SUPPLEMENT

Current Issues in Chronic Myeloid Leukemia: Monitoring, Resistance, and Functional Cure

Jorge Cortes, MD; John M. Goldman, DM, FRCP, FRCPath, FMedSci; and Timothy Hughes, MD, MBBS

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Program Overview

Despite the success with tyrosine kinase inhibitors (TKIs) in most patients with chronic myeloid leukemia (CML), some patients still experience resistance or intolerance and need alternative therapies. How to best assess response to TKI therapy, including how to define suboptimal response versus treatment failure and how monitoring should be conducted, remains controversial. Strategies for overcoming imatinib resistance and preventing it are currently available, but additional options are needed. Several investigational therapies are currently being evaluated as a means of overcoming resistance to imatinib and second-generation TKIs, including ponatinib (AP24534), omacetaxine, and bosutinib (SKI-606). Allogeneic hematopoietic stem cell transplant has also demonstrated efficacy in patients with imatinib-resistant disease. New next-generation TKIs and alternative therapies, once made available, will open new questions regarding optimal selection and sequencing. Finally, a question as to whether a functional cure is now an achievable goal and how it may be realized has become an area of clinical investigation.

This article was adapted from a case-based roundtable discussion titled, Monitoring, Treatment Resistance, and Treatment Failure in Chronic Myeloid Leukemia: Breaking Barriers to Improved Outcomes and Looking Forward to a Cure, which was held in conjunction with the European School of Haematology (ESH) – International Chronic Myeloid Leukemia Foundation (iCMLf) 14th International Conference on Chronic Myeloid Leukemia: Biology and Therapy, held September 20–23, 2012 in Baltimore, MD.

Target Audience

This activity is designed for physicians, physician assistants, nurses, nurse practitioners, and other health care professionals who have an interest in enhancing their knowledge and understanding of the management of chronic myeloid leukemia.

Learning Objectives

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

- Demonstrate appropriate management of patients with CML regarding current practice guideline recommendations for treatment response monitoring and tailoring of therapy based on responses
- Relate causes of primary and secondary resistance, the molecular mechanism underlying TKI-mediated resistance mutations, appropriate testing and monitoring for early detection of the occurrence of mutations, tailoring of therapy based on type of mutation(s), and current and emerging interventions to overcome them
- Convey clinical findings relating to efficacy and safety, as well as trial limitations for agents undergoing investigation for overcoming the T315I mutation, including mechanisms of action, their potential role in the future treatment paradigm, and the importance of clinical trial referral for such patients
- Outline how a cure for CML might be defined and what future strategies may achieve this outcome

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This material has been prepared based on a review of multiple sources of information, but it is not exhaustive of the subject matter. Participants are advised to critically appraise the information presented, and are encouraged to consult the above-mentioned resources as well as available literature on any product or devise mentioned in this program.
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Expected time to complete this activity as designed: 60 minutes

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**Current Issues in Chronic Myeloid Leukemia: Monitoring, Resistance, and Functional Cure**

Jorge Cortes, MD; John M. Goldman, DM, FRCP, FRCPath, FMedSci; and Timothy Hughes, MD, MBBS

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**Abstract**

Despite the success with tyrosine kinase inhibitors (TKIs) in most patients with chronic myelogenous leukemia (CML), some patients still experience resistance or intolerance and need alternative therapies. Monitoring response to TKI therapy is a critical component of managing CML, and molecular response seems to be the most important milestone for predicting long-term outcomes. How best to assess response, including how to define treatment failure, and how monitoring should be conducted remain controversial. Strategies for overcoming imatinib resistance include increasing the imatinib dose or switching to a second-generation TKI. Another approach is to use higher doses of imatinib or second-generation TKIs up front to increase the rate of earlier responses, with the hope that this will translate into a reduced risk of resistance. Several investigational therapies are also being evaluated as a means of overcoming TKI resistance, including ponatinib (AP24534), omacetaxine, and bosutinib (SKI-606). Allogeneic hematopoietic stem cell transplantation has also shown efficacy in patients with imatinib-resistant disease. Alternatives to long-term TKI therapy that are currently being explored include discontinuation of treatment and eradication of minimal residual disease with investigational treatment regimens, such as those involving interferon, hydroxychloroquine, BCL6 inhibitors, and the smoothened antagonists LDF225 and BMS-833923. (JNCCN 2012;10[Suppl 3]:S1-S13)

