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Advancing CML Patient Care: Closing in on a Cure?

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This activity has been designed to meet the educational needs of oncologists, hematologists, and medical professionals who treat patients with chronic myeloid leukemia (CML).

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Explain the relevance of achieving cytogenetic and molecular remission following therapy for CML with respect to progression-free survival and overall survival
- Identify the methods used to assess molecular remission and their level of sensitivity in detecting minimal residual disease
- Explain the mechanisms of imatinib mesylate resistance and the novel strategies developed to overcome this resistance
- Describe the options available for imatinib mesylate-resistant or -relapsing disease and their rationale for use in CML

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Advancing CML Patient Care: Closing in on a Cure?

Of the estimated 1,437,180 new cases of cancer that will be diagnosed in 2008, 4,830 will be due to chronic myeloid leukemia (CML).[1] CML is expected to account for only a small number of the total malignancies to be diagnosed in 2008, a trend that has remained stable for more than a decade. CML-related mortality, however, has significantly declined over time.[1,2] In 1997, there were approximately 4,900 CML-related deaths, whereas estimates for 2008 are for approximately 450 CML-related deaths.[1,2] The use of imatinib mesylate (also referred to as imatinib) should be credited for the recent reductions in CML-related mortality. The effectiveness of imatinib derives from its ability to specifically target the cause of CML, namely, the BCR-ABL fusion protein. The creation of this fusion protein results from the presence of the Philadelphia (Ph) chromosome, which is from the aberrant translocation and fusion of the *breakpoint cluster region (BCR)* gene on chromosome 22 to the *Ableson leukemia (ABL) virus* gene on chromosome 9.[3,4] The resulting BCR-ABL fusion protein is a constitutively active cytoplasmic tyrosine kinase that results in the phenotypic expression of CML: increased myeloid cells, erythroid cells, platelets, and significant myeloid hyperplasia in the bone marrow.[3] The detection of malignant hematopoietic cells is a requirement for the successful diagnosis of CML. A variety of methods are available for the detection of the *BCR-ABL* RNA and the resulting tyrosine kinase gene product. Despite the overall improvement in treatment outcomes associated with the use of imatinib, in some situations, this agent is ineffective or produces adverse events that are intolerable. In such cases, alternative therapies are required. Although there is no pharmacologic cure for CML, agents are being developed with the intention of further improving treatment responses by addressing the causes of imatinib resistance and intolerance. Understanding both the diagnostic- and treatment-related challenges to the management of patients with CML can help produce successful patient outcomes.

Clinical Concepts in CML Diagnosis and Management: The Importance of Assessing Minimal Residual Disease in CML After Therapy

The Natural History of CML

The vast majority of CML patients (90%) present with chronic phase (CP) disease, which is accompanied by an expanded myeloid cell population that is driven by the biology of the Ph chromosome.[5] Without therapy with agents that change the natural history of the disease (allogeneic transplantation, tyrosine kinase inhibitor [TKI] therapy), the median survival time of CP CML is approximately 6 years.[6] Without therapy, CP CML eventually evolves to the advanced-phase (AP) disease, first accelerated phase (characterized by new clonal cytogenetic changes and an increasing blast count), and finally, the fatal blast crisis (BC), where death eventually occurs from bleeding or infectious complications. All therapies, be they transplantation or TKI, work far better in CP disease than in AP disease (Table 1).[6-8]

Assays for the Diagnosis and Monitoring of CML

The successful management of patients with CML requires the continued monitoring of disease burden with several laboratory tests. There are approximately 1,012 leukemic cells present in a leukemia patient at the time of diagnosis.[9] The success or failure of a given treatment regimen can be determined by the reduction in leukemic load. At remission, patients may harbor approximately 109 leukemia cells while appearing to be in remission. With sensitive molecular techniques, leukemia burden may be assessed to lower levels, but approximately 106 leukemia cells is the limit of detection in current methods.[9] Thus,

Table 1. Phases of Disease in CML[6-8]

Phase	Characteristics
Chronic	Indolent course, often asymptomatic and found incidentally on routine physical exam.
	Predominance of mature white blood cells.
	Approximately 90% of patients are diagnosed at this stage.
	Median survival is 4–7 years (pre-tyrosine kinase inhibitor [TKI] therapy).
Accelerated	Transition generally occurs over a period of 1 year or more. Duration is 6 months to 1 year.
	Associated with progressive leukocytosis, thrombocytosis or thrombocytopenia, basophilia, increased blasts, splenomegaly, fever, bone pain.
	Clonal evolution may be present.
Blast	Lasts only a few months—survival is poor if untreated.
	Associated with increasing blasts (>20%), progressive splenomegaly despite treatment, and clonal evolution.

even using very advanced molecular assays, patients may have a considerable reservoir of leukemia cells while in remission. The molecular monitoring of CML is used not only to follow the number of leukemic cells, but also to detect the presence of any mutations in the *BCR-ABL* gene, which could confer a phenotype that is resistant to tyrosine kinase treatment. It is therefore crucial to understand how and when to use the available molecular genetic tools for the initial diagnosis and management of CML. It is equally important to understand how to quantify treatment response and failure so as to know when to maintain, modify, or stop a particular treatment regimen.

Metaphase Cytogenetics for Detection of the Ph Chromosome

Conventional metaphase cytogenetics examines dividing cells for clonal chromosomal abnormalities. It is the gold standard for both detecting the Ph chromosome and determining if there are additional clonal chromosomal abnormalities that also define progressive disease (Table 1).[10,11] Cytogenetics is also used during therapy to define the most commonly used measure of clinical response, based on the disappearance of the Ph chromosome. It should be noted that an adequate cytogenetic assay requires the use of bone marrow–derived cells and the analysis of at least 20 metaphases.

Fluorescent In Situ Hybridization

Fluorescent in situ hybridization (FISH) is a 2-color reaction in which there is a 5 *BCR* fluorescent probe used in combination with a fluorescent probe for 3 *ABL*.[12] Over the years, a number of variations of this methodology have been developed, including S-FISH, triple-probe FISH, and hypermetaphase FISH, all of which are designed to improve the accuracy and sensitivity of the traditional assay.[12] FISH offers several advantages over conventional cytogenetics. First, it can be performed using peripheral blood and does not require the use of bone marrow.[12] Futhermore, FISH can also be performed on both interphase and metaphase nuclei, which allows for a large number of samples to be tested at one time.[12] The end result is an assay that can be more sensitive (0.1–5% sensitivity, depending on probe sensitivity and specificity and lab expertise) than conventional cytogenetics (1–5% sensitivity).[13] FISH is used for both initial CML diagnosis and the monitoring of disease progression,[6,12] although its use in these settings has several important caveats. Its use at diagnosis is suboptimal compared to conventional cytogenetics because FISH only assays for the *BCR-ABL* breakpoint and does not detect the presence of other clonal cytogenetic lesions. In the monitoring of minimal residual disease, FISH suffers in comparison to reverse transcription/polymerase chain reaction (RT-PCR) because it is far less sensitive an assay.

