Abstract: The development of tyrosine kinase inhibitors (TKIs) that inhibit signaling of the constitutive BCR-ABL protein revolutionized the treatment of chronic myelogenous leukemia (CML). These agents have dramatically changed the treatment landscape for CML, shifting the use of allogeneic stem cell transplantation to selected patients in the salvage setting. Four BCR-ABL TKIs are now commercially available for the treatment of CML: the first-generation TKI imatinib, and the second-generation TKIs dasatinib, nilotinib, and bosutinib. Continuous treatment with these agents induces durable responses in a high proportion of patients with chronic-phase CML. Research is focused on identifying which patients can discontinue therapy without a recurrence of disease. For the group of patients with resistance to TKIs, multiple alternative therapies are being evaluated. The third-generation TKI ponatinib is a BCR-ABL inhibitor that has demonstrated significant activity, including in patients with the TKI resistance mutation T315I. The homoharringtonine derivative omacetaxine mepesuccinate, which inhibits protein synthesis, has also demonstrated clinical activity in CML, including in patients with TKI resistance due to T315I and in patients who have TKI resistance despite no evidence of ABL mutations. It is essential that clinicians implement these new agents with care and change therapies only when appropriate in order to preserve as many options as possible for future use if needed.
Target Audience
This activity has been designed for hematologists/oncologists, oncologists, oncology nurses, and hematology/oncology pharmacy specialists who treat patients with chronic myelogenous leukemia.

Statement of Need/Program Overview
The tyrosine kinase inhibitor (TKI) imatinib and the second-generation TKIs nilotinib and dasatinib have revolutionized the treatment of chronic myelogenous leukemia (CML) by effectively targeting the BCR-ABL oncogenic kinase. However, many patients do not respond well to treatment and/or lose their response over time. This unmet need has led to the investigation of novel agents that specifically target TKI resistance in CML. Physicians require education regarding the development of TKI resistance, as well as on the efficacy and safety of emerging treatment options in CML. The US Food and Drug Administration recently approved the use of bosutinib for the treatment of patients with Philadelphia chromosome-positive CML who are intolerant to or have become resistant to prior therapy. Other novel agents with positive results in phase II trials include ponatinib and omacetaxine mesylate. Physicians must be aware of the data supporting the use of these newer agents and become familiar with their optimal implementation.

Educational Objectives
After completing this activity, the participant should be better able to:
- Define tyrosine kinase inhibitor (TKI) resistance in patients with chronic myelogenous leukemia (CML)
- Identify CML patients who should undergo BCR-ABL mutational testing
- Incorporate newly approved agents into the treatment of CML patients with TKI resistance
- Recognize when to discontinue an agent and resume treatment with another one

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Millennium Medical Publishing, Inc. PIM is accredited by the ACCME to provide continuing medical education for physicians.

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The contributing speakers reported the following financial relationships or ownership interests that are relevant to the content of this CME activity:

- Jorge Cortes, MD—Advisor or consultant: Bristol-Myers Squibb Company and ARIAD Pharmaceuticals, Inc; Speaker or member of a speakers bureau: Bristol-Myers Squibb Company and ARIAD Pharmaceuticals, Inc; Clinical research grants: Bristol-Myers Squibb Company and ARIAD Pharmaceuticals, Inc.
- Jerald Radich, MD—Consultant: Novartis, BMS, ARIAD, and Pfizer; Laboratory research support: Novartis.
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Method of Participation
There are no fees for participating in and receiving CME credit for this activity. During the period October 2012 through October 31, 2013, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Postgraduate Institute for Medicine. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on “Find Post-tests by Course” and search by project ID 8940. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

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Chronic myelogenous leukemia (CML) is characterized by the proliferation of a clone of hematopoietic cells driven by the Philadelphia chromosome \([t(9;22)(q34;q11)]\). This translocation leads to formation of the fusion BCR-ABL gene, which encodes a constitutively active BCR-ABL tyrosine kinase. CML is most often diagnosed in the chronic phase (CP-CML), which is characterized by a proliferation of the myeloid spectrum of cells. In the absence of curative therapy, the disease would progress after a period of approximately 4 years to an accelerated phase (AP-CML) heralded by an increase in the number of immature blasts and the presence of new cytogenetic abnormalities aside from the Philadelphia chromosome. From there, patients would progress to blast crisis (BC), which would typically cause death due to bleeding or infectious causes.

The first therapeutic intervention to offer the potential of cure in CML was allogeneic stem cell transplantation (SCT), which is associated with overall survival rates of greater than 5 years in more than 85% of patients in CP-CML, 40% of patients in AP-CML, and 20% of patients in BC-CML (Figure 1).\(^1\) The next major advance in CML, the development of the BCR-ABL tyrosine kinase inhibitor (TKI) imatinib, revolutionized the therapy of CML. Whereas transplantation was previously undertaken as soon as possible after diagnosis, it is now used only as a salvage regimen in selected patients, since the success of TKIs in chronic phase disease is so profound.

