

Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

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Integrating Current Treatment Options for TKI-Resistant Chronic Myeloid Leukemia

Discussants



Jerald P. Radich, MD

Director, Molecular Oncology Lab
Clinical Research Division
Fred Hutchinson Cancer Research Center
Professor of Medicine and Adjunct Professor of Pathology
University of Washington
Seattle, Washington



Neil P. Shah, MD, PhD

Associate Professor, Department of Medicine
Edward S. Ageno Distinguished Professor
in Hematology-Oncology
Leader, Hematopoietic Malignancies Program
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California



Michael J. Mauro, MD

Leader, Myeloproliferative Neoplasms Program
Professor of Medicine and Member
Memorial Sloan Kettering Cancer Center
New York, New York

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Abstract: Chronic myeloid leukemia (CML) is a myeloproliferative disorder that accounts for approximately 10% of new cases of leukemia. The introduction of tyrosine kinase inhibitors (TKIs) has led to a reduction in mortality rates, and the estimated prevalence of CML is increasing accordingly. Most patients with CML are diagnosed in the chronic phase, and approximately 15% to 30% of these patients will meet some definition of resistance to imatinib. In the more advanced phases of disease, the rates of imatinib resistance are much higher. Both the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) guidelines emphasize adequate monitoring of patients to ensure that they are meeting treatment milestones. Loss of response is most commonly associated with the acquisition of resistance-conferring kinase domain point mutations within *BCR-ABL1*. The multiple treatment options available for patients with imatinib-resistant CML include dasatinib, nilotinib, bosutinib, and ponatinib, as well as the non-TKI salvage agent omacetaxine mepesuccinate. Treatment selection is based on factors such as the patient's disease state, prior therapies, comorbidities, treatment toxicity, and goals of therapy. This clinical roundtable monograph provides expert discussion on the monitoring of TKI-resistant CML, when to change therapy, and how to select the best treatment option.

Target Audience

This activity has been designed to meet the educational needs of physicians, nurses, academicians, researchers, investigators, support staff, and program directors from the field of oncology involved in the care of patients with chronic myeloid leukemia.

Statement of Need/Program Overview

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the hematopoietic stem cells. CML is defined in part by the presence of the Philadelphia (Ph) chromosome, a specific chromosomal translocation that results in the fusion of the *BCR* and *ABL* genes. The first-generation tyrosine kinase inhibitor (TKI) imatinib, as well as the second-generation TKIs nilotinib and dasatinib, have greatly improved outcomes in CML by targeting the *BCR-ABL* oncogenic kinase. However, not all patients respond well to these treatments, and even more patients lose response over time. Novel agents in CML include bosutinib, omacetaxine mepesuccinate, and ponatinib. In November 2013, marketing and commercial distribution of ponatinib was temporarily suspended by the US Food and Drug Administration, less than a year after it had received accelerated approval in CML. Guideline recommendations vary regarding the management of CML. Physicians must be aware of how to incorporate novel agents into treatment algorithms and thereby optimize outcomes.

Educational Objectives

After completing this activity, the participant should be better able to:

- Recognize when a CML patient is intolerant to a tyrosine-kinase inhibitor
- Manage adverse events related to tyrosine-kinase inhibitors
- Identify CML patients who are likely to benefit from novel agents
- Implement treatment strategies incorporating novel agents in CML

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Monitoring of TKI-Resistant Chronic Myeloid Leukemia

Jerald P. Radich, MD
 Director, Molecular Oncology Lab
 Clinical Research Division
 Fred Hutchinson Cancer Research Center
 Professor of Medicine and Adjunct Professor of Pathology
 University of Washington
 Seattle, Washington

Chronic myeloid leukemia (CML) is a myeloproliferative disorder marked by the increased proliferation of a granulocytic cell line that retains the ability to differentiate. As many as 95% of patients with CML have the Philadelphia (Ph) chromosome.^{1,2} This chromosomal alteration involves the reciprocal translocation of the long arms of chromosome 22 at the breakpoint cluster region (*BCR*) gene and chromosome 9 at the Abelson leukemia virus (*ABL*) gene (t[9;22]).³ As a result of this translocation, a *BCR-ABL1* fusion gene is created that generates a chimeric protein with constitutively active tyrosine kinase activity.¹ Although the *BCR-ABL1* rearrangement is a hallmark of CML, the *BCR-ABL1* fusion gene and oncoprotein are also associated with other diseases, such as acute lymphoblastic leukemia.⁴

Epidemiology

CML accounts for approximately 10% of new cases of leukemia.⁵ An individual's lifetime risk of developing CML is 1 in 588.⁵ The estimated worldwide annual incidence of CML is 0.6 to 2.0 cases per 100,000 individuals.⁶ The annual incidence of CML in the United States is 1.0 to 1.3 per 100,000 individuals, which translates to approximately 5980 new cases in 2014.^{5,7} The incidence of CML increases with age, and the disease occurs slightly more often in men than in women (male-to-female ratio, 1.3-1.8).⁶ The average age of diagnosis is 64 years.⁵

In 2014, an estimated 810 people will die of CML (550 men and 260 women).⁵ Before the introduction of tyrosine kinase inhibitors (TKIs), the median survival of patients with CML was approximately 6 years; the estimated annual mortality rate was approximately 10% for the first 2 years and 20% to 25% thereafter.^{8,9} Currently, the estimated all-cause mortality rate for patients with CML is 2% for the first 10 years of follow-up.⁹ As a consequence of the introduction of TKIs, overall improvements in the management of CML, and a reduction in mortality

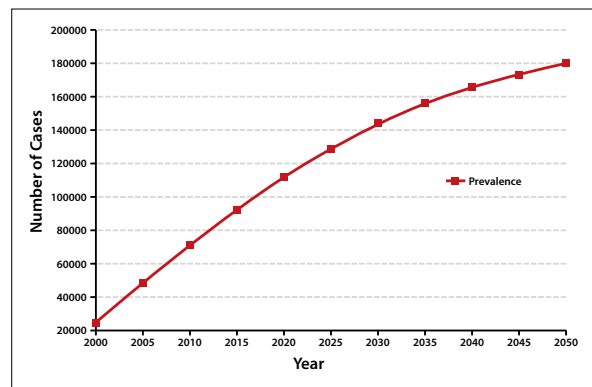


Figure 1. As a consequence of the introduction of tyrosine kinase inhibitors, overall improvements in the management of CML, and a reduction in mortality rates, the estimated prevalence of CML is rising, from 70,000 in 2010 to an estimated 112,000 in 2020. CML, chronic myeloid leukemia. Adapted from Huang X et al. *Cancer*. 2012;118(12):3123-3127.⁹

rates, the estimated prevalence of CML is rising, from 70,000 in 2010 to an estimated 112,000 in 2020 (Figure 1).⁹ It is anticipated that the prevalence of patients living with CML will plateau in the year 2050 at 181,000.⁹

Symptoms and Prognosis

The symptoms of CML are fairly nonspecific. The most common symptoms are splenomegaly, which occurs in 50% to 60% of patients, and an elevated white blood cell count.¹⁰ Other symptoms include weakness, fatigue, night sweats, weight loss, fever, bone pain, hepatomegaly, and pain or a sense of “fullness” in the stomach.⁵ Less commonly, patients may experience bleeding, thrombosis, gouty arthritis, priapism, retinal hemorrhages, or upper gastrointestinal ulceration and bleeding.¹⁰ Up to 50% of CML patients are asymptomatic, and the diagnosis is made after a routine blood test reveals an abnormal white cell count.²

Adverse prognostic indicators include accelerated-phase or blast-phase disease, splenomegaly, hepatomegaly, Ph-chromosome negativity, bone damage, elevated numbers of basophils and eosinophils, abnormal platelet counts, age older than 60 years, and multiple chromosome changes in the CML cells.⁵ Several risk classification systems are in use, including the Sokal,¹¹ Hasford,¹² and European Treatment and Outcomes Study (EUTOS) scores.¹³

Diagnosis

CML is diagnosed by a complete blood cell count with differential, a peripheral blood smear, and bone marrow aspiration with biopsy.^{14,15} The definitive diagnosis of CML is based on the presence of the Ph chromosome (t[9;22]) by cytogenetic analysis of the bone marrow cells, fluorescence in situ hybridization (FISH) analysis of the peripheral blood cells, or quantitative reverse transcription polymerase chain reaction (RT-PCR) in the blood or bone marrow. Most classification schemes will call for a diagnosis via cytogenetic analysis (t[9;22]), chromosome banding analysis of the marrow cell metaphases, and molecular studies examining the *BCR-ABL1* translocation by quantitative RT-PCR.^{15,16} FISH of peripheral blood specimens with dual probes for the *BCR* and *ABL* genes can be used for diagnosis when it is not possible to obtain a bone marrow aspirate.^{15,17}

Phases of Chronic Myeloid Leukemia

CML is divided into 3 phases based on the number of immature white blood cells (myeloblasts) observed in the blood or bone marrow.⁵ The World Health Organization (WHO) defines these as chronic, accelerated, and blast phases.¹⁴ CML is usually diagnosed in the chronic phase. Patients with chronic-phase disease have fewer than 10% blasts and minimal, if any, symptoms; they typically respond to treatment. The chronic phase is marked by proliferation of primarily the myeloid element, which is manifested by an increase in the white blood cell count in the periphery and by expansion of the myeloid series in the bone marrow. There is approximately 100% cellularity. Cytogenetic testing should reveal the presence of the Ph chromosome (t[9;22]) and no other clonal abnormalities. If additional chromosomal abnormalities are present, the disease should be classified as accelerated phase.

Patients with accelerated-phase disease are less responsive to treatment than patients with chronic-phase disease, and they have a higher percentage of blast cells. The precise percentage varies among the classification systems.¹⁴⁻¹⁶ The WHO system delineates the blast percentage as more than 10% and fewer than 20%.¹⁴ Other classification systems define the accelerated phase as a

blast percentage in the blood or bone marrow of at least 15% but less than 30%.¹⁶ In the WHO classification, diagnosis of accelerated-phase disease requires at least 1 of the following characteristics¹⁴:

- A blast percentage of more than 10% and fewer than 20%.
- High basophil counts ($\geq 20\%$ in the peripheral blood).
- Persistent thrombocytopenia ($< 100 \times 10^9/L$) or persistent thrombocytosis ($> 1000 \times 10^9/L$) that is unrelated to therapy.
- Increasing spleen size or high white cell counts that are unresponsive to treatment.
- New chromosomal abnormalities in the leukemic cells.
- Megakaryocytic proliferation that is associated with fibrosis and/or severe granulocytic dysplasia.