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The treatment landscape for chronic myelogenous leukemia (CML) dramatically changed after the FDA approved the tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec, Novartis) in 2001. Imatinib targets BCR-ABL, a fusion protein expressed by the Philadelphia (Ph) chromosome, the result of a chromosomal translocation between chromosomes 9 and 22 that is present in 95% of patients with CML.\(^1\) However, not all patients experience a response to imatinib therapy, and some of those who do eventually develop resistance to this agent. Although many patients have benefited from the introduction of the second-generation TKIs, namely dasatinib (Sprycel, Bristol-Myers Squibb) in 2006 and nilotinib (Tasigna, Novartis) in 2007, resistance is often evident with these agents, especially if there was minimal response to imatinib. Therefore, TKI resistance remains an impediment to successful CML treatment for a small but significant subset of patients. To adequately address resistance to TKI therapy, uniform methodologies for assessing response and defining treatment failure must be established and used. These issues and strategies for overcoming resistance, including the use of emerging therapies, and obtaining a functional cure are described in this article.

**Assessment of Response**

Monitoring response to TKI therapy in patients with CML is a critical component of patient management. Assessment of response to therapy includes evaluation of hematologic, cytogenetic, and molecular responses (Table 1).\(^2,4\) Hematologic response is defined as normalization of WBC count and splenomegaly. In contrast, both cytogenetic and molecular response evaluations focus on the assessment of the BCR-ABL abnormality. Cytogenetic response is determined by the percentage of cells with Ph+ metaphases, whereas assessment of molecular response relies on quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) to measure BCR-ABL transcripts, best expressed on the International Scale (IS).\(^5\) On the IS, a major molecular response (MMR) is defined as a BCR-ABL transcript level of 0.1% or less, which represents a 3-log reduction from a standardized baseline.\(^2\) A complete molecular
The ELN and NCCN Guidelines recommendations were based largely on response data from the IRIS (International Randomized Study of Interferon and STI571) study, which compared the efficacy and safety of imatinib versus interferon alpha (IFN-α) plus low-dose cytarabine in patients with newly diagnosed CML and included an 8-year follow-up report, and clinical experience. Some differences exist between the ELN and NCCN Guidelines recommendations, however (Table 2).

The ELN defines failure and suboptimal response as not achieving the distinct response milestones shown in Table 1 with respect to specific time points. The ELN and NCCN Guidelines recommendations were based largely on response data from the IRIS (International Randomized Study of Interferon and STI571) study, which compared the efficacy and safety of imatinib versus interferon alpha (IFN-α) plus low-dose cytarabine in patients with newly diagnosed CML and included an 8-year follow-up report, and clinical experience. Some differences exist between the ELN and NCCN Guidelines recommendations, however (Table 2). The ELN defines failure and suboptimal response and includes an additional response category (warnings), whereas the NCCN Guidelines do not formally define suboptimal response, but rather define failure and suboptimal response.
Table 2  Response Criteria in Patients With Chronic-Phase Ph+ CML as Defined by the ELN and the NCCN\(^a,b\)

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal Response</th>
<th>Suboptimal Response</th>
<th>Failure</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td>CHR and at least a minor CyR</td>
<td>No CyR</td>
<td>&lt; CHR</td>
<td>BCR-ABL &gt; 10% by qRT-PCR (IS) or &lt; PCyR on bone marrow cytogenetics</td>
</tr>
<tr>
<td></td>
<td>(BCR-ABL \leq 10%) by qRT-PCR (IS) or PCyR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6 mo</td>
<td>At least PCyR</td>
<td>&lt; PCyR</td>
<td>No CyR</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12 mo</td>
<td>CCyR</td>
<td>PCyR(^c)</td>
<td>&lt; PCyR(^c)</td>
<td>&lt; MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>18 mo</td>
<td>MMR</td>
<td>&lt; MMR</td>
<td>&lt; CCyR</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>CCR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Any time during treatment(^d)</td>
<td>Stable or improving MMR</td>
<td>Loss of MMR</td>
<td>Loss of CHR</td>
<td>Increase in transcript levels CCA/Ph+(^e)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCR-ABL KD mutations (still sensitive to imatinib)</td>
<td>Loss of CCyR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCR-ABL KD mutations (poorly sensitive to imatinib)</td>
<td>CCA/Ph+(^d)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCA, clonal chromosome abnormalities; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CyR, cytogenetic response; ELN, European LeukemiaNet; IS, International Scale; KD, kinase domain; MMR, major molecular response; NA, not applicable; NCCN, National Comprehensive Cancer Network; PCyR, partial cytogenetic response.

