therapy of CML patients is the use of early evaluation markers to guide treatment decisions. Response to tyrosine kinase inhibitor therapy can be assessed by hematologic, cytogenetic, and molecular parameters. Patient outcomes at 3 months after initiation of treatment appear to be critical for assessing the long-term outcome of the patient. One important assessment of patient response is calculated as the ratio of the level of the BCR-ABL transcript detected to the level of the control gene (either BCR, ABL, or β-glucuronidase [GUSB], as measured by the ABL assay). At 3 months following initiation of therapy, patients can be grouped into 3 different categories of response to treatment: those with a greater than 10% ratio of BCR-ABL:ABL; those with a 1% to 10% ratio of BCR-ABL:ABL; and those with less than a 1% ratio of BCR-ABL:ABL. Patients with a greater than 10% ratio of BCR-ABL:ABL at 3 months are considered to be a high-risk population with evidence of primary resistance, and they are much more likely to experience an inferior outcome compared with patients who have a lower ratio (<10%). The difference in outcome between patients who have a 1% to 10% ratio, compared with those who have less than a 1% ratio, is much less striking. These outcomes at 3 months form the basis for decisions regarding whether the same therapy should be continued, or whether the patient should switch to a different tyrosine kinase inhibitor. Additionally, poor responses (manifested as a 10% ratio) may be cause to evaluate the patient for possible mutations within the BCR-ABL gene that may render primary resistance.

After this initial 3-month evaluation, a second treatment decision time point occurs after 12 months of treatment. At this time, it is expected that the patient will have a complete cytogenetic response as well as a major molecular response. If these outcomes have not been achieved, some kind of treatment change—either a
Second-Line Therapy: Which to Choose
Second-line treatment is advocated for patients who have demonstrated resistance to first-line therapy. Resistance can be primary, as described above, or secondary, which occurs when a patient who had a good response to treatment suddenly loses this pattern of response. Second-line therapy is also recommended for patients who are intolerant to treatment. For example, although imatinib is typically well tolerated, it may cause a patient to develop severe diarrhea or to gain tremendous water weight. Both of these adverse events may be considered intolerable, especially in light of the fact that other tyrosine kinase inhibitors are readily available for use.

Dasatinib and nilotinib were both originally approved in the second-line setting. When imatinib was the only agent available in the first-line setting, dasatinib and nilotinib were the primary choices for the second-line setting. Now that dasatinib and nilotinib are increasingly being chosen as first-line treatments, a new dominant agent for the second-line setting is emerging—ponatinib. Ponatinib gained FDA approval in 2012 for the treatment of chronic-phase, accelerated-phase, or blast-crisis CML that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. The approval of ponatinib was based primarily on the positive results of the PACE (Ponatinib Ph+ ALL and CML Evaluation) trial, a multicenter, international, phase 2 trial that evaluated ponatinib in CML patients who were resistant or intolerant to prior tyrosine kinase inhibitor therapy. The study included different subtypes of CML patients, including chronic-phase, accelerated-phase, and blast-crisis. In a 12-month follow-up analysis, it was reported that ponatinib was active and well tolerated in all CML subtypes. More than half of patients with chronic-phase CML (56%) achieved the primary endpoint of a major cytogenetic response. This response persisted at 12 months in an estimated 91% of patients (Figure 4). This response rate increased to 70% among chronic-phase patients with the T315I mutation. For patients with accelerated-phase CML, 57% of the overall population achieved the primary endpoint of a major hematologic response. This rate was 50% when restricted only to those accelerated-phase patients with the T315I mutation. For patients with blast-crisis CML (or Ph-positive acute lymphoblastic leukemia), 34% of the overall population achieved the primary endpoint of a major hematologic response. This rate was decreased to 33% when restricted only to those accelerated-phase patients with the T315I mutation. Overall, response rates to ponatinib were higher in patients who were exposed to fewer prior tyrosine kinase inhibitors. However, toxicities associated with ponatinib, particularly thromboembolic complications, are of concern. More information on the incidence of these toxicities, populations at risk, and management will be needed.