This evolution in the treatment paradigm for CML is a testament to the highly effective nature of the TKIs. Among patients with CP-CML who start therapy with the first-generation TKI imatinib, approximately 70% attain the treatment goals set forth by the National Comprehensive Cancer Network (NCCN)\(^4\) and the European LeukemiaNet (ELN),\(^5\) which include a major cytogenetic response (MCyR) by 12 months and a complete cytogenetic response (CCyR) by 18 months.\(^6\) Long-term data support this short-term efficacy and reflect the remarkable

### Table 1. Outcomes: ENESTnd and DASISION

<table>
<thead>
<tr>
<th>Study</th>
<th>ENESTnd: Nilotinib 300 mg BID (n=282)</th>
<th>ENESTnd: Nilotinib 400 mg BID (n=281)</th>
<th>ENESTnd: Imatinib 400 mg QD (n=283)</th>
<th>DASISION: Dasatinib 100 mg QD (n=259)</th>
<th>DASISION: Imatinib 400 mg QD (n=260)</th>
</tr>
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<tbody>
<tr>
<td>MMR, %</td>
<td>44*</td>
<td>43*</td>
<td>22</td>
<td>46*</td>
<td>28</td>
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<tr>
<td>12 months</td>
<td>62*</td>
<td>59*</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCyR, %</td>
<td>80*</td>
<td>78†</td>
<td>65</td>
<td>83†</td>
<td>72</td>
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<tr>
<td>12 months</td>
<td>87‡</td>
<td>85§</td>
<td>77</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AP/BC, n (%)</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>12 (4.2)</td>
<td>5 (1.9)</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td></td>
<td>(P=0.006)</td>
<td>(P=0.003)</td>
<td>(P=NS)</td>
<td>(P=NS)</td>
<td>(P=NS)</td>
</tr>
</tbody>
</table>

*\(P<0.001\) vs imatinib.
†\(P<0.001\) vs imatinib.
‡ \(P<0.0018\) vs imatinib.
§ \(P<0.016\) vs imatinib.

AP/BC=accelerated phase/blast crisis; CCyR=complete cytogenetic response; DASISION=Dasatinib versus Imatinib Study in Treatment-Naive CML Patients; ENESTnd=Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; MMR=major molecular response; NA=not available; NS=not significant.

Data from Saglio G et al,\(^8\) Hughes TP et al,\(^6\) and Kantarjian H et al.\(^17\)
Figure 1. Overall survival with first-line imatinib in chronic myelogenous leukemia in the IRIS (International Randomized Study of Interferon and STI571) study. CML=chronic myelogenous leukemia. Data from Deininger M et al.7

Figure 2. Survival in chronic myelogenous leukemia after allogeneic stem cell transplantation. Patients receiving allografts at the Fred Hutchinson Cancer Research Center from 1995 to the present. Both matched related donors and unrelated donors are included. Figure is courtesy of Dr. Ted Gooley.
change TKIs have made in the natural history of the disease. Overall, approximately 85% of patients who initiate imatinib therapy are alive after 8 years (Figure 2). 

Three second-generation TKIs are also available: nilotinib, dasatinib, and, most recently, bosutinib. These agents have demonstrated more potent activity than imatinib in laboratory studies and enhanced efficacy in randomized clinical trials. Compared with imatinib, nilotinib and dasatinib have demonstrated higher CCyR rates, lower rates of progression to AP and BC, and a higher likelihood of major molecular response (MMR; Table 1). Bosutinib has not demonstrated a significant improvement in 12-month CCyR rates over imatinib, but it is associated with other efficacy improvements, including a higher 12-month MMR rate, faster time to response, less disease progression, and fewer CML-related deaths.

One notable endpoint that has not been observed with second-generation TKIs is an improvement in overall survival over imatinib. It is unclear whether there truly is no difference in survival between first- and second-generation TKIs, or whether there has just not been sufficient follow-up to detect any differences. Second-generation TKIs promote deeper molecular responses, which may eventually translate into an overall survival benefit.

The optimal implementation of TKIs is an important issue. Clinicians and their newly diagnosed patients are presented with the option of starting with the standard first-line therapy, imatinib, or a second-generation TKI. In my clinic, we weigh the pros and cons of each agent. Some patients may prefer imatinib due to its longer track record of impressive safety, thus, reserving dasatinib and nilotinib if the initial therapy fails. However, other patients may prefer to start with a more active second-generation TKI, which is also a reasonable option. Other factors to consider include the patient’s risk profile as assessed by the Sokal, Hasford, or European Treatment and Outcome Study [EUTOS] scores. Many clinicians feel comfortable using imatinib in patients with low-risk disease but may opt for a more potent second-generation agent in patients with intermediate- or high-risk disease who may be further along in the natural history of the disease.