The blast phase is characterized by at least 20% blasts with spread of the blast cells beyond the bone marrow.¹⁴ The WHO classification bases the diagnosis on the presence of 1 or more of the following characteristics¹⁴:

- At least 20% blasts in the peripheral blood white cells or bone marrow cells.
- Extramedullary blast proliferation.
- Large foci or clusters of blasts in a bone marrow biopsy specimen.

As with the accelerated phase, the percentage of blast cells required for diagnosis of blast-phase disease differs according to the guidelines used. The WHO classification calls for at least 20%, whereas the European LeukemiaNet (ELN) classification requires at least 30%.^{14,16} It should be noted that the blast or crisis phase of disease is usually fatal if the patient is not treated aggressively with a transplant. The causes of death during blast crisis are usually complications of infection or bleeding.

Monitoring of Patients With Chronic Myeloid Leukemia

The basic tools for monitoring CML patients are bone marrow cytogenetics for the Ph chromosome and peripheral blood RT-PCR for the *BCR-ABL* transcript. The goal is to first reach a complete cytogenetic response (CCyR), defined as the absence of at least 20 evaluable bone marrow metaphases.

The monitoring guidelines of the National Comprehensive Cancer Network (NCCN) and ELN are slightly different, but can be distilled into a few simple points. First, cytogenetics should be performed until a CCyR is established. Generally, this means testing every 3 months.^{15,16} Once a CCyR is obtained, further cytogenetic testing is not needed unless there is a change in the clinical/laboratory situation (eg, an unexpected rise in the peripheral blood

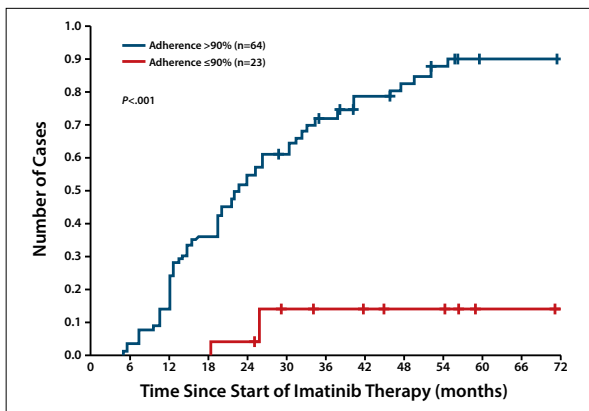


Figure 2. In a study of 87 patients with chronic myeloid leukemia receiving imatinib, 6-year probability of MMR was significantly increased among those with higher adherence rates. MMR, major molecular response. Adapted from Marin D et al. *J Clin Oncol*. 2010;28(14):2381-2388.¹⁸

BCR-ABL). RT-PCR is performed on the peripheral blood every 3 months; once a MMR is established, this testing can be reduced to every 3 to 6 months.

It should be noted that a *BCR-ABL* of 1% roughly equates to the level of CCyR; therefore, some expert centers will use only RT-PCR to monitor patients (after the Ph chromosome has initially been confirmed to make the diagnosis), and only perform cytogenetics if the *BCR-ABL* level is not falling appropriately, or if it rises after initially falling.

An increase in *BCR-ABL1* transcript levels by RT-PCR can be attributed to either the development of resistance or poor adherence to treatment.¹⁵ An unusual spike in the *BCR-ABL1* transcript level in the peripheral blood should prompt physicians to determine the degree of treatment compliance. Patients may be tempted to stop taking their therapy, especially when they experience an excellent response, have symptomatic problems, or must pay for their drug out-of-pocket. These so-called *drug holidays* can lead to an increase in the *BCR-ABL1* transcript level. Studies have shown that rates of compliance with imatinib treatment range from below 25% to 90%, and worse outcomes are associated with lower adherence rates (Figure 2).¹⁸⁻²⁰

Mutational Analysis

The NCCN recommends a *BCR-ABL* kinase domain mutational analysis for all patients who have a suboptimal initial response to TKI therapy.¹⁵ This population includes patients with disease that has progressed to the accelerated or blast phase, as well as patients in the chronic phase who have an inadequate initial response to TKI therapy, loss of hematologic response or cytogenetic relapse, or a 1-log increase in *BCR-ABL1* transcripts with a loss of major molecular response.¹⁵ Mutational analyses are usually

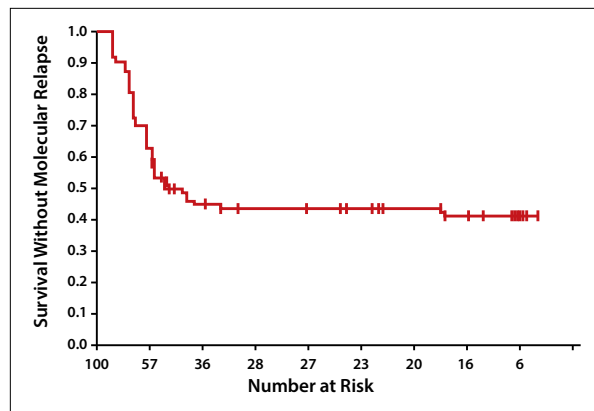


Figure 3. Kaplan-Meier estimates of complete molecular remission after discontinuation of imatinib in patients with chronic myeloid leukemia. For 100 patients, the estimated molecular relapse-free survival was 45% (95% CI, 34%-55%) at 6 months, 43% (95% CI, 33%-53%) at 12 months, and 41% (95% CI, 34%-55%) at 24 months. Adapted from Mahon FX et al. *Lancet Oncol*. 2010;11(11):1029-1035.²³

performed when patients fail to reach the endpoint guidelines or have reached those endpoints and then experience disease progression. *BCR-ABL1* kinase domain point mutations are associated with both imatinib resistance and secondary resistance.²¹ At least 100 different point mutations have been identified thus far.²¹ The T315I mutation is seen in 4% to 15% of patients with imatinib resistance.²¹ Other mutations of note include T315A, V299L, and F359V, which are associated with resistance to dasatinib, and Y253H, E255K/V, L273M, and F359V, which are associated with resistance to nilotinib.¹⁰ Identification of the point mutation at the time of treatment failure is essential for determining the appropriate salvage therapy; second-line and third-line treatment options should be chosen based on the known effectiveness of a specific TKI for a specific point mutation.²²

Using Monitoring to Improve Management

The ways in which monitoring will influence management depend upon the particular patient characteristics. In an older patient whose treatment goals are stable disease and symptom relief, the aim should be to decrease levels of the *BCR-ABL1* transcript or to achieve a cytogenetic response. In younger patients, who may be receiving aggressive treatment, monitoring has the potential to alter the natural history of the disease by preventing the transformation to accelerated phase or blast crisis, which are difficult to treat with TKIs or transplant. The goal for these patients is to achieve complete molecular remission. The latter endpoint is important because approximately 40% of patients who are in sustained complete molecular remission (>2 years of negativity by PCR) can discontinue therapy for up to 2 years (Figure 3).²³ Although this

approach should be used only in the context of a clinical trial, complete molecular remission is becoming an important clinical management goal.

Conclusion

Bone marrow aspirates and biopsies are needed at the time of diagnosis to assess the phase of disease; monitoring can be done thereafter primarily by peripheral blood RT-PCR. Peripheral blood RT-PCR is important for monitoring treatment endpoints and assessing the depth of the response, which translates into the risk of progression. After therapy has been initiated and patients are being followed by RT-PCR, bone marrow cytogenetic analyses can be performed if *BCR-ABL1* transcript levels increase and resistance develops.

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References

- Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature*. 1973;243(5405):290-293.
- Torgerson SR, Haddad RY, Atallah E. Chronic myelogenous leukemia for primary care physicians. *Dis Mon*. 2012;58(4):168-176.
- Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. *N Engl J Med*. 1999;341(3):164-172.
- Naka K, Hoshii T, Tadokoro Y, Hirao A. Molecular pathology of tumor-initiating cells: lessons from Philadelphia chromosome-positive leukemia. *Pathol Int*. 2011;61(9):501-508.
- Leukemia—chronic myeloid (myelogenous). American Cancer Society. <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-key-statistics>. Updated February 10, 2014. Accessed June 5, 2014.
- Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukaemia (CML). *Best Pract Res Clin Haematol*. 2009;22(3):295-302.
- Arias E. United States life tables, 2006. *Natl Vital Stat Rep*. 2010;58(21):1-40.
- Tura S, Baccarani M, Zuffa E, et al; The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med*. 1994;330(12):820-825.
- Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Cancer*. 2012;118(12):3123-3127.
- Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management. *Am J Hematol*. 2012;87(11):1037-1045.
- Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood*. 1984;63(4):789-799.
- Hasford J, Pfirrmann M, Hehlmann R, et al; Writing Committee for the Collaborative CML Prognostic Factors Project Group. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. *J Natl Cancer Inst*. 1998;90(11):850-858.
- Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. *Blood*. 2011;118(3):686-692.
- Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*. 2002;100(7):2292-2302.
- NCCN clinical practice guidelines in oncology. Chronic myelogenous leukemia. Version 3.2014. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Updated January 15, 2014. Accessed June 4, 2014.
- Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.
- Baccarani M, Pileri S, Steegmann J-L, Muller M, Soverini S, Dreyling M; ESMO Guidelines Working Group. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):vii72-vii77.
- Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010;28(14):2381-2388.
- Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics*. 2007;25(6):481-496.
- Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*. 2009;113(22):5401-5411.
- Bhamidipati PK, Kantarjian H, Cortes J, Cornelison AM, Jabbour E. Management of imatinib-resistant patients with chronic myeloid leukemia. *Ther Adv Hematol*. 2013;4(2):103-117.
- Jabbour E, Jones D, Kantarjian HM, et al. Long-term outcome of patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors after imatinib failure is predicted by the in vitro sensitivity of *BCR-ABL* kinase domain mutations. *Blood*. 2009;114(10):2037-2043.
- Mahon FX, Réa D, Guilhot J, et al; Intergroupe Français des Leucémies Myéloïdes Chroniques. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010;11(11):1029-1035.

