

Implementation of Management Guidelines For Chronic Myeloid Leukemia

Perspectives in the United States

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ABSTRACT

Clinical practice guidelines are developed to improve the quality of care and outcomes for patients. Guidelines facilitate clinical decisions, promote efficient use of health care resources, and provide guidance to practitioners. For chronic myeloid leukemia (CML), tyrosine kinase inhibitors (TKIs) have changed the paradigm of therapy by lowering the disease burden and by providing more precise monitoring of response. These advances affect treatment guidelines for CML and inform CML clinical trial protocols.

Guidelines developed by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) synthesize the best available evidence to support decision-making in the management of CML patients. Both guidelines recognize specific milestones for treatment response. At each time point, the ELN guidelines define overall response benchmarks, and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) provide an algorithm that specifies the timing for evaluations of cytogenetic and molecular parameters during therapy. The NCCN Guidelines also include strategies for providing supportive care and for managing toxicities. Molecular monitoring now plays a greater role in CML management. Molecular response as a milestone is currently recommended by the ELN but has not yet been adopted by the NCCN. As evidence continues to accumulate, the NCCN and ELN Guidelines are likely to evolve to reflect new data and standards of care.

Key words: chronic myeloid leukemia, tyrosine kinase inhibitors, imatinib, nilotinib, dasatinib, clinical practice guidelines

INTRODUCTION

Chronic myeloid leukemia (CML) is caused by a translocation between the *BCR* (breakpoint cluster region) gene on chromosome 22 and the *ABL1* (Abelson) oncogene on chromosome 9.^{1,2} The resulting *BCR-ABL1* fusion gene produces a constitutively active tyrosine kinase that promotes dysregulated signaling pathways and abnormal myeloid cell proliferation.¹ Management of patients with CML continues to evolve, with improved sensitivity of monitoring techniques and increased experience with tyrosine kinase inhibitors (TKIs), a class of drugs that inhibit the *BCR-ABL1* oncoprotein.

Advances in treatment and monitoring have required frequent updates to clinical practice guidelines. Such guidelines

represent systematically developed algorithms, which support sound clinical decision-making, minimize practice variation, improve resource management, and promote cost savings by encouraging clinicians to incorporate proven approaches into their practice. Practice guidelines also provide evidence-based information to important stakeholders in the health care delivery system. For managed care organizations, practice guidelines are often a primary source of evidence-based information on cancer treatment.³ Unfortunately, data suggest that 20% to 30% of patients with CML are not being treated according to current CML guidelines.^{4,5}

NEED FOR GUIDELINES IN DISEASE MANAGEMENT AND TREATMENT

By targeting the underlying cause of CML, the *BCR-ABL1* fusion tyrosine kinase, TKIs have transformed the treatment of CML and have improved patient outcomes. This improvement is reflected by a dramatic increase in overall survival among patients treated with TKIs.⁶ CML has evolved from a disease with minimal survival beyond 5 years, short of allogeneic transplantation, to one of long-term progression-free survival and overall survival for most patients treated with TKIs.⁷⁻¹¹

Imatinib (Gleevec, Novartis) was the first TKI approved by the FDA (in 2001). Subsequently, two more-potent TKIs—dasatinib (Spryvel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis)—were approved for CML patients who are resistant to or intolerant of imatinib and, more recently, as initial treatment. Today, imatinib, dasatinib, and nilotinib comprise the FDA-approved armamentarium of TKIs for the treatment of CML.

The National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) develop internationally recognized clinical practice guidelines that synthesize the best available evidence for the management of patients with CML.^{12,13} The NCCN is a U.S.-based nonprofit alliance of 21 cancer centers dedicated to improving patient care and disease management from screening to diagnosis, treatment, and follow-up.¹⁴ The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) are updated at least yearly and are developed through a review of evidence-based studies and the consensus of the panel members.¹³ The ELN is a European Union-funded organization of 175 participating centers in 33 countries.¹⁵ The ELN Guidelines for CML were updated most recently in 2009.¹²

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This article reviews the pathophysiology of CML, the mechanisms of action of TKIs, and established monitoring practices. The NCCN Guidelines for CML (version 2.2012) and the 2009 ELN clinical practice guidelines for CML will be compared and contrasted in terms of recommended treatments, patient adherence, and definitions of treatment success. Although few health economic evaluations have been conducted in the current era of the three TKIs approved for CML, we have briefly reviewed the available literature. We also discuss the current and future implications of increasingly sensitive measures of disease detection and of response to therapy, such as cytogenetic and molecular monitoring.