Bosutinib was approved by the FDA in 2012 for the treatment of chronic-phase, accelerated-phase, or blast-crisis CML that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. It is currently not recommended for the treatment of CML patients in the first-line setting. The approval of bosutinib was in part based upon its activity in a single-arm, open-label, multicenter phase 1/2 study in previously treated CML patients. Among patients with chronic-phase CML previously treated with imatinib only, rates of complete hematologic response, major cytogenetic response, and complete cytogenetic response were 86%, 53%, and 41%, respectively, after 2 years of follow-up. For chronic-phase CML patients who had previously received both imatinib and either dasatinib or nilotinib, the rates of complete hematologic response, major cytogenetic response, and complete cytogenetic response were 73%, 32%, and 24%, respectively. Bosutinib was active in accelerated-phase and blast-crisis CML as well.

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References
Emerging Therapies in Chronic Myelogenous Leukemia

Michael J. Mauro, MD

There are significant questions regarding the optimal first-line therapy for CML patients, as well as the best sequence of therapy. In 2013, there is now a robust treatment arsenal consisting of 5 FDA-approved tyrosine kinase inhibitor agents: imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. These agents have slightly different efficacy and toxicity profiles, and they differ according to whether they can be used in the first-line and second-line settings or restricted to only the second-line setting or beyond.

The identification of BCR-ABL point mutations can help guide treatment decisions. Such mutations often result in a change in the activation status or conformation of the BCR-ABL protein that prevents the tyrosine kinase inhibitor from acting on the clone. For example, certain mutations alter the BCR-ABL protein structure so that the tyrosine kinase inhibitor can no longer directly bind the kinase domain or cannot access the active or inactive conformation of the protein. Mutational analysis is often most informative when a patient develops secondary resistance. Point mutations within the ABL tyrosine kinase, such as Y253 and E255, tend to be less responsive to nilotinib therapy and more responsive to dasatinib. F359 also confers resistance to dasatinib. Nilotinib is clearly the superior agent for this case, as well as for patients with V299 mutations, which develop specifically during dasatinib therapy.

In contrast, patients with point mutations that occur in the P-loop region of the ABL tyrosine kinase, such as Y253 and E255, tend to be less responsive to nilotinib therapy and more responsive to dasatinib. F359 also confers resistance to nilotinib. Notably, the T315I mutation, which confers resistance to imatinib, nilotinib, and dasatinib, is sensitive to the recently approved second-line agent ponatinib. Thus, according to the available evidence, selection of a second-line tyrosine kinase inhibitor should be based on a mutational analysis when identified and if informative.

Recently, a panel of experts on behalf of European LeukemiaNet (ELN) convened to produce recommendations based on BCR-ABL kinase domain mutational analysis. These recommendations supported the incorporation of mutational analysis into treatment decisions for second-line and later therapy of CML patients (Table 2).
The recent approval of ponatinib creates an exciting advance in the treatment of multidrug-resistant CML, as it is currently the only approved tyrosine kinase inhibitor with proven activity in CML patients who harbor the T315I mutation.10 The biochemical basis of this ability to overcome T315I resistance is derived from an important structural feature within the agent that permits it to successfully make hydrophobic contact with the side chain of I315, thereby allowing it to retain activity in the T315I mutant.11 Structure-based drug design also allowed the inclusion of multiple contact points between ponatinib and the BCR-ABL protein, helping to ensure its status as a “pan BCR-ABL” inhibitor.

In a phase 1 dose-escalation trial, ponatinib was very active in a population of heavily pretreated CML patients who were resistant to or who relapsed on tyrosine kinase inhibitor therapy, and this outcome appears to be repeating in the phase 2 PACE trial (Figure 5).12 Among the chronic-phase CML patients included in the phase 1 study, 72% achieved a major cytogenetic response, 63% achieved a complete cytogenetic response, and 44% achieved a major molecular response. In this group of chronic CML patients, the vast majority (93%) had received at least 2 prior tyrosine kinase inhibitor agents, and nearly half (49%) had received imatinib, dasatinib, and nilotinib. Among patients with the T315I mutation, 100% had a complete hematologic response, 92% had a major cytogenetic response, 75% achieved a complete cytogenetic response, and 67% reached a major molecular response. In the phase 2 PACE trial, as was previously discussed, ponatinib showed similarly robust activity in pretreated patients.10 Again, it seemed to be slightly better able to salvage patients who harbored the T315I mutation. A post hoc analysis, however, suggested that this benefit might not be attributable to increased potency against the T315I BCR-ABL mutated protein, but instead may reflect the fact that patients in this study who harbored this mutation were younger, had been exposed to fewer prior tyrosine kinase inhibitors, and had a shorter leukemia duration. Therefore, it may be better to switch patients to ponatinib at an earlier point in the treatment sequence, before they have undergone multiple lines of therapy and developed a more complex resistance profile. This approach remains to be tested in a clinical trial.