Changing Therapy in TKI-Resistant Chronic Myeloid Leukemia

Neil P. Shah, MD, PhD

Associate Professor, Department of Medicine

Edward S. Ageno Distinguished Professor in Hematology-Oncology

Leader, Hematopoietic Malignancies Program

UCSF Helen Diller Family Comprehensive Cancer Center

San Francisco, California

The question of when to change therapy in TKI-resistant CML is an important one because there are numerous second-line and third-line treatment options available. It is particularly important to recognize resistance as soon as possible in patients with chronic-phase CML, who have a favorable outlook when switched to an appropriate therapy in a timely manner. The incidence of resistance to TKIs is directly correlated to the phase of CML. Approximately 35% of patients in chronic-phase disease will meet some definition of resistance to imatinib within the first year of treatment.¹⁻³ In accelerated-phase CML, resistance rates are 45% to 66%, and in blast-phase disease, resistance exceeds 90%.⁴⁻⁶

Resistance can be defined in several ways. *Primary* resistance refers to the lack of an initially acceptable response; *secondary* resistance is the loss of an established response. The criteria for primary resistance include the failure to achieve a complete hematologic response by 3 months, a partial cytogenetic response and/or a *BCR-ABL1* transcript level at or below 10% as measured by the International Scale (IS) within 3 to 6 months, and a CCyR and/or a *BCR-ABL1* transcript level below 1% within 12 months.^{7,8} The rates of both primary and secondary resistance increase as CML disease progresses, with the loss of response occurring more often in patients with advanced or blast-phase CML.^{5,6} Like response, resistance is also described as hematologic, cytogenetic, or molecular; all of these types can occur in the primary or secondary setting. For example, a patient with primary resistance can have a hematologic response but no cytogenetic response, and it is possible to lose cytogenetic or molecular response prior to losing hematologic response.

The NCCN defines a complete hematologic response as the normalization of peripheral blood cell counts (leukocyte count $<10 \times 10^9/L$ and platelet count $<450 \times 10^9/L$); the absence of immature cells in the peripheral blood; and the absence of signs or symptoms of disease, including splenomegaly.⁷ Primary hematologic resistance is defined as the failure to achieve a normal complete blood cell count and differential, as well as persistence of any extramedullary disease. In patients with newly diagnosed

chronic-phase CML, primary hematologic resistance is extremely rare, occurring in approximately 2% to 4%.^{7,9} Primary cytogenetic resistance is more common among these patients. The NCCN recognizes a CCyR as the ultimate goal of treatment for all CML patients.⁷ The minimal acceptable cytogenetic response is defined as a reduction in the level of Ph chromosome-containing metaphases in the bone marrow to 35% or lower by 3 months of treatment.⁷ The NCCN defines cytogenetic resistance as failure to achieve a CCyR (as indicated by the absence of at least 20 evaluable bone marrow metaphases) at 12 months.⁷ Among CML patients who receive imatinib, primary cytogenetic resistance occurs in approximately 35%.¹⁰ In the frontline setting, the rate of primary cytogenetic resistance to the second-generation agents, such as nilotinib and dasatinib, is substantially lower.^{10,11}

Primary molecular resistance is defined as the failure to achieve either an early molecular response (*BCR-ABL1* transcript level $\leq 10\%$ [IS] by 3 to 6 months) or a major molecular response ($<0.1\%$ [ELN]) by 12 months.^{7,8} Approximately 35% of patients fail to achieve an early molecular response with imatinib. This rate is lower—between 10% and 15%—in those treated with the second-generation agents, nilotinib and dasatinib, in the first-line setting (Table 1).^{1,12} Approximately 70% of imatinib-treated patients and 50% of dasatinib- or nilotinib-treated patients fail to achieve a major molecular response by 12 months.^{10,13} It may be that a deeper molecular response is associated with better long-term outcomes, but with relatively limited follow-up to date, favorable outcomes have been seen in patients who achieve a CCyR, irrespective of the degree of their molecular response. Therefore, the NCCN does not view a 3-log reduction in the transcript level (major molecular response) as a treatment endpoint.⁷ Patients whose disease becomes undetectable (≥ 4.5 -log transcript reduction) may be eligible for clinical trials that are evaluating TKI discontinuation in an effort to determine if prolonged treatment-free remission is possible.

Secondary resistance is a bigger concern for patients with CML. It most often occurs when *BCR-ABL1* reac-

Table 1. Resistance Associated With Tyrosine Kinase Inhibitors

Frontline Tyrosine Kinase Inhibitor	Hematologic Resistance	Cytogenetic Resistance (12 months)	Molecular Resistance (3 months)
Imatinib	Rare	++	++
Nilotinib	Rare	+	+
Dasatinib	Rare	+	+

Data from Jabbour E et al. *Blood*. 2014;123(4):494-500¹ and Hughes TP et al. *Blood*. 2014;123(9):1353-1360.¹²

Table 2. Resistance Mechanisms of Tyrosine Kinase Inhibitors

Tyrosine Kinase Inhibitor	Potential Primary Resistance Mechanisms	Documented Secondary Resistance Mechanisms
Imatinib	Insufficient <i>BCR-ABL</i> inhibition, low plasma drug level, low OCT1 expression, <i>BIM</i> polymorphism, high marrow FGF2 expression, poor hematopoietic stem cell reserve, kinase domain mutation, nonadherence	Kinase domain mutation, <i>BCR-ABL</i> gene amplification, nonadherence
Dasatinib, nilotinib, bosutinib	<i>BIM</i> polymorphism, poor hematopoietic stem cell reserve, kinase domain mutation, nonadherence	Kinase domain mutation, nonadherence
Ponatinib	<i>BIM</i> polymorphism, poor hematopoietic stem cell reserve, kinase domain mutation, nonadherence	Compound (≥ 2) kinase domain mutation, nonadherence

tivates as a consequence of mutation, gene amplification, or increased expression, although some patients with secondary resistance do not have any of these features.⁷ It should be noted that loss of response due to treatment nonadherence can appear indistinguishable from secondary resistance. Primary resistance is a clear risk factor for the eventual development of secondary resistance. For example, a patient who fails to achieve a CCyR by 12 months is at higher risk of disease progression than a patient who achieves this milestone. Secondary resistance has been documented in approximately 10% to 15% of patients who have chronic-phase CML treated with imatinib.^{3,14,15} The rates of secondary resistance in frontline treatment with second-generation TKIs appear to be slightly lower than with imatinib, but follow-up has been shorter.¹⁶

Mechanisms of TKI Resistance

Loss of response is most commonly associated with the acquisition of resistance-conferring kinase domain point mutations within *BCR-ABL1*. Such mutations render cells with this modified form of *BCR-ABL1* insensitive to therapy. These mutations are detectable in 30% to 70% of such patients.^{15,17,18} There are close to 100 distinct TKI-resistant point mutations, and they occur in various locations throughout the *ABL* sequence, including the P-loop (adenosine triphosphate-binding domain), the catalytic domain, and the activation loop.^{19,20} The most frequently identified mutations occur in the P-loop; important examples of these mutations include G250E, Y253F/H, and E255K/V.^{21,22} Other mutations that can influence patient response to TKIs

include T315I, M351T, and F359V.²¹ The T315I mutation occurs in 4% to 15% of patients and confers resistance to imatinib, nilotinib, dasatinib, and bosutinib.²⁰

A less common mechanism of resistance involves *BCR-ABL* amplification, which can confer loss of response or secondary resistance.^{18,23} In part, overexpression of *BCR-ABL* allows some of the protein to escape the kinase inhibition achieved by imatinib. In a study of 55 CML patients who had been treated with imatinib for a median of 148 days, 7 exhibited a greater than 10-fold increase in *BCR-ABL* levels despite showing no significant change in the median levels of *BCR-ABL* transcripts.¹⁸ In the same study, point mutations in *BCR-ABL1* were detected in 23 of 66 patients, thus highlighting the prevalence of these mutations in patients treated with imatinib.

Several different mechanisms have been implicated in primary resistance, although the extent to which they are operative in individual patients is unclear (Table 2). Organic cation transporter 1 (OCT1; also termed *SLC22A1*) affects the ability of imatinib to enter CML cells.²⁴⁻²⁷ OCT1 is the principal uptake transporter that moves imatinib into cells. Recent studies suggest that OCT1 allelic splice variants may affect treatment response.^{28,29} Patients with high pretreatment levels of OCT1 exhibited better CCyR rates ($P=.008$), progression-free survival ($P=.01$), and overall survival ($P=.004$) than patients with lower levels.²⁶ Pretreatment OCT1 expression predicted CCyR achievement at 6 months ($P=.002$).²⁶ Among patients enrolled in the TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) trial, the major molecular response rate at 24 months was significantly higher in those with an increased level of

OCT1 activity.²⁷ Importantly, this study determined that patients with the lowest trough levels of imatinib and the lowest levels of OCT1 activity had the lowest rates of major molecular response ($P=.009$) and the highest risk of failed therapy ($P<.001$). In patients with decreased expression of this transporter, lower levels of imatinib are transported into the leukemic cells, thereby reducing efficacy. This mechanism of resistance, however, does not appear to explain primary resistance to the second- or third-generation inhibitors.

Another mechanism implicated in primary resistance is a germline deletion polymorphism of the BH3 domain in the gene *BIM*, which is involved in the proapoptotic response to *BCR-ABL1* kinase inhibitors. This polymorphism results in an altered splicing of *BIM* and diminished function. *BCR-ABL1* kinase inhibitors are capable of entering the cells, but the cells are less likely to undergo apoptosis.^{30,31}

Stromal factors have also been implicated in resistance. A recent report by Traer and associates suggests that fibroblast growth factor 2 may be a stromal factor that enables CML cells to largely escape the proapoptotic effects of *BCR-ABL1* kinase inhibition exerted by imatinib.³² This study identified CML patients without kinase domain mutations who were resistant to multiple kinase inhibitors. These patients exhibited elevated levels of fibroblast growth factor 2 in their bone marrow, which decreased in response to treatment with ponatinib, a kinase inhibitor that targets both the *BCL-ABL1* kinase and the fibroblast growth factor receptor. It is believed that some CML patients present for medical attention with relatively late chronic-phase disease, and may therefore have poor hematopoietic stem cell reserve. This theory is difficult to test, but it is reasonable to surmise that a patient who lacks chromosomally normal stem cells—because the bone marrow has been overrun by CML stem cells and progenitors—will not be able to mount a normal cytogenetic response to any medical therapy.