UNDERSTANDING MOLECULAR PATHOGENESIS

The *BCR-ABL1* fusion gene characterizes leukemic cells in CML and is manifested cytogenetically as the Philadelphia chromosome (Ph).^{1,2} The fused gene encodes an abnormal tyrosine kinase that increases proliferation, inhibits differentiation, and blocks programmed cell death (apoptosis), leading to malignant transformation of myeloid cells.¹

The natural history of untreated CML is typified by an initial indolent chronic phase, followed by an accelerated phase and an acute (blast) phase.^{1,2} Without medical intervention, CML eventually progresses to fatal acute leukemia, generally in 4 to 6 years.⁶ Most patients (90% to 95%) are in the chronic phase at the time of diagnosis. Initial findings may include constitutional symptoms of fatigue, weight loss, night sweats, splenomegaly, and anemia.² Approximately 20% to 40% of CML patients are asymptomatic at this point, and the disease is usually identified by an abnormal white blood cell (WBC) count.² Peripheral blood films often show leukocytosis with immature myeloid cells, and bone marrow exhibits increased cellularity.²

Accelerated-phase CML is marked by an accumulation of genetic changes leading to progressive loss of the leukemic clone's ability to differentiate; this phase predicts a short sur-

vival time.^{1,2} Because both the accelerated phase and the acute phase are associated with a poor prognosis and because few effective treatment options are available for later stages of disease, achieving disease control in the chronic phase is a key initial goal in the treatment of CML.

EVOLUTION IN DISEASE MONITORING AND TREATMENT

Monitoring Treatment Response

Monitoring the response to TKI therapy for CML is important for guiding treatment decisions and for identifying patients with a suboptimal response or treatment failure. Sensitive methods for quantifying *BCR-ABL1* include standard karyotyping, fluorescence *in situ* hybridization (FISH), and quantitative reverse transcription polymerase chain reaction (qRT-PCR) (Table 1).^{16,17} A reduced burden of disease is indicated by increasingly rigorous clinical endpoints, namely hematological response, cytogenetic response (CyR), major molecular response (MMR), or complete molecular response (CMR) (Table 2).^{12,13}

Evolution in Treatment

Suppressive Chemotherapy

The earliest treatment for CML was suppressive chemotherapy. Responses to therapy were evaluated by blood counts, a decrease in spleen size, symptom relief, and survival. Interferon therapy increased the number of patients achieving hematological responses and enabled occasional patients to achieve CyRs.¹⁸⁻²⁰

Imatinib (Gleevec)

Imatinib (Gleevec, Novartis) was the first drug that targeted the *BCR-ABL1* fusion tyrosine kinase in CML.²¹ In the pivotal phase 3 International Randomized Study of Interferon and STI571 (IRIS) trial, imatinib 400 mg/day was associated with rapid, superior CyRs, a significantly lower rate of disease progression, and longer overall survival compared with the previous standard of care (interferon-alfa plus low-dose cytarabine [Depo-Cyt, Enzon]) in patients with Ph+ chronic-phase CML.^{6,10} In a *post hoc* analysis, imatinib's superiority also extended to a molecular response.²² Based on the results of this trial, imatinib replaced interferon-alfa as the standard of care for chronic-phase CML.

Nilotinib (Tasigna)

Nilotinib (Tasigna, Novartis) binds 30 times more tightly to *BCR-ABL1* kinase than imatinib does.^{23,24} The FDA first approved nilotinib in 2007 for patients with chronic-phase or accelerated-phase CML who were resistant to or intolerant of imatinib. FDA approval was granted in 2010 for newly diagnosed patients with chronic-phase CML, based on the ongoing, randomized phase 3 Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study.¹¹

In this trial, patients with newly diagnosed chronic-phase CML were randomly assigned to receive nilotinib (300 mg or 400 mg twice daily) or imatinib (400 mg once daily). At 12 months, MMR rates were significantly higher with the two nilotinib doses than with imatinib (44% and 43% vs. 22%, respectively; $P < 0.001$ for both comparisons).¹¹ The number of patients

Glossary

alloHSCT	allogeneic hematopoietic stem-cell transplantation
<i>BCR-ABL1</i>	breakpoint cluster region–Abelson
CyR	cytogenetic response
CCyR	complete cytogenetic response
CHR	complete hematological response
CML	chronic myeloid leukemia
CMR	complete molecular response
ELN	European LeukemiaNet
FISH	fluorescence <i>in situ</i> hybridization
mCyR	minimal cytogenetic response
MMR	major molecular response
MPR	medication possession ratio
NCCN	National Comprehensive Cancer Network
PCyR	partial cytogenetic response
Ph	Philadelphia chromosome
qRT-PCR	quantitative reverse transcription polymerase chain reaction
TKI	tyrosine kinase inhibitor

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Table 1 Methods of Detecting Disease Burden in Patients With Chronic Myeloid Leukemia

Method	Target	Sensitivity	Advantage	Disadvantage
Cytogenetics	Ph+ metaphases	1% to 5%	Widely available	Low sensitivity; bone marrow only
FISH	<i>BCR-ABL</i> fusion gene	0.1% to 5%	Rapid (1 to 2 days)	Does not detect other clonal events; has not been validated for monitoring response to TKI therapy
qRT-PCR	RNA sequence	0.001% to 0.01%	Highly sensitive	Suboptimal standardization; laboratory-intensive