Clinical Trial Data

A great deal of information has been gained from the multiple clinical studies conducted in CML patients with imatinib resistance or intolerance. In general, patients seem to respond relatively equally regardless of whether they have a BCR-ABL point mutation or not. This finding supports the hypothesis that although point mutations in the BCR-ABL kinase domain may be the visible and measurable sign of tyrosine kinase inhibitor resistance, they actually reflect a more general, and as of yet undefined, root cause of resistance such as the clonal cell’s ability to proliferate or tolerate the selection pressure it is subject to.

Another principle that has been learned from clinical trials in patients with multidrug-resistant CML is that there is a reasonable chance to salvage patients regardless of the presence of BCR-ABL mutations. However, it is becoming increasingly clear that there is a pattern of certain mutations that respond better to certain tyrosine kinase inhibitors. Broadly, imatinib resistance is characterized by a diverse number of mutations located in several regions across the BCR-ABL gene. In contrast, nilotinib resistance is associated with point mutations that are focused primarily on the P loop and the activation loop (A loop) within the ABL kinase domain. Dasatinib resistance appears to be associated with a somewhat higher concentration of patients harboring a T315I mutation. Bosutinib appears to be associated with resistance patterns that are similar to dasatinib, and emerging data will describe what mutations may arise after ponatinib.

Side Effects and Their Role in Decision-Making

The side effect profile of each of the FDA-approved tyrosine kinase inhibitors has become increasingly important in light of the fact that there are now multiple active agents to choose from. Although potential side effects may be less of a consideration with salvage therapy—during which the patient’s disease biology and clinical need may carry more weight—they should still be factored into treatment decisions. Overall, tyrosine kinase inhibitors have a relatively low spectrum of toxicity, an especially important characteristic given the need for their use in long-term maintenance.
One of the primary side effects of concern in CML patients is hematologic toxicity. Often, treatment and induction of remission may necessitate a period of myelosuppression. Thrombocytopenia and neutropenia are of particular concern, given their risk of morbidity. Tyrosine kinase inhibitor therapy in CML patients may result in myelosuppression that is minimal and transient or severe and prolonged. The degree of myelosuppression is likely related to the disease biology and the extent of bone marrow involvement. Compared with imatinib, nilotinib appears to be associated with a reduced incidence of myelosuppression, whereas dasatinib seems to be associated with a higher incidence. In the first-line setting, however, all 3 agents are associated with a more similar frequency of myelosuppression. Dose optimization studies have shown that lower dasatinib concentrations may result in fewer myelosuppression events. Myelosuppression associated with ponatinib appears to consist mostly of thrombocytopenia.

Another side effect of treatment involves metabolism by liver enzymes. All 5 approved tyrosine kinase inhibitors are extensively metabolized by the liver cytochrome P450 (CYP) enzymes. Other drugs that induce or inhibit CYP enzymatic activity may alter the metabolism, and thus the therapeutic effect, of the tyrosine kinase inhibitors. This effect is manageable by avoiding the concurrent use of drugs that utilize the same metabolic pathways, as well as by dose interruptions and reductions as needed. Other biochemical abnormalities associated with tyrosine kinase inhibitors include perturbations in the levels of phosphorous and other electrolytes, and elevations in pancreatic enzymes.