Guideline Recommendations

Both the NCCN and ELN guidelines emphasize adequate monitoring of patients to ensure that they are meeting treatment milestones, which will put them in favorable prognostic categories.^{7,8} The guidelines recommend bone marrow cytogenetic analysis as well as quantitative RT-PCR for *BCR-ABL1* at the time of diagnosis and every 3 months thereafter.^{7,8} A bone marrow assessment after 3 months is not necessary if there is access to a reliable *BCR-ABL1* quantitative PCR test and the patient has achieved a molecular response of 10% or less (as measured on the IS). At that point, it is recommended that clinicians continue to monitor patients every 3 months with quantitative RT-PCR testing to ensure that the level is stable

or decreasing.^{7,8} By 12 months, the goal is to achieve a CCyR, which is determined via a bone marrow aspirate analysis; however, it is possible to forgo the bone marrow biopsy and aspiration procedure in any patient who has achieved a major molecular response of less than 0.1% (as measured on the IS), which is highly suggestive of attainment of CCyR. It is important to continue to monitor patients every 3 months with quantitative RT-PCR. If a patient has adhered to therapy and has a confirmed 1-log or 10-fold increase in the *BCR-ABL1* transcript level by quantitative PCR, a *BCR-ABL1* kinase domain mutation test is recommended.^{7,8} The patient's therapy should then be changed based on the results of the mutation analysis.

The NCCN guidelines designate relatively few time points at which treatment might be reevaluated; response to treatment is classified as either adequate or inadequate.⁷ The ELN has devised definitions of response and recommendations for monitoring.⁸ The most recent iteration of the ELN recommendations, published in 2013, divided patients into 3 categories: optimal, warning, and failure. This approach provides a more nuanced and potentially more precise tool for decisions regarding treatment. The NCCN guidelines define an optimal response as the achievement of a *BCR-ABL1* transcript level of no more than 10% (IS) or a partial cytogenetic response at 3 to 6 months, and a CCyR at 12 months.⁷ The ELN defines an optimal response at 3 months as the achievement of a *BCR-ABL1* transcript level of 10% or lower; at 6 months as a *BCR-ABL1* transcript level of less than 1%, or a CCyR; and then at 12 months as a *BCR-ABL1* transcript level of 0.1% or lower.⁸ The optimal response is associated with the best long-term outcome and indicates that treatment need not be changed at that time.

Failure is defined by the ELN as the absence of a complete hematologic response and/or no cytogenetic response at 3 months.^{7,8} At 6 months, failure is defined as a *BCR-ABL1* transcript level of greater than 10% and/or more than 35% Ph chromosome-containing metaphases. At 12 months, failure is defined as a *BCR-ABL1* transcript level of greater than 1% and any level of cytogenetic persistence. Per the ELN, as with the NCCN, CCyR at 12 months remains an important definition of response and treatment milestone; any patient who does not have a CCyR at 12 months is considered to have failed TKI therapy. Patients meeting the criteria for failure should receive a different treatment to limit the risk for progression and death.

As mentioned above, the ELN guidelines include an intermediate warning category.⁸ The criteria are as follows: at 3 months, a *BCR-ABL1* transcript level greater than 10% and/or between 36% and 95% Ph chromosome-containing metaphases; at 6 months, a *BCR-ABL1* transcript level between 1% and 10% and/or between 1% and 35% Ph chromosome-containing metaphases; and at

Table 3. Adverse Events of Tyrosine Kinase Inhibitors

Tyrosine Kinase Inhibitor	Distinctive Side Effects	Potentially Serious and Irreversible Toxicities
Imatinib	Muscle cramping, superficial edema	None
Dasatinib	Pleural effusion, acne, bleeding	Pulmonary arterial hypertension
Nilotinib	QT prolongation, rash, pancreatitis, hyperglycemia	Sudden death, peripheral arterial occlusive disease
Bosutinib (experience is relatively limited)	Diarrhea	None
Ponatinib	Dry skin, pancreatitis	Thrombotic events

12 months, a *BCR-ABL1* transcript level between 0.1% and 1%. Patients who meet the criteria for the warning category warrant more frequent monitoring to ensure that a rapid change in therapy can be made if needed.

Although there are some subtle differences between the guidelines, both the ELN and the NCCN recognize the importance of adequate disease monitoring and prompt recognition of resistance so that potentially active salvage therapy can be initiated in a timely manner. Patients may also need to change therapy at any time owing to tolerability issues.

It is important to note that, in general, the guidelines were established for patients on first-line therapy. Previous studies have shown that if a patient's first therapy is imatinib and he or she is switched to a second-generation agent, it is important to achieve either a major cytogenetic response or a complete cytogenetic response within 6 to 12 months because overall survival is negatively impacted by failure to achieve this milestone.³³ There is limited experience in managing patients who develop resistance to second-generation agents used in the frontline setting. For example, if a patient (without a mutation) begins treatment with dasatinib and does not respond adequately at 3 to 6 months, there are few data to suggest that response would be improved by switching to an alternative TKI. In addition, it is unclear at what point failure to achieve a response should be considered worrisome when a patient is on second-line or third-line therapy. Certainly, any patient with resistance to second-generation TKI therapy, whether in the frontline setting or beyond, should be evaluated for a possible allogeneic stem cell transplant.

Factors Influencing Management Decisions

Treatment guidelines do not take into account patient characteristics, such as age. It is unclear whether failure to achieve a CCyR or a major molecular response is associated with a worse prognosis in an older patient. In older patients, particularly those with multiple comorbidities who may be far more likely to die of causes unrelated to CML, it is not unreasonable to somewhat relax the desired treatment milestones, although treatment monitoring should certainly be performed. As with younger patients, fit older patients

who do not respond to imatinib should be switched to an alternative second- or third-generation agent.

Treatment with imatinib has been proven safe, without any known serious or irreversible toxicities (Table 3). Among the second-generation agents, there is considerably greater experience—and therefore more reliable toxicity data—for dasatinib and nilotinib than for bosutinib. Patients treated with dasatinib should be monitored for underlying signs of cardiopulmonary disease.⁷ A very small proportion of patients receiving dasatinib may develop pulmonary arterial hypertension.⁷ The condition appears to be largely reversible upon treatment cessation. Dasatinib is also associated with development of pleural effusion.^{7,34} The incidence of pleural effusion appears to be higher in older patients. If a patient has considerably compromised pulmonary status (eg, he or she requires supplemental oxygen), a TKI other than dasatinib may be a better choice.

It has become apparent that nilotinib has a prothrombotic signal.³⁵⁻³⁷ The incidence rates of peripheral arterial occlusive disease and ischemic heart disease are higher with nilotinib than imatinib. In patients who have received 4 years of nilotinib treatment, the overall incidence of clinical cardiac adverse events requiring intervention is approximately 9%.³⁷ These reactions may be more common among older patients and those with risk factors for the development of vascular events, such as hypertension or diabetes. These patients may be better served by an alternative TKI. In addition, nilotinib can prolong the QT interval.⁷ As such, nilotinib is contraindicated for any patient with a history of a prolonged QT interval.⁷ Because nilotinib is associated with development of pancreatitis and hyperglycemia, it may be wise to consider an alternative TKI in patients who have diabetes.^{38,39}

As stated above, only minimal data are available for bosutinib at this time. Bosutinib does not appear to be associated with the same vascular issues as nilotinib or the same pulmonary arterial hypertension issues as dasatinib.^{40,41} Bosutinib is associated with a high incidence of diarrhea, however, which occurs in approximately 75% to 85% of patients (in 9%, it is grade 3 or 4).^{41,42} It may therefore be prudent to avoid bosutinib in patients with gastrointestinal issues.

Ponatinib is a third-generation TKI associated with serious arterial thrombotic events in a minority of patients (cumulative incidence, 11.8%; incidence of all arterial thrombotic events, 17.1%).^{43,44} Although no comparative studies with other TKIs have been published, the incidence of arterial thrombotic events appears to be substantially higher with ponatinib than with other TKIs. Ponatinib has also been associated with pancreatitis. Currently, ponatinib is best reserved for patients who have a *BCR-ABL* T315I mutation or who are resistant to or intolerant of most, if not all, of the other available TKIs.