Resistance to TKIs can occur in several settings. “Primary” resistance occurs when the treatment does not induce the response criteria as defined by the ELN and NCCN guidelines. “Acquired” resistance occurs when patients experience a relapse following an initial response. Approximately half of relapses are characterized by point mutations in the ABL kinase domain that cause a change in the conformational structure of ABL, inhibiting TKI binding and thus allowing the reactivation of the BCR-ABL kinase activity.

Resistance to TKI therapy can be detected early based on BCR-ABL RNA levels as assayed by polymerase chain reaction (PCR) and cytogenetic studies. A BCR-ABL transcript level of greater than 10% after 3 months of therapy is associated with a relatively poor response. Thus, there is an impetus for these patients to switch therapy (eg, to a second-generation TKI if the patient has started on imatinib) if this milestone is not achieved. It should be emphasized, however, that there is no strong data suggesting that treatment changes for any of the milestones alters the natural history of the disease. Indeed, patients who fail to reach milestones should enroll in a clinical trial, if possible.

In the case of patients who initially respond to imatinib and then develop resistance, the choice of next therapy can be influenced by the patient’s ABL mutation status. For patients with no detectable ABL mutation, any second-generation TKI would be acceptable, weighing in contraindications based on patient history and known drug side effects. For patients with an ABL mutation that is characterized by greater sensitivity to one second-generation TKI over another, the choice could be more straightforward. For patients with the T315I mutation, which confers resistance to imatinib, dasatinib, and nilotinib, options include transplantation or a clinical trial with an agent that is active against T315I, such as the third-generation TKI ponatinib.

One important issue in the care of patients with acquired resistance is how long to continue the new agent before proceeding to salvage therapy that may include transplantation. Two major studies have prospectively evaluated this issue. Investigators at the MD Anderson Cancer Center found that a 12-month trial with a different TKI is acceptable, at which point the depth of response should be assessed and the decision to transplant should be made. However, Milojkovic and colleagues determined that BCR-ABL transcript levels should be assessed at 3 months. Patients without a cytogenetic response at that time would then proceed to transplant. Fortunately, previous therapy with a TKI does not negatively affect the transplant, unlike other drugs for CML, such as busulfan and interferon.

Finally, for the group of patients with AP- or BC-CML, a TKI alone is unlikely to be curative; transplantation would be required. However, most investigators would opt for some therapy before transplantation to try to attain the best response possible before proceeding to transplant. Therefore, most patients with AP or BC would be treated immediately with a second-generation drug, followed by transplantation upon attaining a maximal response.

Acknowledgment

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### References


CR-ABL TKIs are a highly effective initial therapy in CP-CML, inducing durable responses in the majority of patients. However, alternative approaches are needed for the 20–30% of patients who fail an initial TKI due to disease progression, relapse, or intolerance. To meet the needs of these patients, a variety of new agents have since been developed, including second-generation and third-generation TKIs and agents with novel mechanisms of action.

**Second-Generation BCR-ABL TKIs**

After it was recognized that some patients develop resistance or intolerance to imatinib, several newer-generation TKIs were developed. The first of these was dasatinib, a TKI that can bind both the active and inactive forms of ABL, thus retaining activity against imatinib-resistant BCR-ABL mutations. In the phase II START-C (SRC/ABL Tyrosine Kinase Inhibition Activity: Research Trials of Dasatinib) trial, dasatinib dosed at 70 mg twice daily demonstrated significant activity in patients with imatinib-resistant or intolerant CP-CML, with 52% of patients attaining a major cytogenetic response (MCyR). Responses were durable, with 2-year MCyR and complete cytogenetic response (CCyR) rates of 62% and 53%, respectively. Approximately 75–80% of patients who achieved an MCyR maintained the response for about 2 years. In 2010, Shah and colleagues reported results from a randomized dose-optimization study showing that administration of dasatinib at 100 mg once daily in patients with CP-CML is as effective as administration at 70 mg twice daily and is better tolerated.

Around the same time, a third BCR-ABL TKI, nilotinib, was developed. Like dasatinib, nilotinib was designed for use in patients with resistance or intolerance to imatinib. In a phase II trial in patients with CP-CML, nilotinib demonstrated significant clinical activity, with overall MCyR and CCyR rates of 59% and 44%, respectively, at 2 years. Responses tended to be durable, with 84% of patients maintaining a CCyR and 77% of patients maintaining an MCyR at 2 years.

Based on these clinical trials, dasatinib and nilotinib have become a standard approach for patients with imatinib resistance. Experience in treating these patients has revealed the importance of early recognition of TKI resistance. It is now understood that the longer the delay between the development of resistance and the switch to an alternative TKI, the lower the likelihood that the patient will respond to the second agent. Data suggest that the response rate to the second agent is at least 50–60% lower in patients who switch only upon loss of a complete hematologic response (CHR) than in patients who switch immediately upon loss of an MCyR. It is therefore important to monitor patients closely in order to recognize treatment failure early and act immediately once resistance is definitively identified.