Quantitative RT-PCR

Reverse transcription polymerase chain reaction (RT-PCR) of the BCR-ABL mRNA is the most sensitive assay available to detect cells that harbor the Ph chromosome. PCR sensitivity far exceeds what is possible with FISH (0.0001% to 0.1% sensitivity).[13] The sensitivity of PCR is achieved by the repeat amplification of target nucleic acid sequences (in this case, BCR-ABL chimeric mRNA), yielding exponential amplification of the target. Thus, after 30 PCR cycles of amplification, the target is amplified over a million times.[13] Quantitative RT-PCR (QPCR) allows for the quantification of transcript, using fluorescent reporters that quantify the amount of target amplified.[13] The two common QPCR methods, TaqMan™ and LightCycler™ systems, differ by how the probe quantifies the amount of target, but have similar test characteristics and performance.[13]

The quality of RNA can influence the amount of BCR-ABL amplified. Thus, most QPCR reactions also amplify a housekeeping gene, and the final result of BCR-ABL is adjusted for the quantity of the housekeeping control. The downside of this method is that not all laboratories use the same housekeeping gene, and thus for the same BCR-ABL level, a ratio value from one lab may be different than the same sample performed at another lab, since each lab is dividing by the amount of a different control gene.[14] Two promising ways designed to solve this reporting inconsistency are the use of log reduction and an international scale. The log reduction method compares the level of *BCR-ABL* decrease in a given sample from a treated patient against a standardized level of *BCR-ABL* from a series of untreated CML patients from across different laboratories.[14] The international scale method is based on the use of one type of standard control that will be used by all laboratories, allowing for uniform data reporting across different laboratories.[14]

CML Staging and Treatment Responses

Diagnostic tests are not only important to determine whether or not a patient has CML but also to allow the physician to determine the stage of disease upon initial presentation, as well as the progression of disease and response to treatment. The importance of accurately determining disease stage is due to the progressively worsening prognosis associated with the progression of disease.

Once a patient with CML begins treatment, monitoring the response to treatment is important (Table 2). A number of response criteria are associated with outcome. The first benchmark of response is the normalization of blood counts (hematologic response), and for patients with CP CML a complete hematologic response (CHR) should be obtained by 3 months of TKI therapy.[6] The next end point relies on the cytogenetic measurement of the Ph chromosome. The most meaningful clinical

Table 2. Treatment Response Types in CML

Level of Response	Definition
Complete hematological response	Normal CBC and differential, no extramedullary disease
Minor cytogenetic response	35%–90% Ph-positive metaphases*
Partial cytogenetic response	1%–34% Ph-positive metaphases*
Complete ctyogenetic response	0% Ph-positive metaphases*
Major molecular response	3-log reduction of BCR-ABL mRNA
Complete molecular remission	Negativity by RT-PCR

*Cytogenetic response is based on analysis of at least 20 metaphases.
CBC=complete blood count; CML=chronic myeloid leukemia; RT-PCR=reverse transcription polymerase chain reaction; Ph=Philadelphia chromosome

end point is the achievement of a complete cytogenetic response (CCyR), defined as the absence of the Ph chromosome in at least 20 metaphase preparations.[6] The last monitoring endpoint relies on the measurement of *BCR-ABL* transcripts (molecular response).[6,15] The reduction of BCR-ABL mRNA by QPCR to 3 logs below a standardized baseline has been deemed the major molecular response (MMR). Lastly, the absence of disease detection by QPCR has been called complete molecular remission, or PCR negativity. This term must be used with caution, since the level of detection of BCR-ABL may vary between laboratories.

The International Randomised Study of Interferon versus STI571 (IRIS) study group demonstrated the relationship between various levels of treatment response and prognostic outcomes. The IRIS trial compared the efficacy of imatinib with the combination of interferon and cytarabine in CP CML patients.[16] In patients receiving 12 months of imatinib, 12-month progression-free survival was found to be 100% in patients with a CCyR and a ≥3-log reduction in *BCR-ABL* transcript (referred to as a major molecular response), 95% in those with a CCyR and <3-log reduction in *BCR-ABL* transcript, and 85% in patients who did not receive a CCyR within 12 months.[16] These data demonstrate the prognostic value associated with current treatment monitoring criteria.

A critical question that remains is the frequency with which disease monitoring should occur in CML patients undergoing treatment. According to the most recent version of the National Comprehensive Cancer Network (NCCN) practice guideline for CML, *BCR-ABL* transcripts should be measured every 3 months, and bone marrow cytogenetics should be checked at 6 and 12 months after the initiation of therapy, until the patient achieves a CCyR. If a patient has yet to achieve a CCyR by 18 months of therapy, the patient should be considered a treatment failure and move on to a second generation TKI, or transplantation. In patients who achieve a CCyR, monitoring is performed by peripheral blood QPCR every 3 months. If a patient has an increasing level of *BCR-ABL* (a 1-log increase or greater), transcript measurement should occur once per month.[6] In addition, in the case of a rise of *BCR-ABL* transcript, the sample should be sequenced for mutations in the ABL kinase domain, since this is a major source of TKI resistance.

Summary

In CML, the *BCR-ABL* fusion gene is both a target for therapy and for monitoring. Accurate diagnostic staging is important since the expectation of outcome is hugely different in CP compared to AP disease or BC. There are clear outcome endpoints based on cytogenetic and molecular assays, and careful adherence to monitoring practice can play a role in optimizing therapy, as well as detecting potential relapse early.

Current Challenges to CML Disease Eradication: Incidence and Mortality of CML

Treatment outcomes in CML have dramatically improved since the introduction of imatinib, as evidenced by the results of the IRIS study.[17] Since the publication of this study, most institutions have replaced interferon-based therapies with imatinib therapy for the first-line treatment of CML patients.[6] In support of such a therapeutic change, the current NCCN guidelines recommend imatinib as the treatment option for first-line therapy for CML.[6] Although imatinib has dramatically improved treatment outcome for many CML patients, this agent is not curative. Imatinib has demonstrated an inability to eradicate all leukemia cells, allowing for the relapse of CML if treatment is discontinued. In some cases, patients may become resistant to imatinib or intolerant of its side effects, rendering this treatment ineffective.

Efficacy of Imatinib in Treating CP CML

The IRIS study compared the efficacy of imatinib (400 mg/day) with the combination of interferon-α (5 million units/m^2 of body surface/day) and cytarabine (20 mg/m^2 of body surface area/day) in 1,106 newly diagnosed CP CML patients.[17] After the first 18 months of follow-up, the rate of major cytogenetic response (MCyR) was 87.1% in the imatinib group and 34.7% in the combination therapy group (P<.001, Figure 1A).[17] CCyR was achieved in 76.2% of CML patients receiving imatinib versus 14.5% in the combination therapy group (P<.001).[17] It was also determined that significantly more patients in

the imatinib group achieved MMR than did those in the combination therapy group (57% vs 24%, respectively; *P*=.003).[16] Patients in the imatinib group also showed an improved progression-free survival (Figure 1B).[17] The results demonstrated that patients in the imatinib group were less likely to progress to advanced stages of CML than were those in the combination therapy group (rate of freedom from progression: 96.7% vs 91.5%, respectively; *P*<.001).[17] The most common adverse events associated with imatinib administration were grade 1 or 2 superficial edema, nausea, muscle cramps, and rashes.[17]