Long-term toxicities are a particular concern for CML patients, given the chronic nature of their disease and the need for maintenance therapy. As the length of time these agents have been studied and used in the clinic has increased, so too has experience with long-term toxicities. Chief among these toxicities is the risk of vascular disease (primarily arterial disease). Peripheral arterial disease is a modest but real side effect associated with nilotinib treatment, and dasatinib has occasionally been linked to pulmonary artery hypertension. Again, this side effect appears to be reversible with proper management and cessation of therapy. Ponatinib has an associated risk of vascular disease to a higher degree than either nilotinib or dasatinib, and further monitoring of this finding is needed, particularly with planned phase 3 trials of ponatinib in newly diagnosed CML.

CML patients should be closely monitored to ensure that any side effects that develop are well-managed. Additionally, the patient must have frequent and direct communication with his or her physician to ensure that even non-hematologic and nonbiologic toxicities are identified. Such events include muscle cramps, food retention, skin rashes, and headaches. Monitoring and controlling these side effects is very important, and the quality of life of CML patients should be held in very high regard when selecting therapy.

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References
The Role of Transplant in CML

Jerald P. Radich, MD

Historically, before the era of targeted therapies, allogeneic hematopoietic stem cell transplantation was the only curative strategy for treating CML patients. Results with transplantation in chronic-phase CML patients treated less than a year from their diagnosis were very strong, with a 5-year survival rate exceeding 85%. These survival rates are affected by the stage of the disease, and they progressively decrease in accelerated-phase (40%) and blast-crisis (10%-20%) CML (Figure 6).

Advances in more accurate human leukocyte antigen (HLA) typing in unrelated donors have made allogeneic hematopoietic stem cell transplantation more accessible to patients. Additionally, the development of less toxic regimens have expanded the number of patients who can be considered for allogeneic hematopoietic stem cell transplantation, and somewhat older patients are now candidates.

The robust activity and high survival rates associated with tyrosine kinase inhibitor therapy have challenged the role of allogeneic hematopoietic stem cell transplantation in the early management of these patients. Indications for the use of hematopoietic stem cell transplantation have dramatically shifted over the years. Previously, patients with any stage of disease were recommended for hematopoietic stem cell transplantation if they were younger than 65 years and had a donor.

In the current era, far fewer patients are considered for hematopoietic stem cell transplantation early in their disease. For chronic-phase CML, most patients who undergo hematopoietic stem cell transplantation are those who are intolerant to the entire tyrosine kinase inhibitor class and are unable to receive any therapeutic dose. Such patients include those who develop hematologic toxicities that cannot be managed through supportive care, such as platelet transfusions and growth factors. Very few patients fall into this category.

The other set of chronic-phase CML patients who should now be considered for hematopoietic stem cell transplantation are those who show profound resistance to at least 2 tyrosine kinase inhibitors. Only approximately half of these resistant patients will achieve a complete cytogenetic response. As some of these patients will experience disease progression, hematopoietic stem cell transplantation can be an attractive option in this setting.

Several studies have investigated the question of how many tyrosine kinase inhibitor agents should be attempted before progressing to hematopoietic stem cell transplantation. A new scoring system can be used to predict the probability that CML patients will achieve a complete cytogenetic response in the second-line setting. This system incorporates 3 factors: cytogenetic
response to imatinib, Sokal score, and recurrent neutropenia during imatinib treatment. Using these factors, patients can be grouped into 3 risk categories: good risk, intermediate risk, and poor risk. When validated in a patient population, these risk categories correlated well with 2.5-year cumulative incidences of complete cytogenetic response (good risk, 100%; intermediate risk, 52.2%; and poor risk, 13.8%; \( P<.0001 \)).

More recently, another group investigated the correlation of response outcomes at 3 months to long-term outcomes with tyrosine kinase inhibitor therapy. A landmark analysis of molecular response, which assessed BCR-ABL levels at 3 months, demonstrated that the cumulative rates of 3-year event-free survival were 95% for those with levels of 1% or less, 98% for those with levels of 1% to 10%, and 61% for those with levels greater than 10% (\( P=.001 \)). A similar significant trend was observed for 3-month cytogenetic responses (97% for 0% Ph-positive, 89% for 1%-35% Ph-positive, and 81% for >35% Ph-positive; \( P=.001 \)). Cytogenetic responses are correlated significantly with 3-year overall survival rates (98%, 96%, and 92%, respectively; \( P=.01 \)).