Although dasatinib and nilotinib induce durable responses in many patients with imatinib-resistant CP-CML, approximately half of patients do not achieve a CCyR with a second-line TKI, and another subset of patients initially respond but eventually develop resistance to these agents. Alternative approaches are needed for this small, but significant, patient population. There is also a need for alternative treatment strategies for the small subset of patients with a detectable T315I mutation in the ABL kinase domain, which is associated with significant resistance to imatinib, dasatinib, and nilotinib. Although a third TKI could be considered in patients who had failed 2 prior lines of TKI therapy, responses to a third TKI tend to be minimal and not very durable.

Research efforts have led to the development of a variety of agents for the treatment of TKI-resistant CML. Although some of these agents have not yielded the anticipated efficacy, others have demonstrated significant clinical activity. One such active agent is bosutinib, a BCR-ABL TKI with similarities to dasatinib and nilotinib but with a unique kinase inhibition profile. For example, bosutinib targets SRC, ABL, and TEC, but it does not inhibit KIT or platelet-derived growth factor receptor (PDGFR). In a phase I/II study, bosutinib demonstrated activity in patients with failure of at least 2 prior TKIs (imatinib and dasatinib and/or nilotinib), with MCyR and CCyR
rates of 32% and 24%, respectively.10 Response rates vary somewhat according to the sequence of therapies. In the second-line setting, in patients with resistance or intolerance to only imatinib, the efficacy of bosutinib is similar to that of dasatinib or nilotinib, with CCyR and MCyR rates of 41% and 53%, respectively.11 Bosutinib was recently approved for use in patients with CML in any stage of disease with resistance or intolerance to prior therapy.12

**Emerging Therapies for TKI-Resistant CML**

Several other novel agents are currently in the investigational stages of development. One agent that has demonstrated significant clinical activity is the third-generation TKI ponatinib, which was structurally designed to bind and inhibit ABL even in the setting of T315I and other BCR-ABL mutants.13 The phase II PACE (Ponatinib Ph+ALL and CML Evaluation) trial is evaluating the efficacy and safety of ponatinib in 449 patients with resistance or intolerance to dasatinib or nilotinib or with the T315I mutation. Among patients with CP-CML, ponatinib has demonstrated significant activity, with a CCyR observed in 66% of patients with T315I and in 37% of patients with resistance or intolerance to dasatinib or nilotinib.14 Ponatinib is active in patients with other ABL mutations and in patients with wild-type BCR-ABL, although it appears to be most effective in patients with ABL mutations. In regard to previous lines of therapy, ponatinib has demonstrated activity in patients exposed to either 2 or 3 prior TKIs. In patients who have failed imatinib, dasatinib, and nilotinib, ponatinib induced CCyR in 34% of patients without T315I and 48% of patients with T315I. The PACE trial also enrolled patients with advanced disease, including 85 patients with accelerated-phase (AP) CML and 94 patients with blast-phase (BP) CML or Ph+ ALL. Ponatinib was active in these patients, inducing major hematologic responses in 58% of patients with AP-CML and 34% of patients with BP-CML or Ph+ ALL. MCyR responses were observed in 39% and 30% of patients, respectively. However, as has been observed for other TKIs, responses to therapy are less durable in AP-CML than in CP-CML, and are even less durable in patients with BP-CML. An ongoing phase II study is evaluating combination therapy with ponatinib and hyper-CVAD to attempt to induce a more durable response.15 Overall, ponatinib appears to be a very active drug in the setting of resistance to multiple therapies, including in patients with T315I. In vitro data suggest that resistance to ponatinib will not readily develop. Ponatinib is currently under FDA review for accelerated approval.

Another interesting agent in development is omacetaxine mepesuccinate. Omacetaxine is a semi-synthetic derivative of homoharringtonine, an investigational agent that initially demonstrated clinical activity during the interferon era and is now gaining renewed interest.16 Omacetaxine acts not through kinase inhibition but by inhibiting synthesis of proteins with a rapid turnover. Thus, it has no effect on structural proteins but it does inhibit synthesis of proteins implicated in cell-cycle progression. Unlike the TKIs, omacetaxine is administered via subcutaneous injection. In a phase II study in patients with T315I who had failed a TKI, omacetaxine was associated with an MCyR rate of 23%.17

Omacetaxine may also be an alternative for patients without relevant ABL mutations, in whom the mechanism of TKI resistance may be unrelated to persistence of kinase activity. Among patients with CP-CML (regardless of mutation status) who had received at least 2 prior TKIs, omacetaxine was associated with an MCyR rate of 27% in patients who had received 2 prior TKIs and in 11% of patients who had received 3 TKIs.18 Responses appeared durable, with a median MCyR duration of 18 months. Survival was also longer than expected for this patient population, with a median OS of 30 months in patients who had failed 2 TKIs and did not reach patients with 3 prior TKIs. Omacetaxine is also active in AP- and BP-CML, although responses are less durable in these settings. Omacetaxine is also currently under review by regulatory authorities. Both ponatinib and omacetaxine appear to be active and may be useful for at least a subset of patients with CML.