\(^a\)ELN criteria refer to previously untreated patients with early chronic-phase CML who are treated with imatinib, 400 mg daily.\(^1\)

\(^b\)NCCN criteria refer to previously untreated patients with chronic-phase Ph+ or BCR-ABL+ CML who are treated with imatinib, 400 mg daily; nilotinib, 300 mg twice daily; or dasatinib, 100 mg daily.\(^4\)

\(^c\)NCCN treatment response criteria that differ from ELN criteria are noted in boldfaced entries.

\(^d\)Refers only to ELN recommendations.


fine target responses at specific time points. These definitions continue to evolve. The NCCN recently updated the treatment algorithm (discussion to follow), with only the 12-month evaluation including a response category corresponding to the ELN suboptimal response category.\(^1\) Revised recommendations from the ELN are expected shortly.

The definition of suboptimal response remains controversial; most notably, some investigators have suggested that overlap exists between the ELN treatment failure and suboptimal response categories.\(^9\) According to the ELN recommendations, patients with a suboptimal response may still experience a substantial benefit from continuing imatinib therapy, although the long-term outcome of treatment would not be as favorable as that for patients who experience an optimal response.\(^2\) Patients with a suboptimal response to imatinib (according to ELN criteria) at 6 and 12 months have been shown to have a worse long-term prognosis, including lower probability of experiencing a complete cytogenetic response (CCyR), and a greater risk of disease progression compared with patients who experience an optimal response.\(^9,10\)
Importance of Molecular Response

Molecular response seems to be an important milestone for predicting long-term outcomes. In a study of 85 patients with CML treated with imatinib, Press et al. showed that failure to achieve a 2-log reduction in BCR-ABL transcript level at the time of CCyR or a 3-log reduction at any time thereafter (median follow-up, 13 months) experienced significantly shorter progression-free survival (PFS). Based on an analysis of data from the Australasian substudy of the IRIS trial, Hughes and Branford suggested...
that patients who achieve only a 1-log reduction in BCR-ABL transcript at 3 months have a much lower probability of achieving a MMR (13% at 30 months) than those with a 1- to 2-log reduction (69%) or those with more than a 2-log reduction (100%). Importantly, a significantly higher risk of resistance (83%) was found for those with a 1-log reduction or less compared with those with a 1- to 2-log reduction (5%) and those with more than a 2-log reduction (0%).

Long-term data from the IRIS trial indicated that patients with transcript levels greater than 10% and greater than 1% at 6 and 12 months, respectively, had shorter event-free survival (EFS) and a higher rate of progression than those with better molecular responses, whereas patients who achieved MMR (BCR-ABL transcript levels ≤0.1% on the IS) experienced durable responses, no progression to accelerated-phase (AP) or blast-phase (BP) disease, and 95% EFS at 7 years (Figure 1). Several follow-up studies have indicated that a BCR-ABL transcript level greater than 10% on the IS at 3 months after initial treatment with imatinib or dasatinib is associated with poorer outcomes, including shorter PFS, shorter overall survival (OS), and lower probabilities of CCyR and MMR. Additional studies have confirmed the predictive value of early molecular response in patients receiving TKIs. In a study of 282 patients with chronic-phase (CP) CML who received imatinib as first-line therapy followed by dasatinib or nilotinib if treatment with imatinib failed, BCR-ABL transcript measurements performed at 3, 6, or 12 months after the start of imatinib therapy were indicative of patient outcomes, including OS, PFS, and cytogenetic response. Consistent with the study results described earlier, the 3-month assessment was the most strongly predictive. Patients with BCR-ABL transcript levels each greater than 8.5% to 9.8% on the IS at 3 months had shorter OS, shorter PFS, shorter EFS, and were less likely to obtain CCyR compared with patients with lower BCR-ABL transcript levels. Similarly, transcript levels greater than 1.67% at 6 months and greater than 0.53% at 12 months were predictive of poor outcomes.