Since the publication of the original papers based on the IRIS study, several long-term study updates have been published. After 5 years of imatinib therapy in newly diagnosed CP CML patients, the event-free survival rate was 83%, with 93% of patients without progression to accelerated or blast phase CML.[18] Although most patients maintained their initial responses to imatinib, 5% experienced a loss of MCyR and 3% experienced a hematologic relapse.[18] The annual rates of both treatment failure and disease progression peaked by year 2 and then steadily decreased with each successive year; by the fifth year, the rates of treatment failure (0.9%) and disease progression (0.6%) were lower than what was found after the initial 12-month follow-up (treatment failure, 3.3%; disease progression, 1.5%).[18]

The response to treatment with imatinib remained an important predictor of disease control during the fifth year of follow-up. In patients with a CCyR 12 months after initiation of imatinib therapy, 97% did not progress to accelerated or blast phase CML at month 60.[18] In patients who had a partial cytogentic response (pCR) 12 months after initiation of imatinib therapy, 93% did not progress to more advanced stages of disease.[18] Overall survival in imatinib-treated patients with a CCyR and MMR at 18 months after treatment initiation was 100% when examined at month 60.[18] The overall survival values decreased to 98% and 87% in CCyR patients who did not achieve a MMR and in patients who did not receive a CCyR, respectively.[18]

The adverse events profile did not change with prolonged therapy, though the incidence of grade 3 or 4 events did decrease after the first year of therapy (particularly myelosuppression).[18] At 6 years following initiation of imatinib therapy in newly diagnosed CP CML patients, 65.8% of the original cohort (n=553) was still receiving imatinib therapy, whereas 35% either crossed over to receiving interferon plus cytarabine or discontinued treatment for any reason.[19] At year 6, the event- and progression-free survival remained the same as the 5-year data (between years 5 and 6, there was 0% progression); the estimated 6-year overall survival rate for CML patients who received imatinib as initial therapy was 88%.[19] At year 6, 325 patients remained in CCyR and 6 patients lost CCyR but maintained a MCyR, along with 9 patients who never achieved CCyR.[19]

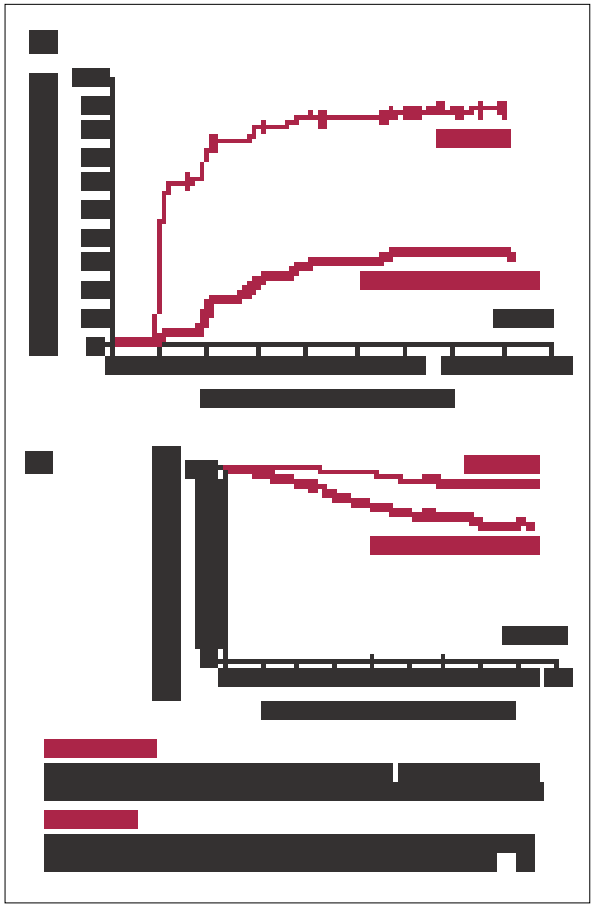

Figure 1. Kaplan-Meier estimates of (A) time to major cytogenetic response and (B) progression-free survival to advanced or blastic phase comparing imatinib with interferon plus cytarabine in patients with CP CML.[17]

Data from the IRIS study and the related follow-up reports suggest that imatinib can maintain long-term control of CML when given to newly diagnosed CP patients. The data are inconclusive regarding the durability of CML disease control when positive responders are removed from imatinib therapy, since few of these patients have been documented. This issue was examined in one study as part of an investigation into the effects of imatinib treatment in CP CML patients who relapse after stem cell transplantation.[20] In this study, 10 CP CML patients who achieved a complete molecular response (CMR) after imatinib rescue were removed from imatinib therapy and followed for a median of 494 days.[20] In this sample, 40% of patients retained their CMR status after being removed from imatinib therapy, whereas the remaining 60% were able to regain CMR status by re-initiating imatinib therapy.[20]

It is important to note that posttransplant CML patients and CML patients who received previous interferon therapy represent distinct patient populations, and their treatment outcomes to imatinib are unlikely to reflect the outcome of patients who did not receive these treatment modalities. Another study directly looked at the issue of discontinuing imatinib therapy in 12 CML patients in whom previous treatment with interferon failed and who acheived undetectable *BCR-ABL* transcripts (molecular remission) for longer than 2 years after receiving continuous imatinib therapy.[21] Molecular relapse occurred in 50% of patients who were removed from imatinib therapy.[21] When patients who relapsed were placed back on imatinib, 2 of the patients achieved molecular remission for the second time, and the remaining patients experienced consistent decreases in *BCR-ABL* transcript number but did not achieve molecular remission during the study period.[21] Although the factors responsible for maintaining response status after discontinuation of imatinib therapy are unknown, the 2007 study by Rousselot and colleagues suggests that prior exposure to interferon therapy may play a role in maintaining treatment response. All 6 patients in whom disease did not recur had previously received an interferon-based regimen, suggesting the possibility that imatinib amplified the biologic effect of prior interferon therapy in the absence of ongoing kinase inhibitor therapy.[21]

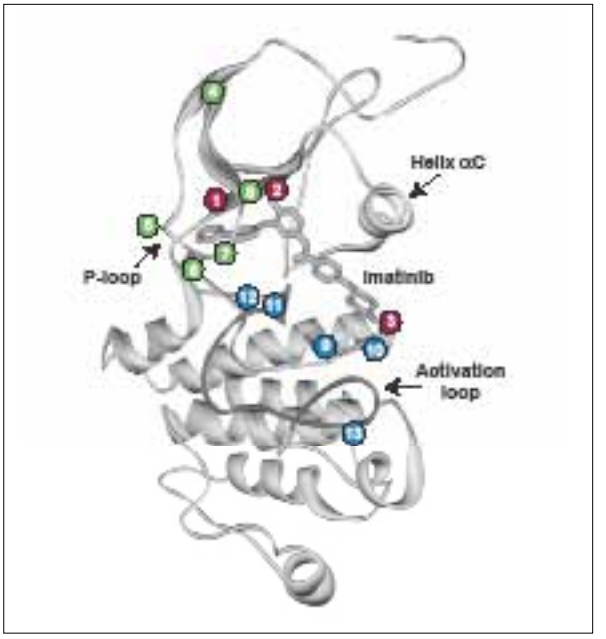

Figure 2. The relation between the *BCR-ABL* gene and imatinib.[24] The numbered circles represent the location of common mutations: 1, F317; 2, T315; 3, F359; 4, M244; 5, G250; 6, Q252; 7, Y253; 8, E255; 9, M351; 10, E355; 11, V379; 12, L387; 13, H396.