BCR-ABL = breakpoint cluster region-Abelson; FISH = fluorescence *in situ* hybridization; Ph+ = Philadelphia chromosome-positive; qRT-PCR = quantitative reverse transcription polymerase chain reaction; TKI = tyrosine kinase inhibitor.
Data from Pelz AF, et al. *Ann Hematol* 2002;81(3):147-153;¹⁶ and Schoch C, et al. *Leukemia* 2002;16(1):53-59.¹⁷

Table 2 2009 European LeukemiaNet (ELN) and 2012 National Comprehensive Cancer Network (NCCN) Response Criteria In Patients With Chronic Myeloid Leukemia

	ELN Guidelines	NCCN Guidelines
Hematological Response		
Complete (CHR)	<ul style="list-style-type: none"> • WBC count < $10 \times 10^9/L$ • Platelet count < $450 \times 10^9/L$ • Differential: no immature granulocytes; basophils < 5% • Nonpalpable spleen 	<ul style="list-style-type: none"> • Complete normalization of peripheral blood counts with leukocyte count < $10 \times 10^9/L$ • Platelet count < $450 \times 10^9/L$ • No immature cells, such as myelocytes, promyelocytes, or blasts, in peripheral blood • No signs or symptoms of disease (e.g., no palpable splenomegaly)
Cytogenetic Response		
None	> 95% Ph+ metaphases	—
Minimal	66% to 95% Ph+ metaphases	—
Minor	36% to 65% Ph+ metaphases	> 35% Ph+ metaphases ^a
Major	—	0% to 35% Ph+ metaphases ^a (complete + partial response)
Partial (PCyR)	1% to 35% Ph+ metaphases	1% to 35% Ph+ metaphases ^a
Complete (CCyR)	No Ph+ metaphases ^b	No Ph+ metaphases ^a
Molecular Response		
Major (MMR)	Ratio of <i>BCR-ABL1</i> to <i>ABL</i> (or other housekeeping genes) $\leq 0.1\%$ on the International Scale	≥ 3 -log reduction in International Scale of <i>BCR-ABL1</i> mRNA
Complete (CMR)	Undetectable <i>BCR-ABL1</i> mRNA transcripts by real-time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10^4)	<i>BCR-ABL1</i> mRNA undetectable by RT-PCR

CBC = complete blood count; mRNA = messenger RNA; Ph+ = Philadelphia chromosome-positive; PCR = polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction; WBC = white blood cell.
^aA minimum of 20 metaphases should be examined.
^bIf marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCyR may be based on interphase FISH of blood cells, provided that it is performed with *BCR-ABL1* extrasignal, dual color, dual fusion, or *in situ* hybridization probes, and that at least 200 nuclei are scored. CCyR = < 1% *BCR-ABL1*-positive nuclei. In many studies, PCyRs and CCyRs are counted together and reported as major CyRs.
Adapted with permission from *NCCN Guidelines for Chronic Myelogenous Leukemia*.¹³
Additional data from O'Brien SG, et al. *N Engl J Med* 2003;348(11):994-1004;¹⁰ Baccarani M, et al. *Best Pract Res Clin Haematol* 2009;22(3):331-341;¹² Hughes TP, et al. *N Engl J Med* 2003;349(15):1423-1432.²²

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achieving a CMR also was significantly higher with nilotinib 300 mg and 400 mg than with imatinib at both 12 months (11% and 7% vs. 1%, respectively; $P < 0.001$ for both comparisons) and 24 months (25% and 19% vs. 9%, respectively; $P < 0.001$ and $P = 0.006$, respectively).²⁵ In addition, significantly fewer progressions (including clonal evolution) occurred in both nilotinib groups than in the imatinib group: two patients for nilotinib 300 mg and five patients for nilotinib 400 mg versus 17 patients for imatinib ($P = 0.0003$ and $P = 0.0089$, respectively). These data showed that disease control was improved with nilotinib compared with imatinib.

Nilotinib was well tolerated and showed consistent safety at 12, 18, and 24 months.^{11,26,27} Nonhematological adverse events of any grade occurring in at least 10% of nilotinib-treated patients included nausea, rash, pruritus, alopecia, headache, fatigue, and myalgia. Peripheral, eyelid, and periorbital edema were less common (in 5% or fewer patients) with nilotinib than with imatinib.¹¹

A preliminary report that included 36 months of follow-up data supported the superior efficacy of nilotinib over imatinib.²⁸

Dasatinib (Sprycel)