The predictive value of early molecular response has also been shown in patients with newly diagnosed CML receiving dasatinib as first-line therapy. In this study, patients with BCR-ABL transcript levels greater than 10% at 3 months experienced a

Figure 1 Event-free survival at (A) 6-, (B) 12-, and (C) 18-month landmarks according to molecular response in patients who received imatinib in the International Randomized Study of Interferon and STI571. From Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood 2010;116:3762. Copyright 2010. Reproduced with permission of American Society of Hematology (ASH).
significant lower rate of CCyR and MMR than patients with lower transcript levels. A cutoff value of 2.2% on the IS at 3 months was predictive of CCyR (this cutoff is lower than that for imatinib described earlier, underscoring the different response kinetics between the agents), and values of 0.92% and 0.57% were predictive of 3-log and 4.5-log reductions, respectively. The results of these studies support the use of earlier molecular testing to assess response in patients with CML, and the 3-month 10% or less BCR-ABL (IS) response cutoff was recently incorporated into the NCCN treatment algorithm.4

No currently available trial data provide information about whether early treatment modification based on early failure improves outcomes in patients with CML receiving imatinib therapy. However, achievement of a BCR-ABL transcript level of less than 10% on the IS using peripheral blood qRT-PCR was shown to be associated with improved outcomes in imatinib-resistant or -intolerant patients who were treated with dasatinib20 or nilotinib.21

Resistance

Approximately 20% to 30% of patients with CML develop either primary or secondary resistance to imatinib.22 Patients with primary resistance (also called refractoriness) exhibit a lack of response to imatinib, characterized by the failure to achieve preset milestones, from the start of therapy. In contrast, patients with secondary resistance (also called acquired resistance) initially experience a response to imatinib but later lose this response.22,23

The underlying mechanisms of resistance to imatinib therapy can be classified as being pharmacologic, leukemia cell–related, or patient-related (ie, poor adherence). Pharmacologic mechanisms include poor intestinal absorption, drug interactions, and drug binding to plasma components, all of which can ultimately affect BCR-ABL kinase inhibition from failure to deliver an effective concentration of imatinib to target cells.22,23 Leukemia cell–related mechanisms represent a major contributor to resistance. Resistance to imatinib may be related to the intrinsic heterogeneity of the disease in different patients, including the presence of quiescent stem cells that are intrinsically resistant to imatinib therapy.22 Amplification of BCR-ABL can lead to resistance through increasing the amount of the target protein needed to be inhibited by a therapeutic dose of imatinib. CML cells that overexpress BCR-ABL have been shown to be less sensitive to imatinib, to yield mutant subclones that are resistant to imatinib, and to acquire mutations at a faster rate than cells with low BCR-ABL expression.22 Recently, activity of the major active influx pump for imatinib, organic cation transporter-1 (OCT-1), has been shown to be predictive of major molecular response to imatinib at 12 and 24 months, and both OS and EFS, with low activity of OCT-1 implicated as an important cause of imatinib failure.24,25 Functional variations in the multidrug transporter protein MDR1 have also been implicated as contributors to resistance through increasing efflux of imatinib.26 Experiments with members of the SRC family kinase (SFK) group of proteins have suggested that many of them are involved in imatinib and nilotinib resistance, although the precise roles of each SFK member have not yet been elucidated.22,27,28 Finally, clonal evolution, characterized by the acquisition of additional cytogenetic abnormalities in proliferating CML cells, has also been identified as a mechanism for resistance.22

Mutations in the kinase domain of BCR-ABL are thought to be a primary cause of resistance in patients with CML, being implicated in up to 40% to 60% of cases of secondary resistance.29,30 More than 100 distinct point mutations responsible for single amino acid substitutions in the BCR-ABL kinase domain have been identified to date.22 However, 85% of mutations occur as a result of 15 amino acid substitutions occurring at 7 main sites. Although it is only present in approximately 15% of patients who develop mutations on imatinib, the T315I mutation remains one of the most important mutations underlying resistance to imatinib and other TKIs.22 Limited data are available regarding the implications of the T315I mutation on patient survival. A retrospective analysis of patients with imatinib-resistant CP-, AP-, and BP-CML showed that patients with T315I mutations had worse OS (12.6 months) than those with other mutations (end point not reached).31 In patients with CP-CML, T315I mutations were associated with worse PFS. A recent analysis of BCR-ABL mutations in Latin American patients with imatinib-resistant CML receiving second-generation TKIs and other treatments showed that patients with the T315I mutation had a poorer OS and PFS compared with patients with other mutations (21% vs.
tations that are present below the detection limit of conventional direct sequencing by sensitive techniques, such as mass spectrometry, may assume increasing importance, because the presence of such mutations at switchover has also been shown to be highly predictive of outcome. 37