Imatinib Resistance

The initial clinical trial of imatinib in CP CML patients indicated a very high efficacy rate, with hematologic and cytogenetic response rates well above 80% in many cases.[17] Although the efficacy of imatinib in CP CML has been established, the use of this agent in more advanced stages of disease has shown less efficacy.[22,23] There are several possible causes for the reduction in efficacy seen with imatinib in advanced stages of CML. Among the best-studied mechanisms of imatinib resistance are *BCR-ABL* mutations, which are common in later stages of CML. Other causes of imatinib resistance include *BCR-ABL* amplification, *BCR-ABL*–independent genetic aberrations, and pharmacokinetic changes. Understanding the potential mechanisms of imatinib resistance will help in the development of alternative therapies to improve patient care.

BCR-ABL point mutations are the most common cause of imatinib resistance. An estimated 50% of CML patients who relapse have at least one *BCR-ABL* mutation.[24,25] Documented *BCR-ABL* gene mutations are numerous, with nucleotide substitutions occurring in many locations within the *BCR-ABL* gene (Figure 2).[24] The consequence of nucleotide substitutions within the *BCR-ABL* gene is the substitution of the corresponding amino acids in the BCR-ABL protein kinase. Overall, there are two major types of mutations associated with the *BCR-ABL* gene: those that directly distort the binding pocket of imatinib within the BCR-ABL kinase domain, and mutations outside of the imatinib pocket that cause a conformational change within the BCR-ABL kinase domain and prevent access to the imatinib-binding pocket.[24] Mutations that directly impair imatinib binding include T315I, F317L, and F359V. Phosphate-binding-loop (P loop) and activation loop mutations such as G350E and Y253F cause conformational changes to BCR-ABL kinase that result in a reduced binding affinity of imatinib for BCR-ABL kinase.[24] It has been postulated that in many cases, these mutations may pre-exist in CML patients (imatinib-resistant cells make up a small portion of the total *BCR-ABL*–expressing cells in a CML patient), and by treating with imatinib, the mutated phenotype is being selected for, eventually representing a larger proportion of all *BCR-ABL*–positive cells.[24]

Not all *BCR-ABL* mutations influence the effectiveness of imatinib by the same magnitude. T315I, G250E, and E255K have the greatest inhibitory effect upon the ability of imatinib to bind to BCR-ABL kinase, whereas M351T and E355G have much less of an influence on binding compared with the wild-type BCR-ABL kinase protein.[24] The clinical consequences associated with mutations that significantly impair imatinib binding to BCR-ABL are important. A controversial finding was the discovery that in some CML patients with either the T315I

or any P loop mutation, the overall and progression-free survival were significantly worse than they were in CML patients who lacked these mutations.[25,26] Although the common *BCR-ABL* mutations have been identified, and many have been shown to have negative treatment-specific consequences, there is a current lack of direction with how and when to assess CML patients for *BCR-ABL* mutations. Currently, there are no guidelines for when patients should be screened for mutations or how often, though the frequency of *BCR-ABL* mutations increases both as the disease advances and as the length of time a patient lives with the disease increases.[14,27] The likely reasoning for a lack of formal instruction on how to address imatinib-resistant mutations stems from two sources. First, only 50% of CML patients develop imatinib-resistant mutations. Second, newer agents—specifically nilotinib and dasatinib—have been shown to overcome most of the identified BCR-ABL kinase mutations.

Other mechanisms besides BCR-ABL kinase mutations have been shown to play a role in imatinib resistance. Amplification of *BCR-ABL* or overexpression of BCR-ABL transcripts has been reported in a minority of imatinib-resistant CML patients.[28,29] A member of the Src kinase family has recently been implicated as playing a role in imatinib resistance.[30] In CML cells from patients with imatinib-resistant CML, unique phosphorylation sites were found for the Src-kinase family member, Lyn kinase.[30] Reducing the expression of Lyn kinase or the use of dasatinib resulted in CML cell death, suggesting that Lyn plays a role in imatinib-resistance.[30]

The Impact of Quiescent Stem Cells on the Curative Ability of Imatinib

A factor that may contribute to imatinib's lack of a curative effect in CML is the presence of CD34+ quiescent CML stem cells. It has been known for decades that pluripotent stem cells are responsible for the presence of BCR-ABL kinase found in multiple types of hematopoietic cells in patients with CML.[31] CD34+ quiescent CML stem cells are able to continuously produce differentiated and actively dividing Ph+ hematopoietic cells, and these stem cells are thought to make up 0.5% of the total CD34+ stem cell compartment.[31] The significance of this finding was demonstrated by in vivo experiments that showed the ability of transplanted CD34+ quiescent CML stem cells to produce the CML phenotype in rodents.[32] In human CML, the significance of quiescent CML stem cells is their resistance to imatinib treatment.[33,34] Even patients who achieve a CCyR after imatinib therapy show evidence of CD34+ quiescent CML stem cells.[34] It has been suggested that the lasting responses to interferon therapy in CML are due to its action at the stem cell level, whereas the rapid responses to imatinib are due to the targeting of a more mature population of CML cells.[31,35] These data suggest that although imatinib is able to effectively control malignant growth found in CML, its inability to affect the CD34+ quiescent CML stem cell population prevents it from being a curative option.

Summary

The use of imatinib has significantly improved treatment outcomes in CML patients. Progression-free and overall survival rates associated with imatinib are superior to what is achieved with interferon therapy. Furthermore, in many patients, imatinib therapy can reduce the number of *BCR-ABL* transcripts to almost undetectable levels. Long-term follow-up data are confirming the durability of response to this agent, though the effects of discontinuing treatment in imatinib responders are not fully known. In other situations, some patients develop resistance to imatinib, an effect that is often the result of point mutations in the BCR-ABL gene. The presence of quiescent CML stem cells represents another mechanism of imatinib resistance and may be responsible for imatinib's inability to cure CML.

Clinical Decisions in the Care and Treatment of Patients With CML: The Patient Who Does Not Respond to Therapy

Nilotinib was recently approved for use in chronic CML patients who do not respond to or who are intolerant of imatinib therapy.[36] Structural differences between nilotinib and imatinib allow for clinical efficacy in situations where imatinib is ineffective. The overall structure of nilotinib was developed based on the crystal structure of the imatinib-ABL kinase protein complex.[37] Therefore, although the overall structures of imatinib and nilotinib are similar, the chemical differences in the nilotinib molecule reduce the reliance upon hydrogen bonds and increase the lipophilic interactions with the ABL kinase structure.[37] The consequence of these changes is that nilotinib has a better topological fit with the ABL protein and is less sensitive to the conformational changes induced by many of the common *BCR-ABL* mutations.[37,38] An in vitro study has shown nilotinib to be 10–40 times more potent in inhibiting wild-type BCR-ABL kinase activity.[38,39] When administered to cell lines that express imatinib-resistant BCR-ABL kinase mutants (eg, E255V, T315I, F317L, M351T, etc), nilotinib was able to potently inhibit cellular proliferation in most cases, except in cells expressing the T315I mutation.[38]

The promising preclinical data prompted the examination of nilotinib in imatinib-resistant CML patients. A phase I study of 119 imatinib-resistant CML (including patients with acute lymphoblastic leukemia) patients examined the effects of nilotinib at doses between 50 and 1,200 mg per day.[40] The pharmacokinetic data revealed