Dasatinib (Sprycel, Bristol-Myers Squibb) is a dual TKI that targets both *BCR-ABL* and *SRC* genes. The drug binds *BCR-ABL1* kinase more potently *in vitro* than does imatinib.²³ Dasatinib was initially approved in 2006 for patients who are resistant to or intolerant of imatinib. In 2010, dasatinib also received FDA approval for patients with newly diagnosed chronic-phase CML, based on the ongoing phase 3 Dasatinib Versus Imatinib in Patients With Newly Diagnosed Chronic Phase CML (DASISION) trial, which compared dasatinib 100 mg/day with imatinib 400 mg/day.⁸

In this study, dasatinib demonstrated higher complete cytogenetic response (CCyR) rates (77% vs. 66%; $P = 0.007$) and higher MMR rates (46% vs. 28%; $P < 0.0001$) when compared with imatinib at 12 months. Fewer dasatinib-treated patients (five) progressed to advanced disease compared with imatinib-treated patients (nine). Rates of progression-free survival and overall survival were similar between the two treatment arms.

More recent follow-up data have supported the superiority of dasatinib over imatinib with regard to CCyR, MMR, and CMR rates.^{29,30} Dasatinib was well tolerated at 12, 18, and 24 months.^{8,29,30} Nonhematological adverse events of any grade occurring in at least 10% of dasatinib-treated patients included diarrhea, rash, headache, musculoskeletal pain, and fluid retention. Although superficial edema occurred less often with dasatinib than with imatinib, pleural effusion was more common with dasatinib.⁸

Summary

In both ENESTnd and DASISION, nilotinib and dasatinib resulted in faster responses and greater reductions of disease burden, and they were associated with lower rates of disease progression compared with imatinib. These studies also provided an overview of the safety of nilotinib and dasatinib in the first-line setting. The patterns of toxicity with these drugs in second-line studies are generally similar to those seen in the first-line setting.^{7,9,31,32} Of note, in second-line studies, cross-intolerance was not evident with dasatinib³³ and was infrequent with nilotinib, occurring in only two of 86 patients.⁷

Discontinuation rates attributable to adverse events were low in both first-line and second-line studies of TKIs.

ELN AND NCCN GUIDELINES

Careful monitoring and assessment of responses to TKI therapy, based on clinical practice guidelines, can promote the optimal management of chronic-phase CML. The updated ELN and NCCN Guidelines^{12,13} offer similar recommendations for the management of CML. These guidelines describe initial treatments and methods of monitoring responses to treatment at specific time points, and both guidelines have established how to manage patients based on their response to treatment at each time point.

Treatment Recommendations for Chronic-Phase Chronic Myeloid Leukemia

Both the ELN and the NCCN Guidelines recommend that patients with chronic-phase CML initiate treatment with a TKI. The ELN Guidelines suggest that all patients with newly diagnosed chronic-phase CML receive imatinib 400 mg/day.¹² Either dasatinib or nilotinib is recommended for patients who show a suboptimal response to or intolerance of initial imatinib therapy. If a patient has a suboptimal response to imatinib, the clinician may continue imatinib at the same dose or consider a trial of high-dose imatinib or a newer TKI. If initial imatinib therapy fails, guideline recommendations include treatment with dasatinib or nilotinib. Patients whose disease has progressed to accelerated-phase or acute-phase CML or who carry the *T315I* genetic mutation may be candidates for allogeneic hematopoietic stem-cell transplantation (alloHSCT).

Recommendations for mutation analysis are evolving. The NCCN Guidelines recommend this step if:

- CML has progressed to the accelerated or acute phase.
- the patient shows an inadequate initial response, defined as a failure to achieve a complete hematological response (CHR) at 3 months, a minimal cytogenetic response (mCyR) at 6 months, or a mCyR at 12 months.
- there is a loss of response (i.e., hematological or cytogenetic relapse or a 1-log increase in *BCR-ABL1* transcript levels and a loss of MMR).¹³

ELN Guidelines recommend mutation analysis in cases of suboptimal response or treatment failure before the patient is switched from one TKI to another.¹²

An expert ELN panel published further recommendations in 2011. These guidelines stated that patients with chronic-phase CML receiving first-line imatinib should undergo analysis of genetic mutations only if they have experienced a suboptimal response or treatment failure according to ELN criteria. In imatinib-resistant patients receiving a second-generation TKI, mutation analysis should be performed if hematological or cytogenetic failure occurs, as defined by ELN criteria.³⁴

An analysis of the Italian Group for Adult Hematologic Diseases (GIMEMA) CML Working Party database, which tested the validity of the ELN and NCCN recommendations, found that genetic mutations were identified more often in cytogenetic suboptimal responders than in molecular suboptimal responders. Further, an increase in *BCR-ABL1*

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transcripts that does not result in the loss of MMR is not sufficiently worrisome to perform mutation analysis. Finally, although definitions of a response to dasatinib or nilotinib in the second-line setting are still provisional, patients who are suboptimal responders and those who fail to respond to treatment often have mutations.³⁵

NCCN Guidelines recommend imatinib, dasatinib, or nilotinib as initial therapy for patients with newly diagnosed chronic-phase CML.¹³ For patients who do not achieve optimal response milestones, treatment options include increasing the imatinib dose, switching to an alternative TKI, performing alloHSCT, or enrolling the patient in a clinical trial. Participation in a clinical study and alloHSCT (depending on the response to TKI therapy) are reasonable options for patients with the *T315I* mutation or other resistant gene mutations. The *T315I* mutation is resistant to all currently approved TKIs.