An alternative strategy is to use higher doses of imatinib or second-generation TKIs up front to increase the rate of earlier responses with the hope that

### Strategies for Overcoming Resistance

Several strategies are being used and/or explored for treating patients with imatinib-resistant CML. The first involves increasing the imatinib dose. Although supportive data for this strategy are generally lacking, imatinib dose increases have been highly effective in some patients. 33 A second strategy entails switching from imatinib to the second-generation TKIs, dasatinib and nilotinib. The results of 4 single-arm, multicenter studies that evaluated dasatinib in patients with CML resistant to or intolerant of imatinib indicated that those with CP-CML experienced a 45% major cytogenetic response (MCyR) rate and a 33% CCyR rate. 34

Major hematologic response rates in patients with AP-CML, myeloid CML, and lymphoid blast CML were 59%, 32%, and 31%, respectively. In a study of patients with imatinib-resistant CP-CML, nilotinib treatment resulted in a 44% MCyR rate and a 46% CCyR rate; 56% of patients in the latter group also experienced a MMR. 35

Analysis of BCR-ABL mutation status is critical for determining the best treatment strategy, including the selection of dasatinib versus nilotinib, for patients with CML experiencing imatinib resistance. Detailed analyses have revealed that some BCR-ABL mutations are less sensitive to dasatinib, whereas others have reduced sensitivity to nilotinib. Table 4 lists those mutations that are clinically relevant, those with minimal impact on response, and those for which more data are needed. 36 Evaluation of mutations that are present below the detection limit of conventional direct sequencing by sensitive techniques, such as mass spectrometry, may assume increasing importance, because the presence of such mutations at switchover has also been shown to be highly predictive of outcome. 37

An alternative strategy is to use higher doses of imatinib or second-generation TKIs up front to increase the rate of earlier responses with the hope that

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. Detected</th>
<th>% Patients With Mutations (n = 386)</th>
<th>% of All Mutations (n = 503)</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
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<tr>
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</tr>
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<td>6</td>
<td>1.6</td>
<td>1.2</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

The mutations listed in this table accounted for 88% of all of the mutations identified at this institution.

Class A indicates currently no compelling clinical evidence to suggest that the mutation would not respond to the inhibitor. Class B indicates that in vitro assessment consistently indicates that the mutation may confer intermediate insensitivity/resistance to the inhibitor, or clinical evidence may be suggestive of reduced sensitivity. At this stage, the presence of these mutations should have no impact on clinical decisions and additional clinical assessment is required before an alternative inhibitor would be recommended. Class C indicates that compelling clinical evidence recommends an alternative inhibitor; V299L, which is very rarely detected in imatinib-treated patients, is a dasatinib class C mutation. Class D indicates no role for second-generation TKI therapy (these mutations represent targets for emerging therapies, such as ponatinib and omacetaxine).

this will translate into a reduction in cases of resistance. Results of recent studies suggest that both nilotinib and dasatinib may be superior to imatinib as front-line therapy. In the phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients) trial, in which nilotinib and imatinib were compared in patients with newly diagnosed CML, nilotinib treatment resulted in significantly higher MMR rates at 12 months (44% and 43% for the 300-mg twice-daily and 400-mg twice-daily doses, respectively) compared with imatinib (22%; P < .001), and significantly higher CCyR rates (80% and 78% for the 300- and 400-mg doses, respectively, vs. 65%; P < .001).38 At 3 years, the rate of transformation to AP and BP was significantly lower for nilotinib- versus imatinib-treated patients.39 In the phase III DASISION (Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients) trial, patients who received dasatinib experienced significantly higher rates of CCyR (77% vs. 66%; P = .007) and MMR (46% vs. 28%; P < .0001) than those treated with imatinib.40 However, 24-month OS was similar between the treatment arms (≈95%).41 These results were confirmed in the phase II SWOG study, which also compared dasatinib and imatinib in patients with newly diagnosed CP-CML. Data from this study suggested that dasatinib treatment induces a deeper molecular response at 12 months (median 3.3-log reduction vs. 2.8-log reduction with imatinib), although the proportions of patients achieving greater than either 4- or 5-log reductions did not differ significantly between groups.42

The benefit of switching patients from imatinib to a second-generation TKI while in CMR was addressed in the ENESTcmr (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—CMR) study.43 Patients with CP-CML who had achieved a CCyR while on imatinib for at least 24 months but who had BCR-ABL+ disease detected on real-time qRT-PCR were randomized to remain on imatinib or switch to nilotinib. Twelve-month results from this trial indicated that the rates of CMR (23.1% vs. 10.7%; P = .02) and MMR (75.0% vs. 35.7%; P = .006) were significantly higher in patients who switched to nilotinib than in those who remained on imatinib. Additional strategies for overcoming imatinib resistance include clinical trials with new agents and/or combinations, and allogeneic hematopoietic stem cell transplantation, which is discussed subsequently.