**Applying New and Emerging Therapies in CML**

The expanding treatment options for CML raise the issue of how best to use these agents at different stages of disease. Many clinicians continue to use imatinib as initial therapy. For patients requiring a change of therapy after imatinib, a second-generation TKI (dasatinib, nilotinib, or bosutinib) would be a logical choice. The 2 agents currently under FDA review—ponatinib and omacetaxine—have not been well studied in the imatinib-refractory setting, aside from in patients with T315I.

With the FDA approval of dasatinib and nilotinib for the first-line treatment of CML, a growing number of patients are receiving these agents as initial therapy. For patients who discontinue dasatinib or nilotinib, the selection of second-line therapy may vary based on the reason for discontinuation. Patients who discontinue initial dasatinib or nilotinib due to tolerability issues may be candidates for imatinib, which may be better tolerated. Patients who discontinue dasatinib or nilotinib due to resistance would most likely not be candidates for imatinib, given the low probability of response; however, data on this sequence are limited. Bosutinib is an interesting option for these patients, as it has demonstrated...
activity after failure of 2 or more TKIs. Additional data on the efficacy of bosutinib in different settings are awaited. Ponatinib would also be a very attractive option, considering its mechanism of action and demonstrated clinical efficacy. Omacetaxine is another intriguing option for TKI-refractory disease, particularly for patients who have developed resistance to TKIs through a mechanism other than an ABL mutation.

The treatment armamentarium for CML is continuing to evolve with the introduction of several new therapeutics and additional agents under review. Ongoing studies will provide information that should help guide the optimal use of these agents. A greater understanding of the activity of these agents in various clinical settings and their relevant mechanisms of resistance should help guide treatment selection and sequencing of therapies based on patient, disease, and therapeutic factors, in order to improve outcomes for individuals living with CML.

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References
Historically, allogeneic stem cell transplantation (SCT) has played an important role in the treatment of CML, as it induces long-term remission in a high proportion of patients. However, allogeneic SCT is associated with a significant risk of morbidity and mortality, and many patients are not candidates for transplantation due to comorbidities, advanced age, or lack of a suitable human leukocyte antigen (HLA)-matched donor. For the group of patients with early CP-CML who have an available donor, a favorable risk profile, and a low risk of transplant-related morbidity or mortality, outcomes with transplantation have been favorable. However, allogeneic SCT is associated with significant morbidity and mortality even for this lower-risk group, highlighting the need for an effective alternative.

The introduction of highly effective therapy has led to a paradigm shift in CML, changing the role of transplant dramatically. TKIs have eliminated the upfront morbidity and mortality associated with transplantation. Longer-term follow-up is confirming the favorable short-term efficacy of TKIs, demonstrating that TKIs can also induce long-term, stable remission, perhaps leading to a functional cure.

Although therapeutic advances have significantly diminished the role of transplantation in CML, allogeneic SCT may still have a role in selected patients with resistance or intolerance to TKIs.

Opinions differ regarding the optimal time to introduce or reintroduce transplantation in these patients. My opinion is that for a patient of an appropriate age and with a favorable transplant risk profile, it is wise to delineate the option early, as it may frame a patient’s tolerability for differing degrees of nonresponse or intolerance to TKI therapy.

If a younger patient is responding poorly to multiple TKI therapies and has a small projected likelihood of long-term stable remission, a stem cell transplant might be pursued directly. Conversely, for an older patient in whom transplant morbidity represents a risk, and who may not have an identified donor, there will be a greater need to remain within the realm of TKI therapy and to establish a stable remission using available non-transplant options.

Another important question regarding transplantation today is whether it is harmful for patients to have been exposed to TKIs prior to transplant. Data from a large prospective registry study suggest that in the case of CP-CML that is not highly proliferative, outcomes after transplant are similar regardless of prior TKI exposure. The effect of therapeutic resistance conferred by a TKI mutation or another mechanism is currently unknown. In general, however, the introduction of TKIs has not affected outcomes after allogeneic SCT.

An important consideration in allogeneic transplantation is the type of conditioning regimen used. Reduced-intensity conditioning regimens decrease the risks associated with transplantation; however, CML is a tenacious disease that may not be amenable to a reduced-intensity conditioning regimen due to the risk of relapse. It may be possible to use a combination of reduced-intensity conditioning transplantation and TKI therapy to enhance therapeutic efficacy while lowering the risks of transplantation.