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References

- Jabbour E, Kantarjian HM, Saglio G, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2014;123(4):494-500.
- Larson R, Kim D-W, Jootar S, et al. ENESTnd 5-year (y) update: long-term outcomes of patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) treated with frontline nilotinib (NIL) versus imatinib (IM) [ASCO abstract 7073]. *J Clin Oncol*. 2014;32(5s)(suppl).
- O'Brien SG, Guilhot F, Larson RA, et al; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348(11):994-1004.
- Lahaye T, Richm B, Berger U, et al. Response and resistance in 300 patients with *BCR-ABL*-positive leukemias treated with imatinib in a single center: a 4.5-year follow-up. *Cancer*. 2005;103(8):1659-1669.
- Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood*. 2002;99(6):1928-1937.
- Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood*. 2002;99(10):3530-3539.
- NCCN clinical practice guidelines in oncology. Chronic myelogenous leukemia. Version 3.2014. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Updated January 17, 2014. Accessed June 4, 2014.
- Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.
- Shah NP. Medical management of CML. *Hematology (Am Soc Hematol Educ Program)*. 2007;2007(1):371-375.
- Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2260-2270.
- Piccaluga PP, Paolini S, Bertuzzi C, De Leo A, Rosti G. First-line treatment of chronic myeloid leukemia with nilotinib: critical evaluation. *J Blood Med*. 2012;3:151-156.
- Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood*. 2014;123(9):1353-1360.
- Signorovitch J, Ayyagari R, Reichmann WM, Wu EQ, Chen L. Major molecular response during the first year of dasatinib, imatinib or nilotinib treatment for newly diagnosed chronic myeloid leukemia: a network meta-analysis. *Cancer Treat Rev*. 2014;40(2):285-292.
- Kantarjian H, Sawyers C, Hochhaus A, et al; International STI571 CML Study Group. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med*. 2002;346(9):645-652.
- Jabbour E, Kantarjian H, Jones D, et al. Frequency and clinical significance of *BCR-ABL* mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. *Leukemia*. 2006;20(10):1767-1773.
- Radich JP, Kopecky KJ, Appelbaum FR, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. *Blood*. 2012;120(19):3898-3905.
- Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the *BCR-ABL* mutation status really matter? *Blood*. 2009;114(27):5426-5435.
- Hochhaus A, Kreil S, Corbin AS, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. *Leukemia*. 2002;16(11):2190-2196.
- Jabbour E, Parikh SA, Kantarjian H, Cortes J. Chronic myeloid leukemia: mechanisms of resistance and treatment. *Hematol Oncol Clin North Am*. 2011;25(5):981-995.
- Bhamidipati PK, Kantarjian H, Cortes J, Cornelison AM, Jabbour E. Management of imatinib-resistant patients with chronic myeloid leukemia. *Ther Adv Hematol*. 2013;4(2):103-117.
- Soverini S, Colarossi S, Gnani A, et al; GIMEMA Working Party on Chronic Myeloid Leukemia. Contribution of *ABL* kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. *Clin Cancer Res*. 2006;12(24):7374-7379.
- Ravandi F. Managing Philadelphia chromosome-positive acute lymphoblastic leukemia: role of tyrosine kinase inhibitors. *Clin Lymphoma Myeloma Leuk*. 2011;11(2):198-203.
- Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by *BCR-ABL* gene mutation or amplification. *Science*. 2001;293(5531):876-880.
- Thomas J, Wang L, Clark RE, Pirmohamed M. Active transport of imatinib into and out of cells: implications for drug resistance. *Blood*. 2004;104(12):3739-3745.
- Crossman LC, Druker BJ, Deininger MW, Pirmohamed M, Wang L, Clark RE. hOCT 1 and resistance to imatinib. *Blood*. 2005;106(3):1133-1134, author reply 1134.
- Wang L, Giannoudis A, Lane S, Williamson P, Pirmohamed M, Clark RE. Expression of the uptake drug transporter hOCT1 is an important clinical determinant of the response to imatinib in chronic myeloid leukemia. *Clin Pharmacol Ther*. 2008;83(2):258-264.
- White DL, Saunders VA, Dang P, et al. CML patients with low OCT-1 activity achieve better molecular responses on high dose imatinib than on standard dose: those with high OCT-1 activity have excellent responses on either dose—a TOPS correlative study [ASH abstract 3187]. *Blood*. 2008;112(11)(suppl).
- Grinfeld J, Gerrard G, Alikian M, et al. A common novel splice variant of *SLC22A1* (OCT1) is associated with impaired responses to imatinib in patients with chronic myeloid leukaemia. *Br J Haematol*. 2013;163(5):631-639.
- Koren-Michowitz M, Buzaglo Z, Ribakovsky E, et al. OCT1 genetic variants are associated with long term outcomes in imatinib treated chronic myeloid leukemia patients. *Eur J Haematol*. 2014;92(4):283-288.
- Ng KR, Hillmer AM, Chuah CT, et al. A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. *Nat Med*. 2012;18(4):521-528.
- Augis V, Airiau K, Josselin M, Turcq B, Mahon FX, Belloc F. A single nucleotide polymorphism in cBIM is associated with a slower achievement of major molecular response in chronic myeloid leukaemia treated with imatinib. *PLoS ONE*. 2013;8(11):e7582.
- Traer E, Javidi-Sharifi N, Agarwal A, et al. Ponatinib overcomes FGF2-mediated resistance in CML patients without kinase domain mutations. *Blood*. 2014;123(10):1516-1524.
- Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. *Am J Hematol*. 2014;89(5):547-556.
- Hochhaus A, Kantarjian H. The development of dasatinib as a treatment for chronic myeloid leukemia (CML): from initial studies to application in newly diagnosed patients. *J Cancer Res Clin Oncol*. 2013;139(12):1971-1984.
- Levato L, Cantaffa R, Kropp MG, Magro D, Piro E, Molica S. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in chronic myeloid leukemia: a single institution study. *Eur J Haematol*. 2013;90(6):531-532.
- Giles FJ, Mauro MJ, Hong F, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia*. 2013;27(6):1310-1315.
- Kim TD, le Coutre P, Schwarz M, et al. Clinical cardiac safety profile of nilotinib. *Haematologica*. 2012;97(6):883-889.
- Engel T, Justo D, Amitai M, Volchek Y, Mayan H. Nilotinib-associated acute pancreatitis. *Ann Pharmacother*. 2013;47(1):e3.
- Palandri F, Castagnetti F, Soverini S, et al. Pancreatic enzyme elevation in chronic myeloid leukemia patients treated with nilotinib after imatinib failure. *Haematologica*. 2009;94(12):1758-1761.
- Gambacorti-Passerini C, Brümmendorf TH, Kim DW, et al. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: minimum 24-month follow-up. *Am J Hematol*. 2014;89(7):732-742.
- Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. *Blood*. 2014;123(9):1309-1318.

42. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011;118(17):4567-4576.

43. Cortes JE, Kim DW, Pinilla-Ibarz J, et al; PACE Investigators. A phase 2

trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369(19):1783-1796.

44. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012;367(22):2075-2088.

Selecting Treatment Options for TKI-Resistant Chronic Myeloid Leukemia

Michael J. Mauro, MD

Leader, Myeloproliferative Neoplasms Program

Professor of Medicine and Member, Memorial Sloan Kettering Cancer Center

New York, New York

The treatment landscape for CML is fortunately very broad. The approved agents include 5 TKIs (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib), as well as the non-TKI salvage agent omacetaxine mepesuccinate. Therapy should be selected based on several different criteria. First and foremost is the stage of disease—whether it is chronic phase, accelerated phase, or blast crisis. There remains an unmet need for treatment options for accelerated-phase CML and blast-phase CML, particularly for patients with resistant disease. The impact of novel treatment options has been much more limited in advanced-phase patients with resistant CML as compared with those with chronic-phase CML. The best approach is to thus treat resistant disease while it is still in the chronic phase.

The patient's treatment history, the duration of disease, their presenting features (including the Sokal risk score), and more subtle elements, such as cytogenetic clonal evolution and specific bone marrow findings, should all be examined in detail when considering best salvage therapy. The treatment history should include those agents the patient responded to previously, the depth of the response, and which treatments have failed. Many of these features impact the predicted response to salvage therapy. Patients who have chronic-phase CML with a minimal response to an initial TKI, such as imatinib, provide an important example. These patients may have lower response rates to subsequent lines of therapy and therefore a very small chance of achieving a durable remission with salvage therapy. Equally important in selecting a treatment for resistant CML is the patient's profile, including the presence of non-CML comorbidities that could affect the risk of treatment toxicity, tolerance of previous therapy, and, importantly, his or her view of the treatment goals. In resistant CML, the goals of therapy and the desire for a response often overshadow the treatment toxicity profile. It is important to carefully balance these considerations because presently, it is expected that an effective treatment will be maintained indefinitely, and long-term tolerance is thus crucial.

Treatment Options

The selective small-molecule TKIs bind to *BCR-ABL1* kinase, resulting in selective inhibition of the *ABL* kinase. Differences in binding properties, such as distinct molecular bonding requirements with the kinase domain, predilection for either the inactive or active kinase domain state for binding, and different steric inhibition introduced in the setting of mutations, define each TKI. The earliest and broadest population of patients with resistant disease are resistant to imatinib. For these patients, there are multiple other agents, including nilotinib, dasatinib, bosutinib, ponatinib, and omacetaxine mepesuccinate. Older therapies are also available. Interferon and cytarabine are generally considered historical agents with lower penetrance (ie, lower response rates, higher toxicity rates). Hydroxyurea is a simple, palliative therapy based on control of the blood cell count.

Imatinib resistance results in alternate lines of TKI therapy. Patients can become resistant to the more recently approved TKIs, such as dasatinib and nilotinib, and some are resistant to second- or third-line therapy.¹⁻⁴ There are now reports of patients with resistance to bosutinib⁵ and, potentially, to ponatinib.⁶ Questions have arisen regarding the utility of lateral movement between second- and third-generation TKIs and how to identify the best option. Taking into consideration prior lines of therapy and defining, as best possible, the disease-specific need for the clinical scenario—whether it is a more common and straightforward situation of CML resistance to single-agent imatinib, nilotinib, or dasatinib, or whether it is CML with multidrug resistance—will help provide the answers to these questions.

Multiple studies have examined imatinib resistance, but studies of patients with dasatinib or nilotinib resistance are more limited. No large trials of patients who have previously been treated with 3 or more lines of therapy have been performed.⁷ However, trials of bosutinib^{8,9} or ponatinib^{6,10} in patients who have received 2 or more lines of therapy have been reported. Many patients in clinical trials

of ponatinib have received 3 or more lines of therapy.^{6,10} In the phase 2 clinical trials for nilotinib^{11,12} and dasatinib,^{13,14} the rates of salvage are nearly equal, with major cytogenetic response and CCyR rates of approximately 50% to 60%. These striking phase 2 data demonstrate that salvage therapy is highly efficacious, with results similar to those of imatinib treatment after interferon.¹⁵ Remarkably, there is no significant drop in efficacy when nilotinib or dasatinib are used to treat patients with imatinib-resistant disease.

There may be some differences in the durability of responses associated with dasatinib or nilotinib in patients resistant to imatinib. This observation raises a previous point related to the proper classification of resistance and its mechanisms. Certain mutations are more likely to appear after certain TKIs. A broad spectrum of mutations, including the T315I mutation, is seen after imatinib treatment.¹⁶ Fewer mutations are observed following dasatinib or nilotinib treatment, but neither agent is effective against the T315I mutation. Patients receiving dasatinib most often develop a V299L, F317L/V/I/C, T315A, or T315I mutation.¹⁷ Mutations associated with nilotinib (Y253H, E255K/V, F359V/C/I) are most commonly seen in both the phosphate-binding loop (P-loop) and the activation loop (A-loop), as well as, to a lesser degree, at the kinase-binding domain of the T315I locus.¹⁷ The T315I mutation is also resistant to bosutinib.⁵ Importantly, ponatinib has demonstrated activity against the T315I mutation both in vitro and in patients.^{10,18-20}

The ability to salvage patients with bosutinib after imatinib or nilotinib/dasatinib has been studied.^{8,9,21} Although the data are based on limited numbers of patients, reasonable activity has been demonstrated for bosutinib therapy after nilotinib and/or dasatinib in the intolerant and resistant CML population.⁸ Intolerant patients were most likely to respond, followed by patients resistant to nilotinib and then by patients resistant to dasatinib. The phase 2 data for bosutinib in imatinib-resistant patients mirror those for nilotinib/dasatinib. In the pivotal study, among the 118 patients who had received prior treatment with imatinib followed by dasatinib and/or nilotinib, a major cytogenetic response was achieved by 32% and a CCyR was achieved by 24% (Figure 4).⁸ The estimated 2-year progression-free survival was 73%, and the estimated overall survival was 83%. Molecular responses were more variable and, in certain groups, very modest.