Emerging Therapies

Several investigational therapies are currently in late-stage trials for use in the treatment of CML, including ponatinib, omacetaxine, and bosutinib. Ponatinib (AP24534) is an orally administered, small-molecule, pan–BCR-ABL inhibitor that was developed as part of a design strategy to create compounds that do not interact with T315I in native ABL but are able to inhibit ABLT315I activity.44 Biochemical and cellular assays showed that AP24534 inhibited growth, proliferation, and signaling mediated by native BCR-ABL and all BCR-ABL mutants tested, including BCR-ABL T315I.44 Ponatinib is currently being evaluated in the PACE (Ponatinib Ph+ ALL and CML Evaluation) trial in patients with refractory CP-, AP-, or BP-CML that is resistant or intolerant to dasatinib or nilotinib, or that carries the resistant T315I mutation.45 Interim results from this trial reported at the 2011 ASH Annual Meeting indicated that of 83 patients with CP-CML assessable at 3 months, 41% of patients with resistance or intolerance to dasatinib or nilotinib and 65% of patients with T315I disease experienced an MCyR.45 A phase II trial designed to evaluate ponatinib as front-line therapy in patients with Ph+ (as determined with cytogenetics or FISH) or BCR-ABL+ (as determined by PCR) CML in early CP-CML is currently enrolling patients (ClinicalTrials.gov identifier: NCT01570868). A randomized, open-label, phase III trial comparing ponatinib and imatinib as front-line therapy in patients with Ph+ acute lymphoblastic leukemia was submitted to the FDA in July 2012 as part of a rolling submission process.

Omacetaxine mepesuccinate (formerly called homoharringtonine) is a cephalotaxine ester derived from the Chinese evergreen tree, Cephalotaxus harringtonia.46 In preclinical studies, omacetaxine was shown to improve survival of mice with native BCR-ABL− or BCR-ABL T315I–induced CML and to suppress proliferation of native BCR-ABL or BCR-ABL T315I leukemic stem cells.46 In fact, omacetaxine seemed to inhibit BCR-ABL T315I cell proliferation to a greater degree than native BCR-ABL cell proliferation.46 Two phase II, open-label studies have evaluated omacetaxine in patients with CML. In a small
study of 7 patients with CP-CML resistant to TKI therapy and harboring the BCR-ABL
mutation, all who received subcutaneous omacetaxine showed complete hematologic response (CHR) after a median follow-up of 11 months, and 6 showed a rapid decline and sustained disappearance of T315I-mutated transcripts. Interim results from a trial of 62 patients with imatinib-resistant CP-CML and BCR-ABL
mutation disease indicated that 76% of patients experienced a CHR and 24% achieved an MCyR at a median follow-up of 19.1 months. In an open-label study in 30 patients with CP-CML with resistance or intolerance to 2 or 3 TKIs, omacetaxine treatment resulted in an 80% CHR rate and a 20% MCyR rate. An analysis of the 2 omacetaxine studies described earlier compared results between patients with CP-CML and those with AP-CML and between those who received 2 versus 3 TKIs. Among patients with CP-CML, the MCyR rate was 20% (median duration, 18 months) and 69% of patients achieved a CHR (median duration, 12.2 months); median OS was 34 months. Patients with AP-CML achieved a 24% CHR rate. Responses were observed, but at lower rates, in patients who received 3 versus 2 TKIs. Despite these positive results, approval of omacetaxine has been slowed down by a request from the FDA for a well-defined in vitro diagnostic assay that can identify patients with the BCR-ABL
mutation (ie, the presumed omacetaxine target population). Once this assay is developed and validated, FDA approval of omacetaxine is expected due to its ability to address BCR-ABL
mutation disease.