NCCN Guidelines also provide strategies for supportive care and offer detailed recommendations for the management of toxicities associated with the three available TKIs.¹³ Vigilant management has the potential to mitigate adverse events and to allow uninterrupted therapy.

Response and Milestones

The ELN and NCCN Guidelines both endorse evaluation-time benchmarks (i.e., at baseline and at 3, 6, 12, and 18 months) for evaluating treatment.^{12,13} Both guidelines require evaluations of *BCR-ABL1* levels every 3 months after the start of treatment, but they vary in length of the monitoring periods and

the frequency of monitoring after response milestones have been achieved (Table 3).

Although the ELN Guidelines acknowledge both cytogenetic and molecular monitoring for determining treatment milestones, the NCCN Guidelines recognize only cytogenetic monitoring for this purpose.^{12,13} From a clinical perspective, meeting milestones can be an early predictor of treatment response or disease progression and affects overall survival.^{6,36-38} At each benchmark, the ELN Guidelines further define overall response criteria as “optimal,” “suboptimal,” or “failure” based on achieving or losing hematological, cytogenetic, and molecular responses and on detecting *BCR-ABL1* kinase-domain mutations (Table 4).¹² Instead of defining a suboptimal response, the NCCN Guidelines provide an algorithm that specifies clinical evaluations and follow-up therapy based on attaining (or not attaining) an anticipated response.¹³

Adherence: Clinical Outcomes and Costs

Several studies have associated poor adherence to TKI therapy with suboptimal outcomes.³⁹⁻⁴¹ In the Adherence Assessment with Glivec: Indicators and Outcomes (ADAGIO) study, patients with chronic-phase CML who showed a suboptimal response to imatinib had significantly poorer adherence to therapy ($P = 0.005$) than had those with optimal responses.³⁹ Another study established that adherence to standard-dose imatinib was an independent predictor of MMR (relative risk [RR], 11.17; $P = 0.001$) and is the only independent predictor of CMR (RR, 19.35; $P = 0.004$).⁴⁰

Table 3 European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) Recommendations For Monitoring and Evaluation Timepoints in Patients With Chronic Myeloid Leukemia

	ELN Guidelines		NCCN Guidelines	
	Assessment	Optimal Response	Assessment	Optimal Response
3 months	<ul style="list-style-type: none"> Hematology qRT-PCR^a Cytogenetics^b 	<ul style="list-style-type: none"> CHR and at least mCyR 	<ul style="list-style-type: none"> Hematology qRT-PCR 	<ul style="list-style-type: none"> CHR
6 months	<ul style="list-style-type: none"> qRT-PCR^a Cytogenetics^{b,c} 	<ul style="list-style-type: none"> At least PCyR 	<ul style="list-style-type: none"> qRT-PCR Cytogenetics^{e,f} 	<ul style="list-style-type: none"> CCyR or PCyR
12 months	<ul style="list-style-type: none"> qRT-PCR^a Cytogenetics^{b,c} 	<ul style="list-style-type: none"> CCyR 	<ul style="list-style-type: none"> qRT-PCR Cytogenetics^{e,g} 	<ul style="list-style-type: none"> CCyR
18 months	<ul style="list-style-type: none"> qRT-PCR Cytogenetics^{b,c} 	<ul style="list-style-type: none"> MMR 	<ul style="list-style-type: none"> qRT-PCR Cytogenetics^e 	<ul style="list-style-type: none"> CCyR

CHR = complete hematologic response; mCyR = minor cytogenetic response; CCyR = complete cytogenetic response; MMR = major molecular response; PCyR = partial cytogenetic response; qRT-PCR = quantitative reverse transcription polymerase chain reaction.

^a Repeat every 3 months until MMR is confirmed, then every 6 months.

^b Perform with chromosome banding analysis of marrow cell metaphases.

^c Repeat every 6 months until a CCyR is confirmed, then every 12 months if no regular monitoring and always when myelodysplastic features, suboptimal response, or failure occurs.

^d Repeat every 3 months. If a CCyR is achieved, repeat every 3 months for 3 years, then every 3 to 6 months.

^e Perform on bone marrow.

^f If no CCyR at 6 months, repeat cytogenetics at 12 months.

^g If no CCyR at 12 months, repeat cytogenetics at 18 months.