These data suggest that patient response at 3 months can be used to help decide whether a hematopoietic stem cell transplantation should be considered. One strategy is that once a patient fails first-line therapy, a discussion regarding hematopoietic stem cell transplantation is held and HLA typing is performed. An early donor search can then be initiated, especially in patients who carry some of the risk factors for failing subsequent therapy. It generally takes approximately 3 to 4 months to identify a donor, a duration that coincides with assessment of the patient’s 3-month response to their second-line therapy. Patients who respond well to salvage therapy can be continued on that regimen, whereas those with a poor response can then proceed to hematopoietic stem cell transplantation. Either way, the major goal is to prevent the patient from progressing to accelerated-phase CML, which responds poorly to both tyrosine kinase inhibitor therapy and hematopoietic stem cell transplantation.

**How Emerging Therapies Affect the Role of Transplant**

An important consideration is the effect of tyrosine kinase inhibitor therapy on hematopoietic stem cell transplantation outcomes. Historically, the treatments that were administered prior to hematopoietic stem cell transplantation (such as busulfan-hydroxyurea and interferon) did not worsen patient outcomes, including regimen-related mortality risk and relapse risk. Studies that have evaluated the effect of imatinib on hematopoietic stem cell transplantation outcomes suggest that there is no obvious effect on patient survival and response. 4,8

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**References**

Michael J. Mauro, MD  One of the most common questions I encounter is how some of the newer tyrosine kinase inhibitor agents should be chosen based on patient characteristics or disease pattern. It remains controversial how quickly to move the patient to the most potent of the tyrosine kinase inhibitors, particularly ponatinib. As was discussed earlier, ponatinib has significant activity in patients with multidrug resistant CML. It performs very well in patients who have received fewer prior lines of therapy.

One trial currently being planned, the EPIC (Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia) trial, is a randomized phase 3 study comparing imatinib vs ponatinib in the first-line setting. This study will provide insight into the toxicity profile found among large numbers of patients who have received fewer prior treatments. Advantages will have to be balanced against any disadvantages that emerge. For example, we want to aim for absolute and rapid success in a patient known to be resistant or intolerant, but this goal must be balanced with potential toxicity. Until we know a bit more about the newest tyrosine kinase inhibitors, there may be some hesitation regarding this decision. In the right setting and with further data on toxicity, however, it is not unreasonable to consider switching to ponatinib directly from any tyrosine kinase inhibitor—even imatinib. It is reasonable to consider switching to ponatinib directly after a patient has shown a high degree of resistance, or perhaps progression or relapse after exposure to only 1 of the more evolved tyrosine kinase inhibitors. Thus, for a patient treated with first-line nilotinib or dasatinib, although one strategy is to switch to the other tyrosine kinase inhibitor prior to moving to ponatinib, it may be that a strategy of directly going to the most potent and newest of the tyrosine kinase inhibitors could offer the best outcome.

Bosutinib is a drug that has been studied for a long period of time and has a fairly strong dossier with regard to activity in CML patients with not only imatinib resistance, but also some nilotinib or dasatinib resistance. There is strong third-line data with bosutinib, and thus its role should not be diminished even with the availability of ponatinib. We do know it has a heightened degree of gastrointestinal and hepatic toxicity. Although these events are not usually dose-limiting or therapy-limiting, they often require management (particularly for diarrhea) and monitoring for liver enzyme elevations and other toxicities. Other than these events, bosutinib can be well-tolerated and is thus a very good clinical option. For the patient with resistance or intolerance to imatinib, nilotinib, and dasatinib, bosutinib should be considered.

Omacetaxine has a different mechanism of action and is a non–tyrosine kinase inhibitor alternative for the patient with multidrug-resistant CML. It is another agent that should not be overlooked. It does have some limitations owing to its complex method of administration. But, if required, omacetaxine can be used to stabilize a patient in chronic phase or can be used for a limited amount of time in advanced phase (based on clinical trial data) to potentially bridge the patient to transplant or other options.