Bosutinib (SKI-606) is small molecule dual inhibitor of both Src and ABL kinases. Bosutinib has been shown to inhibit proliferation and survival of BCR-ABL+CML cell lines and to induce regression of CML tumor xenografts in mice. A phase I/II study evaluated bosutinib in patients with CP-CML for whom imatinib (CP2L cohort) or imatinib plus dasatinib and/or nilotinib (CP3L cohort) failed and in patients with AP-CML for whom any TKI failed (ADV cohort). Patients without and with BCR-ABL mutations experienced CHR rates of 90% and 83%, 77% and 67%, and 39% and 17% in the CP2L, CP3L, and ADV cohorts, respectively. A detailed analysis of patients in the CP3L arm revealed a 32% MCyR rate, 24% CCyR rate, and 73% CHR rate. Responses were observed across all mutations, except for T315I. The phase III BELA (Bosutinib Efficacy and safety in chronic myeloid Leukemia) trial compared bosutinib with imatinib as front-line therapy in newly diagnosed CP-CML. Although efficacy was comparable for patients who stayed on-study, the trial did not meet the primary end point of CCyR at 12 months, most likely because of the higher discontinuation rate in the bosutinib arm from adverse events (primarily gastrointestinal). At 24 months, cumulative CCyR rates were equivalent (79% and 80% for bosutinib and imatinib, respectively) and bosutinib treatment was associated with a significantly higher MMR rate (59% vs. 49%; P = .019). The FDA approved bosutinib in September 2012 as a treatment option for adult patients with Ph+ CML who are resistant or intolerant to prior therapy.

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Recent studies have supported the use of allogeneic HSCT in patients with CML for whom TKI therapy failed. The results of a subgroup analysis of the German CML-Study IV indicated that at a median follow-up of 30 months, patients with CP-CML who underwent allogeneic HSCT after imatinib failure experienced a 3-year OS rate of 91%. In a study of patients with imatinib-resistant CML for whom mutation data were available, allogeneic HSCT resulted in 2-year EFS survival rates of 36% and 58% in patients with and without BCR-ABL mutations, respectively, and the 2-year OS rates were 44% and 76%, respectively. In the entire patient population, which included patients with CP, AP, and BP disease, the MMR rate was 68%. Together, these results indicate that allogeneic HSCT is a viable option for patients who develop resistance to imatinib therapy.

Toward a Functional Cure

For CML, continued imatinib or second-generation TKI therapy that prevents progression to AP disease and the emergence of resistance may be thought of as an “operational” or a “functional” cure. Such ongoing, long-term treatment of CML could be considered akin to the long-term treatment of other chronic diseases, such as hypertension or diabetes. However, several issues arise surrounding the use of long-term TKI therapy, including chronic toxicity that may impact quality of life, late-emerging toxic-
Discontinuation of CML therapy has been evaluated in a small number of studies. Before the imatinib era, IFN with or without cytarabine was the most commonly used regimen in patients with CML. Cessation of IFN therapy after achievement of a deep molecular response has been successful in some patients, with maintenance of MRD and sometimes stable CMR for several years. The multicenter STIM (Stop Imatinib) trial evaluated the outcomes of patients with CML who discontinued imatinib after achievement and maintenance of CMR for at least 2 years. In this study of 100 patients, 61 (61%) experienced a molecular relapse, most (58%) within the first 7 months after cessation of therapy. Of these 61 patients, 56 achieved CMR on reinitiation of imatinib therapy, indicating that their disease remained sensitive to imatinib. Notably, 39% of patients who did not experience a molecular relapse at a median follow-up of 30 months, indicating that imatinib can be safely discontinued in some patients who experience a CMR of at least 2 years’ duration. Similar results were obtained by the CML-8 study investigators in Australia, who evaluated imatinib discontinuation in 40 patients who had sustained a CMR for at least 2 years on imatinib therapy. However, no consensus exists regarding a residual disease threshold for TKI reinitiation after cessation.

Melo and Ross described 3 conceptual models for achievement of functional cure. In the stem cell depletion model, immature CML cells are progressively depleted over years of continued therapy. The risk of relapse after TKI cessation is related to the duration of therapy and the intrinsic sensitivity of CML stem and early precursor cells. The stem cell exhaustion model states that because the CML stem cell pool is relatively small and because of stochastic events that direct self-renewal or proliferation, it may become extinct before diagnosis or early in therapy. The risk of relapse after TKI cessation is related to the depletion of committed CML progenitors and progeny. Finally, in the immunologic control model, a reduction in the level of MRD using TKI therapy is sufficient to overcome T-cell anergy and enables the emergence of an autologous immunologic response that suppresses, but may not eradicate, the CML clone. The risk of relapse on TKI cessation is dependent on the functional immune response and the intrinsic immunogenicity of the CML cells.