Adapted with permission from the NCCN Guidelines for Chronic Myelogenous Leukemia.¹³

Additional data from Bacarani M, et al. *Best Pract Res Clin Haematol* 2009;22(3):331-341.¹²

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Poor adherence has also been implicated as an independent predictor of the loss of CCyRs (RR, 27.8; $P = 0.0002$) in patients receiving long-term treatment.⁴¹ In addition to affecting treatment response, poor adherence to imatinib in patients with CML adversely affects costs and overall health care utilization (see page 646).^{42,43} NCCN Guidelines suggest that reviewing and managing adverse effects of therapy might be helpful in maintaining adherence.¹³

MOLECULAR MONITORING AND RESPONSES: CURRENT AND FUTURE IMPLICATIONS

Early identification of patients who are unlikely to achieve optimal responses is important for improving long-term outcomes with TKI therapy. CyRs have been used to guide treatment decisions, and emerging data suggest that molecular responses may also provide an early indication of treatment failure or success. The ELN Guidelines, but not the NCCN Guidelines, include an MMR milestone to guide treatment decisions.¹²

The definitions of a treatment response in both guidelines are derived from analyses of patients who received imatinib in the first-line setting. As longer-term response data emerge (particularly for progression-free survival and overall survival) for first-line nilotinib and dasatinib, revisions to the response definitions, including the depth of response and the timing of response, may be needed. Given the rapidly evolving nature of these data, it is expected that both the ELN and the NCCN

Guidelines will be revised in the future.

An analysis of the IRIS dataset confirmed that achieving MMRs is a therapeutic milestone and a predictor of disease progression and event-free survival.³⁷ The achievement of MMRs at 12 months, compared with the lack of MMRs at this time point, was associated with superior event-free survival (91% vs. 79%, respectively; $P = 0.001$) and the lack of progression to the accelerated or acute phase (99% vs. 90%, respectively; $P = 0.0004$) at 84 months. At the 18-month time point, MMRs were also superior to the lack of MMR for event-free survival (95% vs. 75%, respectively; $P < 0.001$) and disease progression (99% vs. 90%; $P < 0.001$).

The clinical significance of a molecular response is supported by other studies, such as the German CML Study IV. This trial found that independent of the treatment approach used, MMRs at 12 months, compared with no MMRs at this time point, was associated with superior progression-free survival (99% vs. 95%, respectively; $P = 0.0143$) and superior overall survival (99% vs. 95%, respectively; $P = 0.0156$) at 36 months.³⁶

A retrospective analysis of data from imatinib-treated patients with chronic-phase CML provided an insight into which response parameters and time points have prognostic significance.⁴⁴ Earlier achievement of CCyRs or MMRs predicted the probability of achieving a better interim outcome. Specifically, CCyRs at 6 to 12 months and MMRs at 18 to 36 months were the best predictors of achieving CMRs and also the best predictors of a loss of response or treatment failure.

Table 4 2009 European LeukemiaNet (ELN) Definitions of Response to First-Line Imatinib In Early Chronic-Phase Chronic Myeloid Leukemia

Evaluation Time	Response			
	Optimal	Suboptimal	Failure	Warning
Baseline	• NA	• NA	• NA	• High risk • Positive for CCA/Ph ^a
3 months	• CHR and at least mCyR	• No cytogenetic response	• Less than CHR	• NA
6 months	• At least PCyR	• Less than PCyR	• No CyR	• NA
12 months	• CCyR	• PCyR	• Less than PCyR	• Less than MMR ^b
18 months	• MMR ^b	• Less than MMR ^b	• Less than CCyR	• NA
Any time during treatment	• Stable or improving MMR ^b	• Loss of MMR ^b • Mutations ^c	• Loss of CHR • Loss of CCyR • Mutations ^d • Positive for CCA/Ph	• Increase in transcript levels ^e • Negative for CCA/Ph

CCA = clonal chromosome abnormality; CCyR = complete cytogenetic response; CHR = complete hematological response; mCyR = minor cytogenetic response; MMR = major molecular response; NA = not applicable; PCyR = partial cytogenetic response; Ph = Philadelphia chromosome.

^aCCA/Ph+ is a warning factor at diagnosis, although its occurrence (i.e., clonal progression) during treatment is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least two Ph+ cells.

^bMMR indicates a ratio of *BCR-ABL1* to *ABL1* or other housekeeping genes of $\leq 0.1\%$ on the International Scale.

^c*BCR-ABL1* kinase domain mutations still sensitive to imatinib.

^d*BCR-ABL1* kinase domain mutations poorly sensitive to imatinib.

^eThe significance of the increase may vary by a factor of 2 to 10, depending on the laboratory.