Jerald P. Radich, MD  Common questions I receive from the community concern how best to use these drugs, when to switch them, and how to utilize guidelines. Fortunately, the NCCN and ELN guidelines for monitoring response are now fairly similar. The major difference between these guidelines is when to switch therapies. According to the NCCN guidelines, the recommendation is that if a patient has not achieved a response of 10% BCR-ABL by 3 months of therapy, then an alternative tyrosine kinase inhibitor should be used. The ELN has taken a more conservative approach, choosing a 6-month response as the decision point. Both guidelines are relatively neutral regarding which drugs should be chosen in the first-line setting, and how alternative tyrosine kinase inhibitors should be selected upon treatment failure. I think there is some logic to a strategy of switching directly to ponatinib following first-line failure.

One issue I try to emphasize is the need to not solely rely on the NCCN and ELN guidelines. Different patients have unique needs, and it is important for the patient and the physician to set certain goals for treatment. These goals will influence which drugs are selected, and what is done in terms of monitoring response to treatment. For example, for an older CML patient (≥75 years), the primary goal is to try to outcompete the risks of death. For such a patient, is the most potent agent needed? Or is imatinib adequate? There is no clear answer, but the goal is to improve survival in the short term. In this situation,
it probably does not matter which tyrosine kinase is used. For monitoring, one should also consider what responses seem to impact overall survival. A major cytogenetic response at 12 months is the key response for determining overall survival prognosis. It is the major milestone if the primary goal is to improve overall survival.

Alternatively, for a patient who is a little younger, the goal would be not only to increase overall survival, but also, importantly, to decrease the risk of progression to accelerated-phase or blast-crisis CML. For these patients, it becomes more important to more closely follow the monitoring guidelines. Other outcomes that have been associated with a decreased risk of progression to accelerated-phase or blast-crisis CML is a \( \text{BCR-ABL:ABL} \) ratio of less than 1% and a complete cytogenetic response at 12 months, as well as a major molecular response (0.1% \( \text{BCR-ABL:ABL} \) ratio) at 18 months. These are the milestones to work toward to make an impact on preventing progression to accelerated-phase or blast-crisis CML. In these patients, use of the more potent tyrosine kinase inhibitors, such as ponatinib, may be preferred to achieve these goals.

One issue that is getting more attention now is the patient who may be able to eventually reach a point at which therapy can be discontinued. There is now much greater emphasis in clinical trials to investigate the potential to discontinue therapy.

**Michael J. Mauro, MD** Those are excellent points. It is important to remember that a patient should not be pushed into remission at the expense of significant morbidity. Individual treatment goals are an important discussion to have with every patient. Fortunately, we are now in a good era for treatment because there are many options. These approaches must be carefully navigated, and physicians must advocate for their patients.

**Jerald P. Radich, MD** Another important issue is that in the United States (as opposed to Europe), the majority of the physicians who treat CML are in the community setting. Since it is a relatively rare disease, many of these physicians see very few CML patients annually. In cases where the choice of tyrosine kinase inhibitor is straightforward, these physicians will easily be able to select these therapies. But, in cases where the decision is less clear, they are probably more likely to choose those agents with which they have more experience. Many physicians may not have a great deal of exposure to the tyrosine kinase inhibitors.

**Michael J. Mauro, MD** Additionally, centers with physicians who specialize in CML can partner with community physicians to be available for those cases that are complex and/or challenging.

**Jerald P. Radich, MD** We also are facing the issue that imatinib will become available as a generic agent very soon. When that happens, how will the field be affected? You can imagine different strategies that might be imposed by health organizations. One might be to use the less expensive imatinib until appropriate milestones are not reached, and then switch the patient to an alternative agent. Another approach may be to give the most potent agent upfront, and when a very low molecular burden is reached, then switch the patient to the less expensive generic drug for lifelong maintenance. I think this issue will be an interesting one.

**Michael J. Mauro, MD** Yes. One might fear that we might see a setback in the drug discovery advances that have been made with the broader use of generic imatinib. On the other hand, we might still be able to serve patients well and also take the opportunity to look carefully at how best to use this deep treatment arsenal we have access to.

**Jerald P. Radich, MD** In the forthcoming age of generic imatinib, enrollment in clinical trials might be the best way for patients to access advances in treatment.

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