

A Focus on Chronic Myelogenous Leukemia



ASHP *Advantage* E-Newsletter

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Update on Tyrosine Kinase Inhibitor Therapy for Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML), a hematologic malignancy associated with a chromosomal mutation commonly known as the Philadelphia chromosome, accounts for 10% to 15% of all leukemias in the United States.¹ More than 5,000 Americans will be diagnosed with CML this year. Dramatic improvement in survival has been achieved in recent years from the introduction of tyrosine kinase inhibitors (TKIs). This prolonged survival has been accompanied by new clinical challenges in caring for patients with CML.

ASHP *Advantage* with the support of Novartis Oncology has developed an educational initiative to equip health-system pharmacists to select and manage drug therapy in patients with CML. The initiative comprises a live educational activity on CML, *Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy*, with interactive case studies to be conducted in 17 different locations in cooperation with ASHP state affiliates. Audience response questions are integrated into the case studies, allowing participants to apply the information to different patient scenarios. For the convenience of people unable to travel to one of the 17 locations on the scheduled dates, the educational activity was conducted as a live webinar in April, May, and June. The archived webinar is available as a web-based activity that you can access at <http://www.ashpmedia.org/symposia/cml/> and complete from your desk at home or in your office at any time. The activity has been developed by a group of nationally-recognized oncology experts. One hour (0.1 CEU) of continuing pharmacy education (CPE) credit is offered at no charge. At the conclusion of the knowledge-based educational activity, participants should be able to:

- Describe the epidemiology, molecular biology, clinical presentation, and disease progression of CML.
- Describe the currently accepted standard treatments and response monitoring parameters for CML.
- Describe the role of second-generation TKIs in imatinib-resistant CML and emerging evidence related to their use.
- Identify options for preventing and managing toxicities, drug-drug interactions, and drug-food interactions related to TKIs.
- Identify areas of emerging research related to therapies for CML.

To obtain further details, including a schedule of dates and locations for the live educational activities and to register, go to www.ashpadvantage.com/cml today!

Faculty

Christopher A. Fausel, Pharm.D., BCPS, BCOP
Co-chair, CML Initiative
Clinical Director, Oncology Pharmacy Services
Indiana University Simon Cancer Center
Indianapolis, Indiana

R. Donald Harvey III, Pharm.D., FCCP, BCPS, BCOP
Co-chair, CML Initiative
Assistant Professor
Department of Hematology/Medical Oncology
Director, Phase I Unit
Winship Cancer Institute
Emory University
Atlanta, Georgia

Ashley Morris Engemann, Pharm.D., BCOP
Clinical Associate
Department of Medicine
Duke University Medical Center
Durham, North Carolina

Amy Hatfield Seung, Pharm.D., BCOP
Pharmacy Clinical Specialist,
Hematologic Malignancies
Director, PGY2 Oncology Residency
Program
Sidney Kimmel Comprehensive
Cancer Center
Johns Hopkins Hospital
Assistant Clinical Professor
University of Maryland School of
Pharmacy
Baltimore, Maryland

Joseph S. Bubalo, Pharm.D., BCPS, BCOP
Oncology Clinical Pharmacy Specialist
Assistant Professor of Medicine, Division of
Hematology and Medical Oncology
Oregon Health Sciences University
Hospitals & Clinics
Portland, Oregon

Let Us Know

ASHP *Advantage* is interested to know how educational activities affect pharmacy practice and patient outcomes, and what educational needs might remain after an activity. Therefore, participants in the live educational activity will be asked how information gleaned from the activity might be applied in clinical practice and what educational needs remain. Participants in the live webinars will receive a brief e-mail survey from ASHP *Advantage* with questions designed to ascertain the potential or documented impact of information obtained from the webinar on clinical practice and identify any unmet educational needs. Please complete the evaluation or survey to provide us with feedback about changes in practice, patient outcomes, and unmet educational needs. The aggregate information also will be used to plan future educational activities.

Breaking News from June 2010 ASCO Annual Meeting

Research to improve the prognosis and outcomes in patients with CML continues at a rapid pace, with news of progress continually emerging. The TKI imatinib is well established as the standard of care.² However, resistance to imatinib can develop, leading to treatment failure. Ongoing clinical trials continue to define the optimal use of imatinib and second-generation TKIs in patients with CML.

The American Society of Clinical Oncology (ASCO) Annual Meeting, the premier event for sharing late-breaking clinical research findings in the oncology community, was held June 4-8, 2010, in Chicago, Illinois. The 52nd American Society of Hematology Annual Meeting and Exposition will be held December 4-7, 2010, in Orlando, Florida.

According to current clinical practice guidelines of the National Comprehensive Cancer Network (NCCN), imatinib is standard first-line therapy for CML in the chronic phase, with the second-generation TKIs dasatinib and nilotinib reserved for patients who develop resistance to or are unable to tolerate imatinib.² The results of recent research into the use of these second-generation agents as initial therapy were presented at the recent ASCO meeting.