Data from Baccarani M, et al. *Best Pract Res Clin Haematol* 2009;22(3):331-341.¹²

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More recent studies have focused on outcomes correlated with earlier treatment responses. In the German CML Study IV, landmark cytogenetic and molecular responses after 3 months of treatment with imatinib predicted long-term progression-free survival and overall survival. A *BCR-ABL1* level of less than 1% on the International Scale was associated with a 5-year overall survival rate of 97%, and a *BCR-ABL1* level equal to or greater than 10% was associated with a 5-year overall survival rate of 87%. After 3 months, landmark CyRs, in comparisons of Ph+ metaphases of 35% or less with metaphases of greater than 35% and Ph+ metaphases of 65% or less with metaphases of greater than 65%, were also significantly associated with progression-free survival and overall survival.⁴⁵

In one study, *BCR-ABL1* transcript levels of less than 10% after 3 months of treatment with imatinib (or with second-line nilotinib or dasatinib) strongly predicted long-term event-free survival, progression-free survival, and overall survival.⁴⁶ Similar correlations of 3-month assessments of CCyRs or *BCR-ABL1* transcript levels with positive long-term outcomes have been presented.⁴⁷⁻⁴⁹ If these data are confirmed, future guidelines may suggest a change in therapy at this early time point. Further guideline updates may be required after more sensitive technologies (e.g., DNA PCR and digital PCR) are evaluated in clinical trials.^{50,51}

Recent studies suggest that patients with CMRs for 2 or more years might be able to discontinue TKI therapy. In the STop IMatinib (STIM) study, for example, a subset of patients with chronic-phase CML achieved durable CMRs (defined as *BCR-ABL1/ABL* transcript levels below the detection threshold for at least 2 years, in which the assay sensitivity was greater than a 5-log reduction) could stop taking imatinib without relapsing within the follow-up period.⁵² Twelve months after imatinib was discontinued, the survival rate without molecular relapse was 41%. All patients who relapsed remained sensitive to imatinib.

Updated results, which included a median follow-up period of 22 months, found that an additional 11 of 39 patients had relapsed. A multivariate analysis identified two independent risk factors for molecular relapse: the Sokal risk score (low vs. intermediate vs. high; $P = 0.0009$) and the duration of imatinib therapy before the cessation of treatment (less than 60 months vs. 60 months or more; $P = 0.0183$).⁵³

Results from the STOP 2G-TKI pilot study also indicate that nilotinib and dasatinib can be discontinued in some CML patients with stable CMRs who are resistant to or intolerant of imatinib.⁵⁴ An intensive interest in understanding relapse-free survival after discontinuation of TKIs is reflected in numerous prospective studies.⁵⁵⁻⁵⁸

Although this is an intriguing approach, further study is needed, and discontinuation of TKI therapy is not recommended except in a clinical trial. Although NCCN and ELN Guidelines define CMR, neither guideline recommends discontinuation of TKI therapy in patients who have undetectable *BCR-ABL1* transcript levels.^{12,13} If additional studies confirm the value of prognostic factors, such as the Sokal risk group and the duration of prior treatment, guidelines may someday include recommendations about which patients can safely discontinue TKI therapy.

HEALTH ECONOMICS OF TREATMENT WITH TYROSINE KINASE INHIBITORS

Oncology treatment guidelines synthesize data and expert opinions in order to provide recommendations that will improve cancer outcomes and quality of care. Not only do they enable effective communication of clinical advances to the community; they can also form the basis for determining the most efficacious and cost-effective strategies.⁵⁹

To our knowledge, however, the two sets of clinical practice guidelines for the management of CML have not been compared from a health economics perspective. Given the rapidly evolving data, it is likely that standards of care will also change and make such evaluations problematic until the evidence base becomes more robust.

Indeed, economic comparisons of the available TKIs have been difficult, because only relatively short-term data are available. The National Health Service in the U.K. recently conducted a cost-effectiveness analysis of dasatinib and nilotinib in CML patients with chronic-phase CML who were resistant to or intolerant of imatinib. This study concluded that until longer follow-up data for progression-free and overall survival become available, the cost-effectiveness of dasatinib and nilotinib for imatinib-resistant patients is highly uncertain.⁶⁰ Phase 3 studies of first-line dasatinib and nilotinib in patients with chronic-phase CML require longer-term data before the cost-effectiveness of imatinib, nilotinib, and dasatinib can be compared.

To date, the economic analyses of TKI therapy in patients with CML have been limited to the economic consequences of nonadherence to TKIs and to the economic implications of pleural effusions. In addition to suboptimal outcomes, poor adherence is associated with greater overall health-care utilization and medical costs.

A retrospective analysis of claims data in the U.S. found an inverse relationship between the medication possession ratio (MPR) for imatinib and costs. (The MPR reflects the degree to which a patient had access to imatinib during the treatment interval.) For every 10% reduction in the MPR, there was a 14% increase in health care costs, excluding the cost of imatinib, and a 15% increase in overall medical costs.⁴²

In another claims data analysis in the U.S., imatinib-treated patients with a high MPR (85% or greater) had significantly lower disease-related and total health care costs, as well as lower resource utilization, compared with patients with a low MPR (less than 85%).⁴³

One study examined the economic consequences of nonadherence to second-line treatment of CML, as reflected by the use of nilotinib and dasatinib in two large U.S. claims databases. Patients receiving nilotinib were significantly more adherent than those receiving dasatinib. Moreover, utilization of health care resources was lower with nilotinib, which translated into lower medical service costs compared with the costs for patients receiving dasatinib.⁶¹ This study was conducted when nilotinib had been available for only about 1 year, and the sample size for nilotinib was relatively small. A clearer picture should emerge as more data on nilotinib and dasatinib become available in both first- and second-line settings.