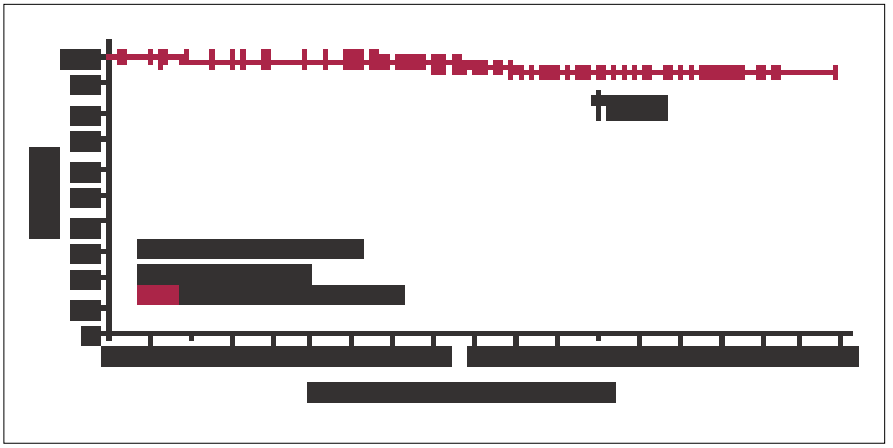

Figure 3. Overall survival in CP CML patients resistant or intolerant to imatinib who have received nilotinib.[41]

that the mean peak concentration of 3.6 mM occurred 3 hours after administration of nilotinib in patients receiving 400 mg twice per day.[40] The half-life of this agent was 15 hours, and the steady-state concentration of nilotinib was reached by the eighth day of treatment.[40] During steady-state administration, the area under the concentration-time curve increased among patients receiving 50–400 mg of drug, but plateaued in patients receiving more than 400 mg of nilotinib; as well, exposure was greater for twice-daily dosing than once daily at the total dose of 800 mg (400 mg BID).[40] Patients who received less than 600 mg/day of nilotinib did not experience any adverse events that required dose modifications.[40] The most common adverse events included rash, pruritus, dry skin, constipation, thrombocytopenia, neutropenia, and anemia.[40] Nilotinib use resulted in hematologic response rates of 92% in CP, 74% in AP, and 39% in BP patients.[40] The proportion of patients with a cytogentic response was similar in the CP and AP groups (53% vs 55%, respectively); 27% of BP patients exhibited such a response.[40]

A phase II study of nilotinib examining the efficacy of 400 mg twice per day treatment in CP or AP CML patients resistant or intolerant to imatinib utilized a single-arm, open-label, nonplacebo-controlled study design.[41] In CP CML patients (N=280) receiving at least 6 months of follow-up, nilotinib treatment resulted in a CMR in 74% of patients (90% in those who were imatinib-intolerant), whereas a MCyR occurred in 48% of patients.[41] Overall survival at 12 months was estimated to be 95% in this population of CML patients (Figure 3).[41] Importantly, in most instances, cross-intolerance to the hematologic and nonhematologic adverse events associated with imatinib did not occur in patients receiving nilotinib (this was true for both CP and AP CML patients).[41,42] In patients with AP CML (N=119), a hematologic response was achieved in 47% of patients, and 29% of patients achieved a MCyR.[43] The 12-month overall survival was estimated to be 79% among imatinib-resistant or imatinib-intolerant AP CML patients (Figure 4).[43]

Although neither severe peripheral edema nor pleural effusions occurred in the majority of patients (1% or less of patients), grade 3 or higher elevations in bilirubin and lipase were found in a subset of patients (rates were similar for both CP and AP CML patients).[41,43] Prolongation of the QTc interval is another concern based on preclinical data (a black box warning about this adverse event is currently on the package insert for nilotinib); however, it appears that very few people (≤4%) experience increases in QTc interval above 60 milliseconds.[36,41,43] With proper screening of patients at risk for changes in QTc interval and monitoring for change, related adverse events should be avoidable. Lastly, additional data from phase II clinical trials have shown that the presence of certain baseline *BCR-ABL* mutations (namely, mutations at positions 253, 255, and 359 in the kinase domain) at the start of nilotinib treatment in CP CML patients who do not respond to imatinib therapy result in fewer cytogenetic responses and greater progression risk compared with patients who lack mutations or have other mutations at the start of nilotinib treatment.[44]

Another phase II, open-label study examined the efficacy of nilotinib in CML patients refractory or intolerant to both imatinib and the other second-generation BCR-ABL kinase inhibitor, dasatinib. Nilotinib was administered for a median duration of 81 days in a total of 42 patients (containing a mixture of CP, AP, and BP CML patients).[45] At the time of the report, 13 patients remained on nilotinib, with 29 patients discontinuing therapy due to adverse events or disease progression.[45] In CP patients, 31% obtained a MCyR, 39% had a CMR, and disease progression occurred in 2 patients (5%).[45] In AP phase, 22% had a return to chronic phase, 6 patients were unevaluable, and 1 patient died.[45] In BP patients, 18% achieved a CMR and 24% had disease progression.[45]

Dasatinib is a synthetic compound originally designed as a Src kinase inhibitor approved for use in chronic, acclerated, or myeloid or lymphoid BP CML patients who are resistant or intolerant to previous thera-

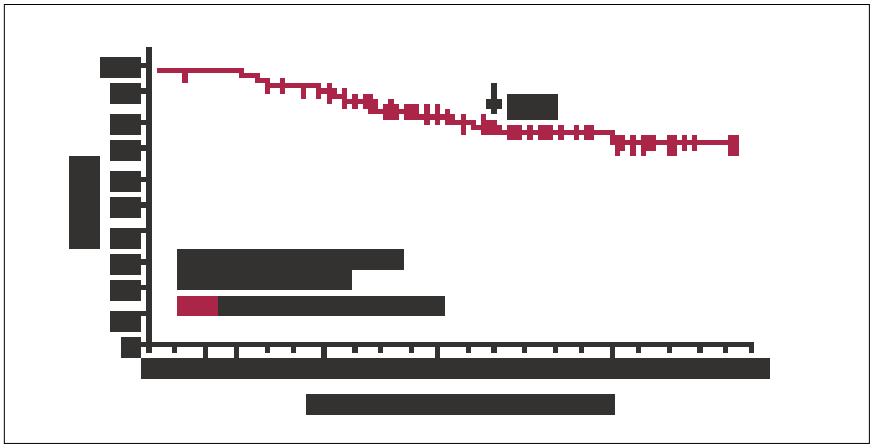

Figure 4. Overall survival in advanced-phase CML patients resistant or intolerant to imatinib who have received nilotinib.[43]