First-Line Nilotinib in Early Chronic-Phase CML

An update with 18-month data from the Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients, a phase III, randomized, open-label study known as ENESTnd, was presented at the ASCO meeting.³ In this study, the efficacy and safety of imatinib 400 mg once daily (the current standard of care) and two dosing regimens of nilotinib were compared in 846 adults with newly-diagnosed CML in the chronic phase. After 12 months, nilotinib 300 mg twice daily and 400 mg twice daily both induced significantly higher rates of and shorter times to major molecular response (the primary endpoint) and complete cytogenetic response (a secondary endpoint) compared with imatinib. The 12-month major molecular response rate was 44%, 43%, and 22% with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg once daily, respectively. The complete cytogenetic response rate was 80%, 78%, and 65% with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg once daily, respectively. These findings also were presented at the 51st American Society of Hematology Annual Meeting and Exposition in December 2009 and published online by Saglio and colleagues on June 5, 2010 in the *New England Journal of Medicine*.^{4,5} In February 2010, the Food and Drug Administration granted nilotinib priority review for the treatment of adults with newly-diagnosed CML in the chronic phase based in part on these data.

A protocol extension allows patients with a suboptimal response to or treatment failure while receiving imatinib to escalate the imatinib dosage or switch to nilotinib.⁶ Follow up is planned for 5 years. The 18-month data presented at the ASCO meeting are consistent with the 12-month findings of significantly higher rates of major molecular response and complete cytogenetic response from both dosages of nilotinib compared with imatinib. The 18-month findings also

demonstrate an increase in molecular responses and significantly lower rates of progression to advanced disease with the use of nilotinib, resulting in fewer deaths from CML compared with imatinib. Three times more patients receiving nilotinib achieved undetectable disease at the molecular level than patients treated with imatinib.

A 24-month update of a phase II clinical trial known as GIMEMA of the safety and efficacy of nilotinib 400 mg twice daily in patients with early chronic-phase CML also was provided at the ASCO meeting.^{7,8} The intention-to-treat complete cytogenetic response rate (the primary endpoint) was 78% after 3 months and 96% after 6 months, 12 months, and 18 months. The major molecular response rates after 1 month, 2 months, 3 months, 6 months, 12 months, and 18 months were 3%, 21%, 52%, 66%, 85% and 87%, respectively. One patient with a T315I mutation progressed to advanced phase CML within 6 months, but no additional patients progressed during the second year of treatment. Adverse events included increases in bilirubin, liver enzymes, lipase, and amylase (without pancreatitis) and were primarily grade 1 or grade 2 in severity and manageable with dosage reduction. These findings demonstrate that the response to nilotinib is stable over a long period, and provide added support for the use of nilotinib as first-line therapy for early chronic-phase CML.

First-Line Dasatinib in Early Chronic-Phase CML

The efficacy and safety of imatinib and dasatinib for treating newly-diagnosed chronic-phase CML were compared in the Dasatinib versus Imatinib Study in Treatment-Naive CML Patients (DASISION). In this phase III, open-label study, 519 adults with newly-diagnosed chronic-phase CML were randomly assigned to receive single daily doses of dasatinib 100 mg or imatinib 400 mg for at least 12 months. Results were presented at the ASCO meeting and published simultaneously online on June 5, 2010 in the *New England Journal of Medicine*.^{9,10} Significantly higher rates of and shorter times to complete cytogenetic response (the primary endpoint) and major molecular response (a secondary endpoint) were achieved with dasatinib than imatinib. The complete cytogenetic response rate was 77% with dasatinib and 66% with imatinib. The major molecular response rate was 46% with dasatinib and 28% with imatinib. Five (1.9%) patients receiving dasatinib and 9 (3.5%) patients receiving imatinib progressed to the accelerated phase or blast crisis. The safety profiles of the two drugs were similar. The DASISION data will be submitted to worldwide regulatory authorities for approval of dasatinib as first-line therapy for newly-diagnosed adults with chronic-phase CML in 2010. The DASISION, ENESTnd, and GIMEMA findings suggest that second-generation TKIs may take the place of imatinib in treating newly-diagnosed chronic-phase CML.