Several strategies are being investigated for their ability to eradicate leukemic stem cells. Stem cell eradication may theoretically be achieved through inhibiting self-renewal of stem cells; reversing the dormancy of stem cells, thereby increasing their susceptibility to TKI therapy; inducing differentiation of stem cells; inducing death of stem cells; and blocking autophagy in stem cells. Because second-generation TKIs have been shown to be incapable of eradicating leukemic stem cells in in vitro studies, combination therapies involving a TKI and agents with activity against CML acting through non–BCR-ABL kinase mechanisms may be required. Thus, evaluation of new targets/agents with differing mechanisms of action is warranted, as is the simultaneous targeting of more than 1 pathway. Several combination therapy regimens are currently under investigation.

As mentioned earlier, IFN played an important role in the management of CML before the imatinib era. This coupled with the fact that IFN therapies have improved in recent years (particularly with the introduction of pegylated IFN) prompted evaluation of combination TKI/IFN therapy. The phase III SPIRIT (STI571 Prospective Randomized Trial) study randomized patients with untreated CP-CML to imatinib alone, imatinib plus pegylated IFN-α2a, or imatinib plus cytarabine. Compared with patients who received single-agent imatinib, patients in the imatinib plus pegylated IFN-α2a arm experienced a similar rate of cytogenetic responses at 12 months but a significantly higher rate of superior molecular responses (defined as a ≤ 0.01% decrease in the ratio of BCR-ABL:ABL transcripts, corresponding to a ≥ 4-log reduction from standardized baseline level) at 12, 18, and 24 months. Similarly, the Nordic CML Study Group reported significantly improved MMR rates with the combination of imatinib and pegylated IFN-α2b at 12 months compared with imatinib alone (82% vs. 54%, P = .002) in a phase II trial. In contrast, the German CML Study group found that adding pegylated IFN-α2b to imatinib had no clear effect regarding MMR or survival. Likewise, adding pegylated IFN-α2b and granulocyte-macrophage colony-stimulating factor
to high-dose imatinib did not significantly improve the cytogenetic or molecular response rates. Additional trials are currently evaluating combination TKI/IFN therapy: a French group is conducting a study of nilotinib plus pegylated IFN-α2a (ClinicalTrials.gov identifier: NCT01294618) and a group at MD Anderson Cancer Center is assessing the utility of adding pegylated IFN-α2a to current TKI therapy in patients who have MRD (ClinicalTrials.gov identifier: NCT01392170).

Other ongoing combination-therapy trials in CML include a phase II study that is comparing imatinib with imatinib plus hydroxychloroquine (ClinicalTrials.gov identifier: NCT01227135). Hydroxychloroquine has been used as an antimalarial drug for decades, but is now the first agent to be evaluated in CML for its anti-autophagic properties, because inhibition of autophagy combined with TKI therapy has been shown to result in the near-complete elimination of CML stem cells. TKIs are also being evaluated in combination with the smoothened (SMO) antagonists, LDE225 and BMS-833923. SMO is a component of the hedgehog signaling pathway, which has been implicated in CML; furthermore, the combination of SMO antagonists and TKIs have been shown to be effective in reducing CML stem cell numbers in culture. Finally, BCL6 has been identified as a critical effector in CML stem cells, and administration of a peptide inhibitor of BCL6 in human CML cells has been shown to compromise colony formation and leukemia, making this of interest for continued investigation.

Conclusions

As the CML treatment landscape continues to evolve, growing evidence supports the importance of achieving early, deep molecular responses, early intervention for suboptimal response, and rational selection of next-line TKI therapy based on BCR-ABL mutation profile. Several promising new agents and strategies are currently being explored with the goal of overcoming, or even avoiding, resistance to TKI therapy. Further studies with these and other agents, and combination regimens and other strategies, will be critical for defining the pathway to functional cure for patients with CML.

References


Cortes-Franco J, Raghunadharao D, Parikh P, et al. Safety and efficacy of subcutaneously-administered omacetaxine mespescuccinate in chronic myeloid leukemia (CML) patients who are resistant or intolerant to two or more tyrosine kinase inhibitors—results of a multicenter phase 2/3 study [abstract]. Blood 2009;114:Abstract 861.