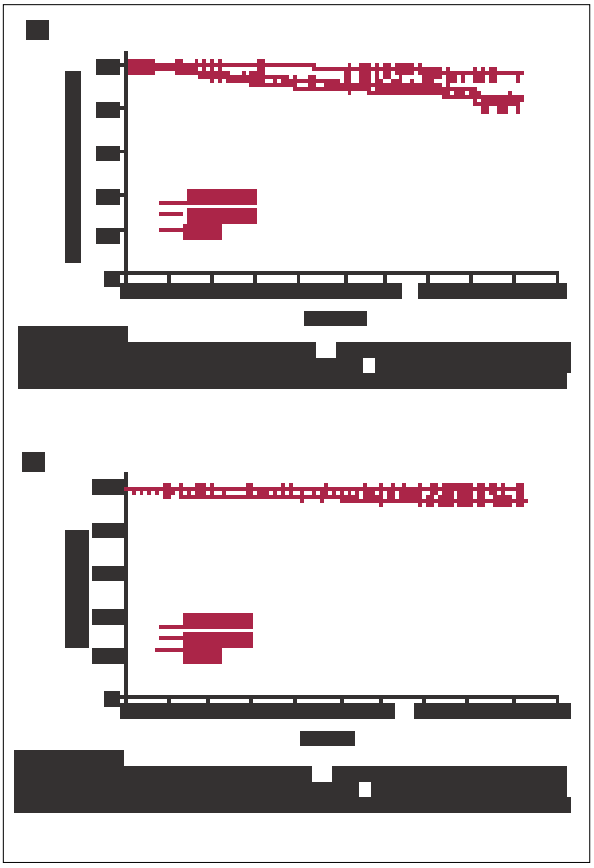

Figure 5. Kaplan-Meier analysis of (A) progression-free survival and (B) overall survival in imatinib-resistant or imatinib-intolerant CP CML patients receiving dasatinib.[48]

pies, including imatinib.[37,46,47] Dasatinib is also active against platelet derived growth factor receptor (PDGFR), c-Kit, human epidermal growth factor receptor (HER)1, EPHA2, and p38 MAP kinase.[37] In vitro studies have demonstrated that dasatinib is a more potent inhibitor of BCR-ABL kinase than imatinib, and that it exhibits activity against the majority of imatinib-resistant *BCR-ABL* mutants.[47] In mice injected with Ba/F3 cells that were transfected with various versions of the *BCR-ABL* gene, dasatinib was able to prevent the development of disease, unlike what was seen in the vehicle control group, in which mice developed progressive disease.[47] Of note is the finding that dasatinib, like nilotinib and imatinib, was unable to prevent the development of disease in mice receiving the T315I mutant.[47]

An open-label phase II clinical investigation examined the efficacy and safety of dasatinib administered at a dose of 70 mg twice per day in CP CML patients who were intolerant or resistant to imatinib.[48] Dasatinib was administered in 387 patients with a median follow-up of 15.2 months.[48] CMR was achieved in 91% of patients, whereas 59% obtained MCyR (49% achieved CCyR).[48] The 15-month progression free survival was 90% and the overall survival at this time point was 96% (Figure 5A and B).[48] Nonhematologic adverse events consisted of diarrhea, headache, fatigue, dyspnea, pleural effusion, and peripheral edema.[48] Grade 3 or 4 hematologic events consisted of anemia, thrombocytopenia, neutropenia, and leukocytopenia.[48] In another phase II trial, high-dose imatinib (800 mg/day) was compared with dasatinib (70 mg twice/day) in 150 CP CML patients resistant to standard-dose imatinib.[49] Significantly more patients had CMR response in the dasatinib group (93%) compared with those receiving imatinib (82%; P=.034).[49] Dasatinib also resulted in a higher number of MCyRs (52% vs 33%; P=.023) and improved progression-free survival (P<.0001) relative to imatinib.[49] The occurrence of nonhematologic adverse events was similar between the two groups. Patients in the dasatinib group experienced a higher incidence of pleural effusion and cytopenia.[49]

To address the adverse events seen with dasatinib when administered at two 70 mg doses per day, a year-long, open-label, randomized trial was developed to compare the safety and efficacy of dasatinib at a total

dose of 100 mg/day (either 100 mg once/day or 50 mg twice/day), with 140 mg/day (either 140 mg once/day or 70 mg twice/day) in CP CML patients (N=662) resistant or intolerant to imatinib.[50] The results indicated that the proportion of patients with CMR, MCyR, or CCyR was similar in all dosing groups.[50] The incidence of pleural effusion, neutropenia, and thrombocytopenia was significantly reduced in the group that received the single 100 mg dose of dasatinib compared with all of the other dosing regimens.[50] Because of the ability to maintain efficacy and reduce adverse events, the single 100 mg/day dose of dasatinib was found to have the best overall risk-benefit ratio of all the dosing regimens examined in CP CML patients.[50] In an open-label clinical trial examining 9-month follow-up data in 48 BP CML patients resistant or intolerant to imatinib, the administration of dasatinib at a dose of 70 mg twice per day resulted in 27% of patients achieving CMR and 38% of patients achieving MCyR.[51] In this population of CML patients, the median progression-free survival was 4.3 months.[51] The types and rates of adverse events reported in this study were similar to what has been shown in CP CML patients.[51]

Frontline Therapy With Dasatinib or Nilotinib

The currently available second-line BCR-ABL kinase inhibitors, dasatinib and nilotinib, are only approved for use in CML patients who are intolerant or resistant to prior imatinib therapy.[36,46] However, the efficacy and safety these agents have demonstrated as second-line options for CML treatment has prompted investigation into their utility a first-line therapeutic options.

A phase II trial of 37 newly diagnosed CP CML patients examined the efficacy of dasatinib at a dose of 100 mg/day for a period of 12 months.[52] At 12 months, 100% of the evaluable patients achieved a CCyR, and 32% had a MMR.[52] The cytogenetic response data was compared with two historical control groups that received either 400 mg or 800 mg of imatinib.[52] In comparison with either of the imatinib groups, significantly more dasatinib-treated patients achieved a CCyR.[52] The adverse event profile was similar to what has been reported in other dasatinib studies.[52] In 49% of patients, adverse event–related treatment interruptions occurred.[52]

In another study, 32 newly diagnosed CP CML patients received nilotinib at a dose of 400 mg/day and were assessed for up to 12 months.[53] Similar to what was seen in the dasatinib trial, 100% of the evaluable patients receiving nilotinib achieved a CCyR by 12 months, a value that was significantly higher than the historical control groups, which consisted of either 400 mg or 800 mg of imatinib.[53] The proportion of patients receiving nilotinib who achieved a MMR at 12 months was 45%, a value that significantly improved upon the values obtained in the imatinib historical control groups.[53] Adverse events seen in patients receiving first-line nilotinib were similar to what has been previously shown in patients receiving this agent as second-line therapy.[53] A total of 12 patients had adverse event–related interruptions in treatment administration. In summary, both studies that examined dasatinib or nilotinib as first-line therapy showed improvement in the rapidity and proportion of cytogenetic response, yet had less effect on depth and number of molecular responses with early follow-up, and acceptable toxicity, suggesting that further study is needed to fully understand the optimal role these agents will have in treating newly diagnosed CML.

Summary

For many institutions, imatinib is the first-line treatment of choice for CML. However, issues related to compliance, treatment failure, and intolerance to adverse events limit prolonged use of imatinib in a subset of CML patients. Related to the issue of treatment failure, imatinib is still not a proven curative option for CML. As a result, the second generation of BCR-ABL kinase inhibitors, dasatinib and nilotinib, have been introduced. Both of these second-line agents have shown the ability to successfully combat a variety of *BCR-ABL* mutations. These agents differ significantly, however, with regard to the adverse event profile, a factor that needs to be considered when deciding which agent to use in a particular patient. A major concern with the use of these second-generation BCR-ABL kinase inhibitors is selection for highly treatment-resistant versions of *BCR-ABL*, such as the T315I mutation, for which there is currently no approved agent. It has been suggested that combination therapy with a number of different agents, including multiple BCR-ABL kinase inhibitors, may be able to target both the immature stem cells and the more mature and differentiated hematopoietic cells in CML. Since long-term safety and efficacy data are currently lacking for both dasatinib and nilotinib, it is recommended that the use of these agents be limited to their indications.