In addition to their role prior to transplantation, TKIs may also have a role after transplant to protect against relapse. Several studies have reported a benefit with the use of TKI therapy post-transplant to protect against relapse. Thus, TKIs and transplantation may not be mutually exclusive. Overall, the selection of appropriate patients, the use of lower-dose conditioning therapy, and the application of advances in protection against graft-versus-host disease and infection all lower the risks associated with allogeneic transplantation. The use of allogeneic SCT in CML has declined dramatically, but it still remains a viable treatment option for selected patients.

Feasibility of Stem Cell Eradication of CML

TKI therapy provides exquisite control of leukemia down to a level detectable only by DNA or RNA sequencing analysis. An increasing proportion of patients are able to maintain a state of remission that is either consistent or fairly consistent with no detectable evidence of CML by any means. Although this state may represent a functional cure, the leukemic potential still appears to exist, at least for many patients. An
actual cure, defined as a lack of disease regrowth in the absence of therapy, remains an important goal.

The effect of CML therapy, including TKIs, at the stem-cell level is a topic of research. The STIM (Stop Imatinib) study prospectively evaluated whether imatinib could be discontinued without relapse in patients with a complete molecular remission (CMR) of at least 2 years' duration.1 In an interim analysis, approximately 40% of patients remained in molecular remission for at least 12 months. For the remaining 60% of patients who relapsed off therapy, reintroduction of imatinib led to a response in all cases. Thus, while imatinib may allow some patients to stop therapy, it does not necessarily eradicate a punitive stem cell that may harbor BCR-ABL.

Even among patients who respond rapidly to imatinib and attain long-term molecular remission that permits discontinuation of therapy without relapse, there may still be a population of cells that harbor the BCR-ABL translocation but have been rendered nonproliferative. Perhaps we should reconsider the definition of an actual cure and not require that the marker be absent, but rather accept the presence of residual nonproliferative CML cells. Other hematologic malignancies use similar approaches, such as the detection of core binding factor in leukemia or inversion 16 or t(8;21) in AML.

In vitro studies have shown that quiescent stem cells are resistant not only to imatinib, but also to more potent second-generation TKIs, such as dasatinib,2 suggesting that ongoing therapy would be necessary to suppress the CML clone. However, as noted by Melo and Ross, this pessimistic prediction does not align with the outcomes observed when therapy was stopped in the STIM trial.3 The absence of early relapse does not indicate that a patient is cured. It may, however, indicate that proliferation of CML is just below the limit of detection by standard assays.

Moving forward, our ongoing quest remains to define the residual CML population that must be managed, assess its potential for proliferation in the setting of more potent TKI therapy, and determine whether it is necessary to eradicate residual CML cells, or whether “cure” in CML can be redefined as a prolonged period without proliferation.

Acknowledgment
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References
Discussion: Role of Novel Agents in Chronic Myelogenous Leukemia

H&O  What is your overall assessment of the current state of chronic myelogenous leukemia (CML) treatment?

Jorge Cortes, MD: In many cases, patients will respond to initial treatment and, with careful managing and monitoring, will have good long-term outcomes. The treatment is more complicated for patients with more refractory disease. Previously, we had few options for these patients, but now our treatment options are expanding.

Michael J. Mauro, MD: Yes; we now have multiple active agents with different properties and mechanisms of action, including novel tyrosine kinase inhibitors (TKIs) and new drugs with alternative mechanisms of action. The development of these agents gives us more options for patients with refractory disease.

Jerald Radich, MD: There is almost an embarrassment of riches for treating chronic phase CML, with several highly effective TKIs available. Alas, we have made far less impressive progress on advanced phase disease. Thus, a main goal in therapy is to keep patients out of advanced phase disease. Monitoring and compliance are big considerations.

Jorge Cortes, MD: One caveat as we discuss these new therapies is the importance of careful implementation of each therapy. In our referral patients, we are seeing a growing number of patients who have jumped quickly from one drug to another for reasons of minor adverse effects rather than true TKI intolerance. This observation is supported by the discontinuation rates being reported in the frontline studies, which are higher than expected based on the established efficacy and safety profiles of these agents. In these patients, rapidly switching between TKIs could be a dangerous practice, as it may eliminate the availability of these valuable options down the road, before they are properly evaluated.

Therefore, clinicians must be careful that the increased availability of drugs does not lead them to switch prematurely to alternative agents. Patients should be educated about the side effects associated with these drugs, and they should be supported in the management of those effects. In some cases, however, switching to another drug is clearly the correct decision. The challenge will be finding the right balance between switching prematurely and continuing too long on an ineffective drug.

Michael J. Mauro, MD: I agree; we must be careful not to drive patients into states of resistance through the inappropriate use of multiple drugs. The good news is that even our prototype drug is highly effective in a large number of patients, and the higher doses are even more effective. Hopefully, a conservative approach and very careful use of newer drugs will reign supreme. On the other hand, we must counter the notion that CML is like a cold that we can treat with a simple antibiotic first and then with a more potent antibiotic second. We do have data showing that careful consideration of our best treatment options first really can give us the best outcome.