The findings concerning bosutinib were somewhat overshadowed by the recent phase 1 and 2 data of ponatinib in CML patients who are resistant and/or intolerant to multiple lines of therapy.^{6,10} The introduction of ponatinib was a major advance in the treatment of resistant CML. In phase 1 trials, ponatinib showed a high degree of activity in patients with relapsed or resistant disease who had previously received multiple lines of therapy (50% had received prior imatinib, dasatinib, and nilotinib).¹⁰ A complete

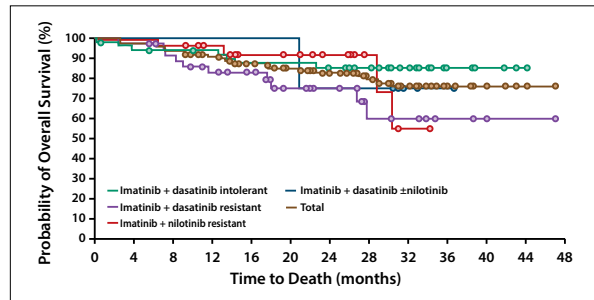


Figure 4. Overall survival in a phase 1/2 study evaluating bosutinib in 118 patients with chronic-phase chronic myeloid leukemia who were resistant or intolerant to imatinib. Adapted from Khoury HJ et al. *Blood*. 2012;119(15):3403-3412.⁸

hematologic response was achieved by 98% of patients, a major cytogenetic response was achieved by 72%, a major molecular response was achieved by 44%, and a CCyR was achieved by 63%.¹⁰ Importantly, all 12 of the patients with the T315I mutation had a complete hematologic response, 92% achieved a major cytogenetic response, 75% achieved a CCyR, and 67% achieved a major molecular response. The phase 2 PACE (Ponatinib Ph ALL and CML Evaluation) trial showed a high degree of activity of ponatinib in the setting of multidrug-resistant CML and in patients who had failed more than 1 line of therapy, and it confirmed the high rate of activity in the T315I setting.⁶ Among the patients with chronic-phase CML, 56% had a major cytogenetic response (70% of patients with the T315I mutation), 46% had a CCyR (66% of patients with the T315I mutation), and 34% had a major molecular response (56% of patients with the T315I mutation). In accelerated blast crisis, ponatinib showed more limited activity, with 55% of these patients achieving a major hematologic response and 39% achieving a major cytogenetic response. Although treatment with ponatinib is clearly a good bridge to more definitive options in many patients, only half of the patients with accelerated-phase disease and a minority of the patients with blast-phase disease achieved hematologic remission (31% had a major hematologic response and 23% had a major cytogenetic response). The majority of patients (91%), however, are estimated to have achieved a sustained major cytogenetic response lasting at least 12 months. Long-term follow-up of the PACE trial showed similar results (Figures 5 and 6).^{22,23}

In October 2013, the US Food and Drug Administration (FDA) requested that the marketing of ponatinib be suspended because of toxicity concerns related to vascular occlusive events.²⁴ Ponatinib is a rationally designed multiple-kinase inhibitor with a high degree of activity in wild-type *BCR-ABL1* and resistant *BCR-ABL1* variant disease. Some of the observed side effects, such as hypertension, might have been predicted given its vascular endothelial growth factor (VEGF) inhibitory properties. Some of the

Table 4. Cardiovascular Events^a at 5-Year Follow-Up of the ENESTnd Trial

	Nilotinib 300 mg BID (n=279) ^b			Nilotinib 400 mg BID (n=277) ^b			Imatinib 400 mg QD (n=280) ^b		
	Total, n (%)	Y1-4, n ^c	Y5, n ^d	Total, n (%)	Y1-4, n ^c	Y5, n ^d	Total, n (%)	Y1-4, n ^c	Y5, n ^d
Ischemic Heart Disease	11 (3.9)	11	0	24 (8.7)	14	10	5 (1.8)	3	2
Ischemic Cerebrovascular Events	4 (1.4)	3	1	9 (3.2)	5	4	1 (0.4)	1	0
Peripheral Arterial Disease	7 (2.5)	4	3	7 (2.5)	5	2	0	0	0

^aAll events, regardless of whether they were treatment-related. ^bSafety analyses were based on patients who received ≥ 1 dose of study treatment. ^cMinimum follow-up of 48 cycles. ^dEvents reported between the 48-cycle and 60-month data cutoffs.

ENESTnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Pts.

Data from Larson R et al. ASCO abstract 7073. *J Clin Oncol*. 2014;32(5s)(suppl).²⁷

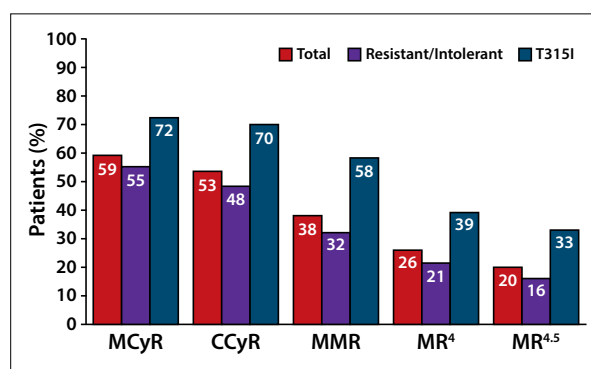


Figure 5. Response among patients with chronic-phase chronic myeloid leukemia in a long-term analysis of the PACE trial. The median follow-up was 30 months.

CCyR, complete cytogenetic response; MCyR, major cytogenetic response; MMR, major molecular response; MR, molecular response; PACE, Ponatinib Ph ALL and CML Evaluation.

Adapted from Kantarjian HM et al. ASCO abstract 7081. *J Clin Oncol*. 2014;32:5(suppl).²²

toxicities seen with ponatinib overlap significantly with reactions commonly observed with other TKIs for CML, such as pancreatic enzyme elevation, myelosuppression, and skin reactions. Vascular disease as a category is a toxicity seen with nearly all of the TKIs; ponatinib is associated with a higher rate of arterial disease and a somewhat lower rate of venous occlusive disease, with events usually occurring early after treatment exposure in a dose-related manner.^{6,10} A recent analysis indicated that there may be a reduction in vascular events with lower amounts of ponatinib exposure.²⁵ These data demand careful assessment of the risk-to-benefit ratio for ponatinib therapy. Despite the apparent signal and concern, such risk is acceptable for many patients with resistant disease given the remarkable efficacy of the drug. The mechanism of action for such toxicity and thus the optimal risk mitigation strategy must be clearly elucidated. In December 2013, the FDA indicated that the marketing of ponatinib could continue after several safety measures had

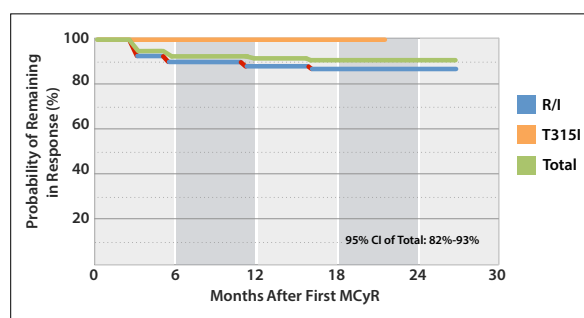


Figure 6. MCyR in a long-term analysis of the PACE trial.

MCyR, major cytogenetic response; PACE, Ponatinib Ph ALL and CML Evaluation; R/I, resistant/intolerant.

Adapted from Cortes JE et al. ASH abstract 650. *Blood*. 2013;122(21 suppl).²³

been implemented, including narrowing of the indication, revision of the dosage recommendations, and the addition of warnings and precautions about the risk of blood clots and severe narrowing of blood vessels.²⁶

Vascular disease, particularly peripheral arterial disease, has been observed with nilotinib as well. At the 5-year analysis of ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Pts), nilotinib patients treated with either 300 mg twice daily or 400 mg twice daily developed approximately 5% higher rates of arterial occlusive events, including cardiovascular, cerebrovascular, and peripheral arterial disease, in comparison with patients in the imatinib arm (Table 4).²⁷ Dasatinib is also known to cause the vascular toxicity of pulmonary arterial hypertension (PAH) in a small but relevant number of patients.²⁸ The mechanism leading to PAH remains elusive but is under investigation, especially given the divergent nature of the effects that TKIs may have on PAH.

Not surprisingly, patients in the salvage setting have often received multiple lines of therapy and have a reduced amount of normal hematopoiesis in reserve, with enhanced myelosuppression. An examination of TKI toxicities reveals more severe events, including thrombocytopenia and bleed-

ing, in patients with resistant or advanced-stage disease. Overall, the toxicity profiles of the various TKIs are similar whether they are used as frontline therapy or in later settings.

A Non-TKI Option

Omacetaxine mepesuccinate is an inhibitor of protein synthesis. It received accelerated approval in October 2012 and full approval in February 2014 for the treatment of adults with chronic-phase or accelerated-phase CML who have lost their response to or could not tolerate at least 2 TKIs.^{29,30} The approval was based on an analysis of 111 patients with CML from 2 clinical trials. The rates of major cytogenetic response were 18.4% in the patients with chronic-phase disease and 14.3% in those with accelerated-phase disease. The median durations of response were 12.5 months and 4.7 months, respectively. The safety evaluation was drawn from 163 patients with CML in 3 single-arm studies.^{29,30} The most common adverse reactions of any grade were thrombocytopenia, anemia, neutropenia, diarrhea, nausea, fatigue, asthenia, injection site reaction, pyrexia, and infection. Omacetaxine was evaluated in 2013 in a multicenter, noncomparative, open-label phase 2 study of patients resistant to or intolerant of at least 2 TKIs.³¹ In patients with chronic-phase CML, the median progression-free survival was 7.0 months (95% confidence interval [CI], 5.9-8.9 months), and the overall survival was 30.1 months (95% CI, 20.3 months-not reached). A hematologic response was achieved or maintained in 67% of patients, with a median response duration of 7.0 months. Among the 10 patients (22%) who achieved a major cytogenetic response, there were 2 (4%) with a CCyR. An analysis of 2 phase 2 trials (CML-202 and CML-203) in patients with advanced CML previously treated with TKIs was recently published.³² The patients were in accelerated phase (n=55) or myeloid blast phase (n=44). A major hematologic response was achieved by 37% of the patients in the accelerated phase and 9% of the patients in the blast phase. Among the patients with a T315I mutation, these rates were 22% and 5%, respectively.