The Future of CML Therapy: New Targets, Novel Agents, and Combinations

The currently available BCR-ABL kinase inhibitors have significantly improved treatment outcomes for many CML patients. However, even with the Federal Drug Administration (FDA) approval of second-generation BCR-ABL kinase inhibitors, therapy still fails either due to lack of treatment efficacy or adverse events. There are currently two major classes of BCR-ABL kinase inhibitors under development: Src/ABL kinase inhibitors (similar to dasatinib) and agents that specifically target the T315I *BCR-ABL* mutation. It is through the development of new agents that treatments for CML will continue to improve in efficacy and in their adverse events profiles.

Table 3. Efficacy of Bosutinib in Acclerated/Blast Phase CML Patients[56,57]

Efficacy in CP					
	CHR	**MCyR**	**CCyR**	**MMR**	**CMR**
IM only (n=115)	89%	41%	30%	33%	19%
Prior DAS or NIL (n=37)	77%	20%	–	16%	8%
Efficacy in Advanced Disease					
	HR	**CHR**	**MCyR**	**CCyR**	**MMR**
IM only (n=22)	43%	29%	30%	15%	23%
Prior DAS or NIL (n=23)	18%	9%	13%	13%	%

Table 4. Developmental Status of Selected CML Therapies With Specific Activity Against T315I BCR-ABL Mutants

Agent	**Current Development Stage**
MK-0457	Phase II (halted)
Homoharringtonine	Phase II
PHA-739358	Phase II
XL228	Phase I
AP24534	Phase I (filed)
SGX393	Preclinical

Src/ABL Kinase Inhibitors

Bosutinib (also known as SKI-606) is a Src/ABL kinase inhibitor that has been shown to be more potent than imatinib at inhibiting BCR-ABL kinase activity.[54,55] A phase I/II study was conducted in which 18 CP patients with relapsed, refractory, or imatinib intolerant CML were administered 400, 500, or 600 mg per day of bosutinib for between 30 and 192 days.[56] Most toxicities were grade 1 or 2, with diarrhea being the most common adverse event.[56] A dose reduction was required in 5 patients in the 600 mg group for the occurrence of grade 3 rash and thrombocytopenia.[56] A CMR was achieved in all relapse patients, and of the 7 patients treated for longer than 12 weeks, 3 achieved a CCyR.[56] Of the 7 patients with a CMR, 6 had imatinib-resistant BCR-ABL mutations, including T315I.[56] Of importance was the finding that bosutinib did not result in pleural effusion or pulmonary edema.[56] Based on the observed toxicities, 500 mg/day was determined to be the dose of bosutinib to use in further clinical investigation.

Phase II studies of bosutinib are currently under way, though only preliminary results have been reported. In 98 CP CML patients for whom imatinib therapy failed, bosutinib was administered at 500 mg/day with a median treatment duration of 5.1 months.[55] In patients resistant to imatinib 42% achieved a MCyR and 33% had a CCyR, whereas 57% of those intolerant to imatinib achieved an MCyR and 43% had a CCyR.[55] A MMR was achieved in 33% of evaluable imatinib-resistant patients.[55] Gastrointestinal adverse events were most frequent (usually grade 1 or 2). Common grade 3 or higher adverse events included thrombocytopenia (9%), neutropenia (8%), increased alanine aminotransferase (6%), and rash (9%).[55] One patient developed pleural effusion.[55]

Another phase II trial examined the efficacy of 500 mg/day bosutinib in patients with AP and BP CML for whom previous therapy with BCR-ABL kinase inhibitors failed.[54] Of the 57 patients examined, a CMR was achieved by 29% of AP patients and 25% of BP patients.[54] In patients exposed only to prior imatinib, 36% had a MCyR, and in patients exposed to multiple BCR-ABL kinase inhibitors, 30% had an MCyR.[54] The adverse events were similar to those found in previous trials of bosutinib; though in this trial, fluid retention was reported in 14% of patients, and 3% of subjects reported pleural effusion.[54]

INNO-406 is another Src/ABL kinase inhibitor being developed for the treatment of CML. Phase I data have examined the effect of INNO-406 (30–1,060 mg/day) in 41 imatinib-intolerant or imatinib-resistant patients in varying stages of CML for a median period of 42 days.[57] Of the 41 patients initially participating in the study, 22 discontinued due to disease progression, 4 stopped treatment with INNO-406 to pursue other treatment options, and 1 withdrew due to toxicity.[57] CCyR was achieved in 29% of the patients who did not respond to imatinib, including 1 patient with a MMR and 1 patient with a minor CR.[57] In CP patients who did not respond to previous BCR-ABL kinase inhibitor therapy, 1 had a CCyR; 2 patients in the AP group achieved a CMR.[57] A significant adverse event was the reversible grade 2 or 3 elevation of transaminase levels. Dose-limiting toxicity was reported in 1 patient receiving twice daily 480 mg of INNO-406.[57] The study concluded by confirming that twice daily dosing of 240 mg of INNO-406 was the recommended dose to be used for further clinical study.[57]

T315I BCR-ABL Kinase Inhibitors

The currently available second-generation BCR-ABL kinase inhibitors have shown the ability to effectively treat patients with a number of imatinib-resistant BCR-ABL kinase mutations. Unfortunately, none of the currently available pharmacologic therapies for CML are active

against the T315I BCR-ABL mutation.[37] New agents are being developed that specifically target the T315I mutation, some of which are still in preclinical development and a number of which have been tested in humans.

A previously studied agent, homoharringtonine (HHT), is the furthest along in clinical development, with a series of phase II clinical trials having been reported. In one open-label phase II clinical trial, 19 treatment-resistant CML patients with the T315I mutation received subcutaneous HHT at a dose of 1.25 mg/m^2 twice per day for 14 days on a 28 day cycle until a hematologic response occurred.[58] These patients could also receive maintenance therapy at the same dose, but for 7 days in a 28-day cycle for a maximum of 24 months.[58] Adverse events reported in patients receiving HHT included coronary syndrome, neutropenia, and thrombocytopenia.[58] No patient was removed from therapy because of adverse events, though 4 patients experienced progressive disease and were removed from the study.[58] T315I transcript levels were undetectable in 1 AP patient and 4 CP patients. Two patients achieved CMR.[58]

Aurora kinases are involved in normal chromatid segregation and their overexpression is believed to play a role in tumorigenesis.[59] PHA-739358 is an aurora kinase inhibitor that is believed to be effective against CML because of its dual activity against aurora kinase and BCR-ABL kinase, including the T315I mutant.[60] An important in vitro finding that may prove clinically useful is the pharmacologic synergism that occurs when imatinib and PHA-739358 are combined with imatinib-resistant leukemia cell lines.[60]