Jerald Radich, MD: For chronic phase disease, the adage “just don’t do something, stand there” is often appropriate—give the TKI time to work, and follow guidelines from the National Comprehensive Cancer Network and the European LeukemiaNet in regards to treatment milestones. Don’t jump ship by expecting miraculous results quickly.

Acknowledgment

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Chronic Myelogenous Leukemia

- Characterized by the proliferation of a clone of hematopoietic cells driven by the Philadelphia chromosome (9:22)(q34;q11). This translocation leads to formation of the fusion BCR-ABL gene, which encodes a constitutively active BCR-ABL tyrosine kinase.
- Most often diagnosed in the chronic phase, which is characterized by a proliferation of the myeloid spectrum of cells.
- In the absence of curative therapy, the disease would progress after approximately 4 years to an accelerated phase heralded by an increase in the number of immature blasts and the presence of new cytogenetic abnormalities side from the Philadelphia chromosome. From there, patients would progress to blast crisis, which would typically cause death due to bleeding or infectious causes.

Treatments for CML

- Allogeneic stem cell transplantation
  - The first therapeutic intervention to offer the potential of cure in CML.
- Imatinib
  - Revolutionized the therapy of CML.
- Novel tyrosine kinase inhibitors
  - Have demonstrated more potent activity than imatinib in laboratory studies and enhanced efficacy in randomized clinical trials.

Second-Generation TKIs Approved for CML

- Dasatinib
  - Demonstrated significant activity in patients with imatinib-resistant or intolerant chronic phase CML, with 52% of patients attaining a MCYR.
- Nilotinib
  - Demonstrated significant clinical activity in patients with imatinib-resistant or intolerant chronic phase CML, with overall MCYR and CCYR rates of 59% and 44%, respectively, at 2 years.
- Bosutinib
  - Demonstrated activity in patients with failure of at least 2 prior TKIs (imatinib and dasatinib and/or nilotinib), with MCYR and CCYR rates of 32% and 24%, respectively.

TKI Resistance in CML

- “Primary” resistance occurs when the treatment does not induce the response criteria as defined by the ELN and NCCN guidelines.
- “Acquired” resistance occurs when patients experience a relapse following an initial response.
- Approximately half of relapses are characterized by point mutations in the ABL kinase domain that cause a change in the conformational structure of ABL, inhibiting TKI binding and thus allowing the reactivation of the BCR-ABL kinase activity.

Options for Patients With TKI Resistance in CML

- Approximately half of patients do not achieve a CCYR with a second-line TKI, and another subset of patients initially respond but eventually develop resistance to these agents.
- A small subset of patients have a detectable T315I mutation in the ABL kinase domain, which is associated with significant resistance to imatinib, dasatinib, and nilotinib.
- Responses to a third TKI tend to be minimal and not durable.

Emerging Therapies for TKI-Resistant CML

- Ponatinib
  - Structurally designed to bind and inhibit ABL, even in the setting of T315I and other BCR-ABL mutants.
- Omacetaxine
  - A semi-synthetic derivative of homoharringtonine, an investigational agent that initially demonstrated clinical activity during the interferon era. Acts not through kinase inhibition but by inhibiting synthesis of proteins with a rapid turnover. Thus, it has no effect on structural proteins but it does inhibit synthesis of proteins implicated in cell-cyclic progression.
**Ponatinib: Clinical Trial Data**

- The phase II PACE (Ponatinib Ph-ALL and CML Evaluation) trial is evaluating the efficacy and safety of ponatinib in 692 patients with resistance or intolerance to dasatinib or nilotinib or with the T315I mutation.
- Among patients with chronic phase CML, ponatinib has demonstrated significant activity with a CR rate observed in 36% of patients with T315I and in 32% of patients with resistance or intolerance to dasatinib or nilotinib.
- Ponatinib is active in patients with prior ABL, non-response, and in patients with wild-type BCR-ABL, although it appears to be most effective in patients with ABL mutation.
- Ponatinib has demonstrated activity in patients exposed to either 2 or 3 TKIs, in patients who have failed imatinib, dasatinib, and nilotinib. Ponatinib induced CR in 3% of patients with T315I and 4% of patients with T315I.


**Omacetaxine: Clinical Trial Data**

- Among patients with chronic phase CML (regardless of mutation status) who had received at least 2 prior TKIs, omacetaxine was associated with an MCR rate of 22% in patients who had received 2 prior TKIs and in 11% of patients who had received 3 TKIs.
- Responses appeared durable, with a median MCR duration of 18 months.
- Survival was also longer than expected for this patient population, with a median overall survival of 30 months in patients who had failed 2 TKIs and not reached in patients with 3 prior TKIs.