Emerging Treatment Options

There is a need to look beyond just *BCR-ABL1* kinase inhibition as a treatment option for CML. One possible approach is to combine an *ABL* kinase inhibitor with a microRNA site inhibitor, which would have a synergistic effect to direct *BCR-ABL* kinase inhibition.³³ There has been long-standing interest in the continued pursuit of immune-based therapy and checkpoint inhibitors, such as those against CTLA-4 and PD-1, given that CML is a very immune-responsive disease.³⁴

Novel agents continue to be brought forward and explored. Although it has been postulated that additional

central mechanisms of resistance and targets would be identified in Ph-positive leukemia, it appears that CML most often involves the continual redirection back to *BCR-ABL* kinase reactivation and persistence. Perhaps the most intriguing idea is the notion that patients with and without kinase domain mutations respond to novel *BCR-ABL* inhibitors, suggesting that mutations may be a “signature” or manifestation of a more common and universal mechanism of resistance allowing for persistence of the clone and genesis of mutant clones.

Conclusion

Many options are available for the treatment of resistant CML, and new therapies are emerging. Management of CML requires careful identification of an appropriate risk-to-benefit scenario for each patient and proposed or current therapy, a clear understanding of disease resistance, and proper monitoring. The selection of a treatment is based on analysis of the patient's disease state, prior therapies, and comorbidities, as well as a discussion with the patient about the toxicity profile, the goals of therapy, and the next steps after remission. Allogeneic stem cell transplant should be considered for patients who develop high levels of resistance, particularly those whose disease has undergone transformation to advanced phases of Ph-positive leukemia or who present with de novo advanced forms of Ph-positive leukemia.

Acknowledgment

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References

1. Cortes J, Jabbour E, Kantarjian H, et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. *Blood*. 2007;110(12):4005-4011.
2. Soverini S, Gnani A, Colarossi S, et al. Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. *Blood*. 2009;114(10):2168-2171.
3. Khorashad JS, Milojkovic D, Mehta P, et al. In vivo kinetics of kinase domain mutations in CML patients treated with dasatinib after failing imatinib. *Blood*. 2008;111(4):2378-2381.
4. Soverini S, Colarossi S, Gnani A, et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. *Haematologica*. 2007;92(3):401-404.
5. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. *J Clin Oncol*. 2009;27(3):469-471.
6. Cortes JE, Kim DW, Pinilla-Ibarz J, et al; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369(19):1783-1796.
7. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. *Blood*. 2009;114(20):4361-4368.
8. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood*. 2012;119(15):3403-3412.
9. Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. *Blood*. 2014;123(9):1309-1318.
10. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012;367(22):2075-2088.

11. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. *Leukemia*. 2013;27(1):107-112.
12. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. *Blood*. 2011;117(4):1141-1145.
13. Kantarjian H, Pasquini R, Hamerschlak N, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: a randomized phase 2 trial. *Blood*. 2007;109(12):5143-5150.
14. Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. *J Clin Oncol*. 2009;27(21):3472-3479.
15. Hochhaus A, Druker B, Sawyers C, et al. Favorable long-term follow-up results over 6 years for response, survival, and safety with imatinib mesylate therapy in chronic-phase chronic myeloid leukemia after failure of interferon-alpha treatment. *Blood*. 2008;111(3):1039-1043.
16. Bhamidipati PK, Kantarjian H, Cortes J, Cornelison AM, Jabbour E. Management of imatinib-resistant patients with chronic myeloid leukemia. *Ther Adv Hematol*. 2013;4(2):103-117.
17. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.
18. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*. 2009;16(5):401-412.
19. Cortes J, Kim DW, Pinilla-Ibarz J, et al. A pivotal phase 2 trial of ponatinib in patients with chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukemia resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 12-month follow-up of the PACE trial [ASH abstract 163]. *Blood*. 2012;120(21)(suppl).
20. Kantarjian HM, Kim DW, Pinilla-Ibarz J, et al. Efficacy and safety of ponatinib in patients with accelerated phase or blast phase chronic myeloid leukemia or Philadelphia-positive acute lymphoblastic leukemia: 12-month follow-up of the PACE trial [ASH abstract 915]. *Blood*. 2012;120(21)(suppl):915.
21. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011;118(17):4567-4576.
22. Kantarjian HM, Kim D-W, Pinilla-Ibarz J, et al. Ponatinib (PON) in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation: longer-term follow up of the PACE trial [ASCO abstract 7081]. *J Clin Oncol*. 2014;32(5)(suppl).
23. Cortes JE, Kim D-W, Javier Pinilla-Ibarz J, et al. Ponatinib In patients (pts) with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 2-year follow-up of the PACE trial [ASH abstract 650]. *Blood*. 2013;122(21)(suppl).
24. FDA Drug Safety Communication: FDA investigating leukemia drug Iclusig (ponatinib) after increased reports of serious blood clots in arteries and veins. US Food and Drug Administration. <http://www.fda.gov/Drugs/DrugSafety/ucm370945.htm>. Issued October 11, 2013. Accessed June 5, 2014.
25. Hochhaus A, Pinilla-Ibarz J, Kim D-W, et al. Clinical impact of dose modification and dose intensity on response to ponatinib (PON) in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias [ASCO abstract 7084]. *J Clin Oncol*. 2014;32(5s)(suppl).
26. FDA Drug Safety Communication: FDA requires multiple new safety measures for leukemia drug Iclusig; company expected to resume marketing. US Food and Drug Administration. <http://www.fda.gov/Drugs/DrugSafety/ucm379554.htm>. Issued December 20, 2013. Accessed June 6, 2014.
27. Larson R, Kim D-W, Jootar S, et al. ENESTnd 5-year (y) update: long-term outcomes of patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) treated with frontline nilotinib (NIL) versus imatinib (IM) [ASCO abstract 7073]. *J Clin Oncol*. 2014;32(5s)(suppl).
28. Montani D, Bergot E, Günther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation*. 2012;125(17):2128-2137.
29. Cortes J, Digumarti R, Parikh PM, et al; Omacetaxine 203 Study Group. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. *Am J Hematol*. 2013;88(5):350-354.
30. Khoury HJ, Cortes J, Baccarani M, et al. Omacetaxine mepesuccinate in patients with advanced chronic myeloid leukemia with resistance or intolerance to tyrosine kinase inhibitors. *Leuk Lymphoma*. 2014 Apr 28. [Epub ahead of print]
31. Yu Y, Yang L, Zhao M, et al. Targeting microRNA-30a-mediated autophagy enhances imatinib activity against human chronic myeloid leukemia cells. *Leukemia*. 2012;26(8):1752-1760.
32. Held SA, Heine A, Mayer KT, Kapelle M, Wolf DG, Brossart P. Advances in immunotherapy of chronic myeloid leukemia CML. *Curr Cancer Drug Targets*. 2013;13(7):768-774.
33. Omacetaxine mepesuccinate. US Food and Drug Administration. <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm325990.htm>. Updated October 26, 2012. Accessed June 5, 2014.
34. Alvandi F, Kwitkowski VE, Ko CW, et al. U.S. Food and Drug Administration approval summary: omacetaxine mepesuccinate as treatment for chronic myeloid leukemia. *Oncologist*. 2014;19(1):94-99.

Integrating Current Treatment Options for TKI-Resistant Chronic Myeloid Leukemia: General Discussion

H&O What are some issues raised by guideline recommendations?

Jerald P. Radich, MD An interesting issue is early response, and by that we mean response at 3 to 6 months. It appears that patients have a considerably worse progression-free survival if they do not reach a level of 10% (as measured by the IS) by 3 to 6 months, no matter which TKI they are started on. Patients who do not have an early response are less likely to achieve a complete major molecular response and have worse progression-free survival. The issue then becomes how to treat these patients. The NCCN says to switch treatment

at 3 months, and the ELN says to switch at 6 months. But it is not known whether switching will have any benefits, and whether the biology of a poor early response can be trumped or not. Currently, we are moving away from waiting to change therapies until patients fail or lose a response toward changing therapies quite early.

Michael J. Mauro, MD That is a great point. The optimal time to change therapies is one of the most difficult controversies in CML. I am intrigued by recent reports examining how to use the absolute level at baseline and the rate of decline to help determine whether a patient

is resistant.^{1,2} For a patient who does not have an early molecular improvement or response by enhanced criteria, the threshold to switch is lower for imatinib than in a patient receiving dasatinib or nilotinib in the frontline setting. According to the guidelines, a patient who is not responding to initial treatment with nilotinib or dasatinib should be switched at 6 months. Perhaps based on the fact that fewer options exist for such patients, this notion avoids much of the controversy involving the pharmacoeconomics, toxicity, and best algorithm debates concerning when to switch. It may be possible to fine-tune how we define the patient's resistance with a more creative interpretation of how to define an early molecular response, but this idea is controversial.

Jerald P. Radich, MD Your previous discussion about nuances and the creation of guidelines is very important. Just by their generation, guidelines tend to be restricted to simple algorithms. Therefore, it is important that guidelines are considered in a clinical context rather than followed with blind obedience. For example, a patient with a *BCR-ABL1* transcript level that decreases from 100% to 11% (according to the IS) is likely achieving an acceptable level of response at 3 months, even though he or she does not meet the 10% cutoff specified by the guidelines. In fact, this type of patient is probably achieving a better response to treatment than a patient who goes from 12% to 9% in 3 months. In many patients, the kinetics are likely to provide more information than the actual level. The key is to assess the patient and determine his or her kinetic response to better understand the goals of treatment.