A phase II trial was recently reported that examined the efficacy and safety of subcutaneous PHA-739358 (250 or 330 mg/m^2 per day for 3 consecutive weeks every month) in CML patients with the T315I mutation who did not respond to prior BCR-ABL kinase therapy.[61] In 2 of 6 patients with the T315I mutation, a CMR was achieved, and 1 of these patients had both a CCyR and CMR after 3 months of therapy.[61] In the second patient that achieved a CMR, a minor CR was reached after 3 treatment cycles, though a minimal CR persisted after 9 months of therapy. Grade 4 neutropenia and an infusion reaction were reported in 1 patient.[61]

Another agent with activity against aurora kinase is MK-0457, which also inhibits FLT3, JAK-2, BCR-ABL kinase, and various mutated (including T315I) forms of BCR-ABL kinase.[62] A phase I dose-finding study examined doses of MK-0457 ranging from 8 to 32 mg/m^2 per hour in 15 CML patients (11 patients had the T315I mutation).[62] Of the 14 evaluable patients, 11 had either a hematologic, cytogenetic, or molecular response, including all the patients with the T315I mutation.[62] No significant adverse events were reported. Further study will examine the effect of 36 mg/m^2 per hour of MK-0457.[62]

Summary

The currently approved BCR-ABL kinase inhibitors, dasatinib and nilotinib, have proven effective in treating CML patients who are resistant or intolerant to imatinib. However, some patients become resistant or intolerant to the effects of these agents. Furthermore, such agents become less effective in more advanced disease. It is therefore important to continue the search for new compounds that improve upon the efficacy and tolerability of currently available BCR-ABL inhibitors. Several compounds are in preclinical or clinical development and the results are promising. A number of agents are showing initial efficacy and minimal adverse events in the treatment of pharmacotherapy-resistant T315I mutations. Further development of these agents will seek to better optimize dosing and administration protocols, and also to determine long-term efficacy and safety.

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Advancing CML Patient Care: Closing in on a Cure?

Posttest Questions *Circle the correct answer for each question below.*

1. When examining a CML patient for minimal residual disease, which of the following diagnostic tests is preferred?
   a. Cytogenetics
   b. Fluorescence in situ hybridization (FISH)
   c. Reverse transcriptase polymerase chain reaction (RT-PCR)
   d. A + C
   e. B + C

2. The accelerated and blast phases of CML are not associated with an increased probability of imatinib resistance?
   a. True b. False

3. Which of the following represents the most frequent cause of imatinib resistance?
   a. BCR-ABL amplification
   b. BCR-ABL mutations
   c. Dysfunction of non-BCR-ABL kinases
   d. Presence of quiescent CML cells

4. Which of the following BCR-ABL phenotypes is insensitive to both imatinib and nilotinib?
   a. A380S b. F317V
   c. M351T d. T315I

5. Which of the following agents used in the treatment of CML is known to have significant inhibitory activity against Src kinase?
   a. Dasatinib b. Imatinib c. Nilotinib
   d. A + C e. A + B

6. Which of the following agents in development is specifically associated with the development of fluid retention?
   a. INNO-406
   b. MK-0457
   c. SGX-393
   d. SKI-606

7. The likelihood of disease progression in CML is highest at what time point after the initiation of imatinib therapy?
   a. 1 year b. 2 years c. 3 years d. 4 years

8. Which of the following statements regarding CML stem cells is false?
   a. CML stem cells can populate up to 1.0% of the CD34+ stem cells
   b. Imatinib resistant
   c. Prevent cure of CML
   d. Produce Ph+ hematopoietic cells

9. Which of the following agents has not been examined as frontline therapy in patients with newly diagnosed CML?
   a. Dasatinib b. Bosutinib c. Nilotinib
   d. A + B e. B + C

10. Which of the following agents currently under development for the treatment of CML specifically target T315I mutations?
    a. INNO-406 b. PHA-739358 c. XL-228
    d. A + C e. B + C

Activity Evaluation Form: **Release date:** January 2009 **Expiration date:** January 31, 2010

Participants requesting credit must read and review the CME activity. A certificate will be issued only upon receipt of a completed activity posttest with a score of 70% or better, along with a completed evaluation and certificate information form.
Participants requesting CME credit can submit their posttest, evaluation, and certificate information form in any of the following ways:
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Fax: (610) 636-7410; **Online:** http://www.curatiocme.com/posttest/cmesupp

If you mail or fax your completed posttest, evaluation, and certificate information form, your certificate will be sent to you in approximately 4 to 6 weeks.

CERTIFICATE INFORMATION Please complete to receive credit for this program. Please print clearly.

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Please check one: ✹ MD ✹ DO ✹ Non-Physician I claim _____ *AMA PRA Category 1 Credits*™ <up to 1.5 credits>.
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Posttest answers: Please fill in your answers to the right: 1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10____

Signature _____

✹ I would like to receive information about future educational activities on the topic of neuropathic pain.

(Evaluation continues on the following page.)

EVALUATION

1. Please rate on a 5-point scale (1=Poor; 5=excellent).

	Poor				Excellent
• Clinical Concepts in CML Diagnosis and Management: The Importance of Assessing Minimal Residual Disease in CML Following Therapy					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5
• Current Challenges to CML Disease Eradication: Incidence and Mortality of CML					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5
• Clinical Decisions in the Care and Treatment of Patients with CML: The Patient Who Does not Respond to Therapy					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5
• The Future of CML Therapy: New Targets, Novel Agents, and Combinations					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5

2. This activity was fair, balanced, and free of commercial bias. ✹ Yes ✹ No

If you felt the activity was biased, please explain: _____

3. Please rate how well the following learning objectives were met:

	Poor				Excellent
• Explain the relevance of achieving cytogenetic and molecular remission following therapy for CML with respect to progression-free survival and overall survival	1	2	3	4	5
• Identify the methods used to assess molecular remission and their level of sensitivity in detecting minimal residual disease	1	2	3	4	5
• Explain the mechanisms of imatinib mesylate resistance and the novel strategies developed to overcome this resistance	1	2	3	4	5
• Describe the options available for imatinib mesylate-resistant or -relapsing disease and their rationale for use in CML	1	2	3	4	5

(If you felt the learning objectives were not met, please explain.) _____

_____

4. This educational activity has contributed to my professional effectiveness and improved my ability to do the following:

	Strongly Disagree				Strongly Agree
• Identify patients for treatment	1	2	3	4	5
• Treat/manage patients	1	2	3	4	5
• Improve standard of care	1	2	3	4	5

5. After participating in this activity, I am committed to making a change in my practice.

Please rate on a 5-point scale (1=Strongly Disagree; 2=Strongly Agree) 1 2 3 4 5

6. If you are committed to making a change in your practice, list what changes you plan on making. _____

_____

7. What were the strengths of this activity? _____

_____

8. Questions or comments regarding this activity _____

9. How did you hear about this activity? (Please check all that apply.)

✹ Direct mailing ✹ Curatio Web site ✹ Announcement postcard ✹ Colleague ✹ E-mail

✹ Other (Please specify.) _____

10. Suggested topics and/or speakers you would like for future programs: _____

11. What is/are your preferred format(s) for earning continuing medical education credits? (Please check all that apply.)

✹ Satellite symposium ✹ Grand rounds ✹ CD-ROM ✹ Dinner meetings ✹ Internet activities ✹ Podcast