**Allogeneic Stem Cell Transplantation in CML**

- Historically, allogeneic SCT has played an important role in the treatment of CML, as it induces long-term remission in a high proportion of patients.
- Allogeneic SCT is associated with a significant risk of morbidity and mortality, and many patients are not candidates for transplantation due to comorbidities, advanced age, or lack of a suitable HLA-matched donor.
- For the group of patients with early chronic phase CML who have an available donor, a favorable risk profile, and a low risk of transplant-related morbidity or mortality, outcomes with transplantation have been favorable. However, allogeneic SCT is associated with significant morbidity and mortality even for this lower-risk group, highlighting the need for an alternative approach.

**Does TKI Use Affect Outcomes?**

- Data suggest that in the case of chronic phase CML that is not highly proliferative, outcomes after transplant are similar regardless of prior TKI exposure.
- The effect of therapeutic resistance conferred by a TKI mutation or another mechanism is currently unknown.
- In general, the introduction of TKIs has not affected outcomes after allogeneic SCT.

Emerging Treatment Options for TKI-Resistant Chronic Myelogenous Leukemia

CME Post-Test: Circle the correct answer for each question below.

1. Chronic myelogenous leukemia (CML) is most often diagnosed in which phase?
   a. Accelerated phase
   b. Blast phase
   c. Chronic phase
   d. Early phase

2. Which therapy is associated with overall survival rates of greater than 5 years in more than 40% of patients in accelerated phase CML?
   a. Allogeneic stem cell transplantation
   b. Dasatinib
   c. Imatinib
   d. Nilotinib

3. Overall, approximately how many CML patients who initiate imatinib therapy are alive after 8 years?
   a. 55%
   b. 60%
   c. 70%
   d. 85%

4. In CML, a BCR-ABL transcript level of greater than ____ after 3 months of therapy is associated with a relatively poor response.
   a. 5%
   b. 10%
   c. 15%
   d. 20%

5. Approximately how many CML patients fail initial therapy with a tyrosine kinase inhibitor due to disease progression, relapse, or intolerance?
   a. 5–15%
   b. 20–30%
   c. 40–50%
   d. 60–70%

6. In the phase II START-C trial of dasatinib dosed at 70 mg twice daily in patients with imatinib-resistant or intolerant chronic phase CML, how many patients attained a major cytogenetic response?
   a. 41%
   b. 52%
   c. 65%
   d. 77%

7. In the phase II PACE trial, ponatinib was associated with a complete cytogenetic response rate of ____ among chronic phase CML patients with resistance or intolerance to dasatinib or nilotinib.
   a. 23%
   b. 37%
   c. 48%
   d. 51%

8. In a phase II study in CML patients with T315I who had failed therapy with a tyrosine kinase inhibitor, omacetaxine was associated with a major cytogenetic response rate of ____.
   a. 23%
   b. 37%
   c. 48%
   d. 51%

9. Data from a large prospective registry study in patients with chronic CML that was not highly proliferative suggest that outcomes after transplant are improved in patients who received prior therapy with a tyrosine kinase inhibitor.
   a. True
   b. False

10. In an interim analysis of the STIM study, which prospectively evaluated whether imatinib could be discontinued without relapse in CML patients with a complete molecular remission of at least 2 years' duration, approximately ____ of patients remained in molecular remission for at least 12 months.
    a. 20%
    b. 30%
    c. 40%
    d. 50%
Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree     2 = Disagree     3 = Neutral     4 = Agree     5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:
1. Define tyrosine kinase inhibitor (TKI) resistance in patients with chronic myelogenous leukemia
2. Identify CML patients who should undergo BCR-ABL mutational testing
3. Incorporate newly approved agents into the treatment of CML patients with TKI resistance
4. Recognize when to discontinue an agent and resume treatment with another one

Based upon your participation in this activity, choose the statement(s) that apply:
☐ I gained new strategies/skills/information that I can apply to my area of practice.
☐ I plan to implement new strategies/skills/information into my practice.
☐ I need more information before I can implement new strategies/skills/information into my practice behavior.
☐ This activity will not change my practice, as my current practice is consistent with the information presented.
☐ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice?

How confident are you that you will be able to make this change?
☐ Very confident       ☐ Unsure       ☐ Somewhat confident       ☐ Not very confident

What barriers do you see to making a change in your practice?

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree     2 = Disagree     3 = Neutral     4 = Agree     5 = Strongly Agree

The content presented:
Enhanced my current knowledge base
Addressed my most pressing questions
Promoted improvements or quality in health care
Was scientifically rigorous and evidence-based
Avoided commercial bias or influence
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)
My opportunity for learning assessment was appropriate to the activity

Handout materials were useful:
☐ Yes       ☐ No       ☐ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey?
☐ Yes       ☐ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by project ID 8940. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

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