H&O What questions do you receive from community physicians?

Michael J. Mauro, MD Community physicians frequently ask whether to initiate treatment with a second- or third-line agent. The more conservative approach is to use imatinib early and then use the second-generation and third-generation TKIs as salvage therapy. There are currently not enough data to determine whether these 2 approaches are similar enough in outcome to be interchangeable.

Jerald P. Radich, MD It is a tough question. For physicians in the community, who see few CML patients, the differences between imatinib and the second-generation TKIs are not very noticeable. For example, 3 of 5 patients who receive imatinib will achieve a CCyR, as compared with 4 of 5 patients who receive a second-generation TKI. Therefore, the choice of therapy often depends on the goals of treatment. If the goal is to increase survival in an older patient, either imatinib or a second-generation TKI is likely sufficient. In a younger patient who requires

a faster and deeper response, starting with a more potent drug makes more sense.

Community physicians frequently ask me about the cycling of drugs. For example, if a patient is resistant and begins a new agent, at what point should the depth of response be measured? Often patients are cycled through drugs very quickly, and it becomes difficult to identify intolerance or resistance when several drugs are used in a short amount of time; it may be that a certain agent was not used long enough to control symptoms and improve disease.

Michael J. Mauro, MD That scenario invokes the axiom that intolerance and even resistance are inversely proportional to the number of treatment options. Currently, we are much more critical of treatment response and toxicities. We know that dose intensity is linked to efficacy, and we want the perfect world of a nontoxic therapy with the best response.

H&O What are some areas of future research?

Jerald P. Radich, MD With the current treatment options being so effective, future research will likely focus on the molecular biology of resistance. It would be helpful for research to provide ideas on how to help patients adhere to medications. We also need research on how to predict toxicities, which are likely related to the genetics of the patient's own germline DNA. Lastly, we need to know which patients may safely discontinue medication, and why biologically some can do this. Thus, any way to predict and modify toxicities—and thereby increase adherence—will have a significant effect on managing the disease.

Michael J. Mauro, MD Yes, I agree. An important unmet need in CML is how to avoid resistance by managing the excellent therapies that are available. One way to do that is to individualize management by determining whether a patient is at risk for certain toxicities, understanding more about the disease biology to better predict early responses, and evaluating the trajectory of response and kinetics. The goal is to achieve a so-called “personalized medicine” approach to CML.

Acknowledgment

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References

1. Branford S, Yeung DT, Parker WT, et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline [published online May 23, 2014]. *Blood*. 2014. pii: blood-2014-03-566323.
2. Hanfstein B, Shlyakhto V, Lausker M, et al. Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib [published online May 6, 2014]. *Leukemia*. 2014. doi:10.1038/leu.2014.153.

Slide Library

Treatment Options for CML

- TKIs
 - Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib
- The non-TKI salvage agent omacetaxine mepesuccinate

TKI, tyrosine-kinase inhibitors; CML, chronic myeloid leukemia

Resistance in CML

- Primary resistance refers to the lack of an initially acceptable response
- Secondary resistance is the loss of an established response
- The rates of both primary and secondary resistance increase as CML disease progresses, with the loss of response occurring more often in patients with advanced or blast-phase CML
- Resistance is described as hematologic, cytogenetic, or molecular; all of which can occur in the primary or secondary setting

CML: Secondary Resistance

- Secondary resistance is a bigger concern than primary resistance
- It most often occurs when BCR-ABL1 reactivates as a consequence of mutation, gene amplification, or increased expression
- Secondary resistance has been documented in approximately 10% to 15% of p¹⁹ patients who have chronic-phase CML treated with imatinib. The rates of secondary resistance in frontline treatment with second-generation TKIs appear to be slightly lower than with imatinib, but follow-up has been shorter⁴

1. O'Brien AD, et al. *N Engl J Med*. 2013;368(11):994-1004. 2. Karsenti H, et al. *N Engl J Med*. 2013;368(11):994-1004. 3. Gouton M, et al. *J Clin Oncol*. 2009;27(15):1737-1742. 4. Rudolph SD, et al. *Blood*. 2012;120(18):3595-3605.

TKIs: Resistance

- Most patients with resistant disease are resistant to imatinib
- Patients can become resistant to the more recently approved TKIs, such as dasatinib and nilotinib, and some are resistant to second- or third-line therapy
- There are now reports of patients with resistance to bosutinib and, potentially, to ponatinib

Factors to Consider in the Management of Resistant CML

- The patient's treatment history: Which agents the patient responded to previously, the depth of the responses, and which agents failed
- The duration of disease
- The presenting features (including the Sokal risk score)
- Cytogenetic clonal evolution
- Bone marrow pathologic findings

CML Therapy: Beyond TKIs

- Omacetaxine mepesuccinate
 - An inhibitor of protein synthesis
 - Received FDA accelerated approval in October 2012 and full approval in February 2014 for the treatment of adults with chronic-phase or accelerated-phase CML who have lost their response to or could not tolerate at least 2 TKIs
 - Evaluated in a phase 2 study of patients resistant to or intolerant of at least 2 TKIs. In patients with chronic-phase CML, the median PFS was 7.0 months, and overall survival was 30.1 months. A hematologic response was achieved or maintained in 67% of patients, with a median response duration of 7.0 months

FDA, US Food and Drug Administration; PFS, progression-free survival; CML, chronic myeloid leukemia

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Integrating Current Treatment Options for TKI-Resistant Chronic Myeloid Leukemia

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

1. Approximately how many patients with chronic myeloid leukemia (CML) have the Philadelphia (Ph) chromosome?
 - a. As many as 80%
 - b. As many as 85%
 - c. As many as 90%
 - d. As many as 95%
2. How many patients with CML are asymptomatic?
 - a. Up to 20%
 - b. Up to 30%
 - c. Up to 40%
 - d. Up to 50%
3. According to the European LeukemiaNet (ELN) classification, what percentage of blast cells is required for the diagnosis of blast-phase disease?
 - a. At least 20%
 - b. At least 30%
 - c. At least 40%
 - d. At least 50%
4. Approximately how many CML patients in chronic-phase disease will meet some definition of resistance to imatinib within the first year of treatment?
 - a. 35%
 - b. 45%
 - c. 55%
 - d. 65%
5. According to the NCCN, what is the ultimate goal of treatment for all CML patients?
 - a. Complete cytogenetic response
 - b. Complete hematologic response
 - c. Major molecular response
 - d. Primary response
6. How many CML patients have the T315I mutation?
 - a. 4% to 15%
 - b. 12% to 21%
 - c. 23% to 33%
 - d. 45% to 51%
7. In the TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) trial, which patients had the highest rate of major molecular response at 24 months?
 - a. Those with decreased expression of BCR-ABL
 - b. Those with a germline deletion polymorphism of the BH3 domain in the gene BIM
 - c. Those with an increased level of OCT1 activity
 - d. Those with the T315I mutation
8. In phase 2 clinical trials for nilotinib and dasatinib, approximately how many patients achieved a major cytogenetic response or complete cytogenetic response?
 - a. 20% to 30%
 - b. 30% to 40%
 - c. 40% to 50%
 - d. 50% to 60%
9. In a phase 1/2 study of bosutinib, among 118 patients who had received prior treatment with imatinib followed by dasatinib and/or nilotinib, how many achieved a major cytogenetic response?
 - a. 32%
 - b. 42%
 - c. 52%
 - d. 62%
10. In an open-label phase 2 study of omacetaxine in CML patients resistant to or intolerant of at least 2 tyrosine kinase inhibitors, what was the overall survival?
 - a. 18.3 months
 - b. 24.7 months
 - c. 30.1 months
 - d. 41.1 months

Evaluation Form: Integrating Current Treatment Options for TKI-Resistant Chronic Myeloid Leukemia

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 10001**. Upon successfully registering/logging in and completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

- ☐ MD/DO ☐ PA/PA-C ☐ NP ☐ RN ☐ PharmD/RPh ☐ PhD
☐ Other, please specify:

2. What is your area of specialization?

- ☐ Oncology, Hematology/Oncology ☐ Oncology, Medical ☐ Oncology, Other ☐ Other, please specify

3. Which of the following best describes your *primary* practice setting?

- ☐ Solo Practice ☐ Group Practice ☐ Government
☐ University/teaching system ☐ Community Hospital
☐ HMO/managed care ☐ Non-profit/community ☐ I do not actively practice
☐ Other, please specify:

4. How long have you been practicing medicine?

- ☐ More than 20 years ☐ 11-20 years ☐ 5-10 years ☐ 1-5 years
☐ Less than 1 year ☐ I do not directly provide care

5. Approximately how many patients do you see each week?

- ☐ Less than 50 ☐ 50-99 ☐ 100-149 ☐ 150-199 ☐ 200+
☐ I do not directly provide care

6. How many patients do you currently see each week with chronic myeloid leukemia?

- ☐ Fewer than 5 ☐ 6-15 ☐ 16-25 ☐ 26-35 ☐ 36-45 ☐ 46-55
☐ 56 or more ☐ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Recognize when a CML patient is intolerant to a tyrosine-kinase inhibitor

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

Manage adverse events related to tyrosine-kinase inhibitors

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

Identify CML patients who are likely to benefit from novel agents

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

Implement treatment strategies incorporating novel agents in CML

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

The content was evidence based

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

The educational material provided useful information for my practice

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

The activity enhanced my current knowledge base

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

- ☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)

☐ I do plan to implement changes in my practice based on the information presented

☐ My current practice has been reinforced by the information presented

☐ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

- ☐ Apply latest guidelines ☐ Choice of treatment/management approach
☐ Change in pharmaceutical therapy ☐ Change in current practice for referral
☐ Change in nonpharmaceutical therapy ☐ Change in differential diagnosis
☐ Change in diagnostic testing ☐ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

- ☐ Very confident ☐ Somewhat confident ☐ Unsure ☐ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

- ☐ Formulary restrictions ☐ Insurance/financial issues ☐ Time constraints
☐ Lack of multidisciplinary support ☐ System constraints
☐ Treatment-related adverse events ☐ Patient adherence/compliance
☐ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

- ☐ Yes ☐ No, please explain:

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

Request for Credit (*required fields)

Name* _____

Degree* _____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

E-mail* _____

Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

- ☐ I participated in the entire activity and claim 1.50 credits.
☐ I participated in only part of the activity and claim ____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: 10001