Discontinuation of Long-Term Imatinib Therapy

The possibility of safely discontinuing long-term imatinib therapy without risking a relapse in patients with a sustained response to the drug has been explored in clinical trials, but the practice has not yet been recommended in NCCN guidelines because of insufficient data.² Promising results were obtained in the multicenter Stop Imatinib (STIM) trial and an associated pilot study designed to evaluate the long-term consequences of imatinib discontinuation in patients with CML who had been treated with the drug for at least 3 years with a complete molecular remission (CMR) for at least 2 years.^{11,12} An update on enrollees in the STIM study and patients participating in the pilot study was provided at the American Society of Hematology Annual Meeting in December 2009.¹³ Eight (53%) of 15 pilot study patients remained in CMR after imatinib discontinuation with a median follow-up time of 42 months (range 37-49 months).¹³ The median follow-up time for 69 enrollees in the STIM study was 17 months (range 6-24 months). Thirty seven (54%) STIM study patients relapsed (i.e., experienced loss of CMR) within the first 6 months, and two patients relapsed during month 7 and month 18, respectively, after imatinib discontinuation. The probability of remaining in CMR 12 months after imatinib discontinuation was 45%. The use of interferon alfa prior to imatinib did not affect the probability of relapse. All of the patients in molecular relapse exhibited sensitivity to imatinib after a rechallenge with the drug. Male patients had a significantly better

probability of survival without molecular relapse than did women. Patients who relapsed had significantly lower cytotoxic natural killer (NK) cell counts in their peripheral blood prior to imatinib discontinuation than patients who remained in CMR. These data reinforce prior findings suggesting that it may be feasible to discontinue long-term imatinib therapy in patients with CML who have achieved a sustained molecular response, especially male patients and patients without low cytotoxic NK cell counts.

Role of Therapeutic Drug Monitoring of Imatinib Therapy for CML

Imatinib is the standard of care for CML, but inadequate response and treatment failure can occur in part because exposure to imatinib varies widely among patients receiving the same dosage. This variability may be related to differences in drug metabolism by cytochrome P-450 (CYP) enzymes, drug interactions, patient-specific variables (e.g., body weight), and nonadherence to the prescribed regimen.¹⁴ Recent data suggest that maintaining an adequate imatinib trough plasma concentration (e.g., approximately 1000 ng/mL or higher) may correlate with favorable clinical responses in patients with CML. Severe adverse effects may reflect high imatinib plasma concentrations, although the relationship between concentration and toxicity is not necessarily linear. Imatinib is metabolized primarily by CYP3A4, and drugs that induce or inhibit the isoenzyme could affect imatinib plasma concentrations. Therapeutic drug monitoring may be useful during imatinib therapy in certain patients with CML and an inadequate response to or toxicity from initial therapy. Additional research is needed to clarify the relationship between imatinib plasma concentration and response and the role of imatinib therapeutic drug monitoring in patients with CML. Routine monitoring is not widely recommended and currently is not the standard of care.

Tyrosine Kinase Inhibitors and Pregnancy

Male and female patients with CML who wish to or inadvertently conceive may seek advice on whether to discontinue TKI therapy because of concerns about the fetus. Although these concerns must be weighed against the risk of relapse from interruption of therapy, recent data suggest that imatinib therapy may be safely interrupted without undue risk of relapse in selected patients with a sustained response.¹³ Limited information is available about the use of imatinib and other TKIs before conception and during and after pregnancy.¹⁵

Animal data suggest that fertility is unlikely to be affected by imatinib therapy, but semen cryopreservation, ovarian or oocyte retrieval and storage, and embryo cryopreservation might be considered for patients receiving imatinib who wish to conceive because of limited fertility data in humans. The use of imatinib by men at the time of conception does not appear to increase the risk of congenital abnormalities in offspring, so interruption of therapy is not necessary for men who wish to conceive. However, congenital abnormalities have been reported in offspring conceived during imatinib therapy in the mother, especially when exposure was during the first trimester. Women receiving imatinib who wish to conceive should discontinue the drug at least a few days before attempting to conceive to allow washout of the drug; these women should not allow more than 6 months to elapse without imatinib therapy if conception has not occurred (i.e., therapy should resume and attempts to conceive should be postponed if more than 6 months have elapsed without imatinib therapy). Alternatives to imatinib for CML treatment in women with loss of complete hematologic response during pregnancy include interferon alfa during the second and third trimesters and regular leukapheresis in all three trimesters. These therapies might be considered for women with loss of major molecular or complete cytogenetic response during pregnancy. Breastfeeding should be strongly discouraged for mothers taking imatinib because the drug and its active metabolite are excreted into human milk, with the potential to harm the nursing infant.¹⁶ Postpartum resumption of imatinib therapy may be postponed to allow breastfeeding in women with a major molecular response.

Fewer data are available for second-generation TKI use before and during pregnancy than for imatinib. Women should be advised to avoid becoming pregnant while taking nilotinib or dasatinib because of the potential for fetal harm.^{17,18} It is not known whether nilotinib or dasatinib is excreted in human breast milk, so mothers taking these drugs should not breast feed.^{17,18} Animal studies suggest that dasatinib may impair male fertility, but nilotinib did not appear to affect male fertility.^{17,18} The implications of these findings for humans are unclear.

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