Finally, a study examined the costs associated with pleural effusions. This analysis used data from 48 dasatinib-treated patients who had experienced pleural effusions at a large cancer

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center. Finding that managing pleural effusions was costly, the authors suggested that this factor be considered when selecting a TKI.⁶² A more comprehensive examination of the costs associated with the side effects of all three available TKIs would provide a better basis for treatment selection.

CONCLUSION

The management of CML has undergone important changes over the previous decade; advances in the field have dramatically transformed CML treatment, monitoring, and expected outcomes. Given the rapid evolution of technology, the education of clinicians involved in patient management is crucial. Because a substantial percentage of CML patients are not treated according to clinical practice guidelines,⁴ it is important to be aware of the ELN and NCCN recommendations,^{12,13} which are key sources of evidence-based information to guide clinicians and stakeholders in the management of CML. Advances in disease management, including treatment selection, appropriate clinical monitoring, follow-up strategies, and indications for switching therapy, necessitate timely revisions to existing guidelines. In the future, molecular monitoring will play a greater role in identifying patients who are at risk of treatment failure or the loss of response, in guiding treatment modification, and in identifying patients who might be candidates for more aggressive therapies.

REFERENCES

1. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. *Blood* 2008;112(13):4808–4817.
2. Vardiman JW. Chronic myelogenous leukemia, BCR–ABL1+. *Am J Clin Pathol* 2009;132(2):250–260.
3. Danielson E, DeMartino J, Mullen JA. Managed care and medical oncology: The focus is on value. *JNCCN J Natl Compr Cancer Network* 2010;3:S28–S37.
4. Quintas-Cardama A, Flamm M, Lill M, et al. Resource utilization and perceptions of major molecular response in chronic myeloid leukemia (CML): Results of a Delphi panel study (Abstract). *Value Health* 2011;14(3):A157.
5. Pasquini R, Cortes JE, Kantarjian HM, et al. Survey of the frontline treatment and management of chronic myeloid leukemia (CML) in a real-world setting: Third annual update of the Worldwide Observational Registry Collecting Longitudinal Data on Management of Chronic Myeloid Leukemia Patients (the WORLD CML Registry). Presented at the American Society of Hematology annual meeting, San Diego, December 10, 2011. Available at: <https://ash.confex.com/ash/2011/webprogram/Paper40024.html>. Accessed June 14, 2012.
6. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355(23):2408–2417.
7. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR–ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007;110(10):3540–3546.
8. 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.
9. 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.
10. O'Brien SG, Guilhot F, Larson RA, et al. 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.
11. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010;362(24):2251–2259.
12. Baccarani M, Castagnetti F, Gugliotta G, et al. Response definitions and European LeukemiaNet management recommendations. *Best Pract Res Clin Haematol* 2009;22(3):331–341.
13. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia*. Version 2.2012. Available at: www.nccn.org/professionals/physician_gls/PDF/cml.pdf. Accessed July 5, 2011.
14. National Comprehensive Cancer Network. About NCCN. Available at: www.nccn.org/about/default.asp. Accessed March 22, 2011.
15. European LeukemiaNet. Available at: www.leukemia-net.org/content/home. Accessed March 22 2011.
16. Pelz AF, Kroning H, Franke A, et al. High reliability and sensitivity of the BCR/ABL1 D-FISH test for the detection of BCR/ABL rearrangements. *Ann Hematol* 2002;81(3):147–153.
17. Schoch C, Schnittger S, Bursch S, et al. Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: A study on 350 cases. *Leukemia* 2002;16(1):53–59.
18. Talpaz M, Kantarjian HM, McCredie K, et al. Hematologic remission and cytogenetic improvement induced by recombinant human interferon alpha A in chronic myelogenous leukemia. *N Engl J Med* 1986;314(17):1065–1069.
19. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: Improved survival irrespective of cytogenetic response. *Lancet* 1995;345(8962):1392–1397.
20. 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.
21. Mauro MJ, Druker BJ. STI571: Targeting BCR–ABL as therapy for CML. *Oncologist* 2001;6(3):233–238.
22. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2003;349(15):1423–1432.
23. O'Hare T, Walters DK, Stoffregen EP, et al. *In vitro* activity of Bcr–Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res* 2005;65(11):4500–4505.
24. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr–Abl. *Cancer Cell* 2005;7(2):129–141.
25. Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome–positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol* 2011;12(9):841–851.
26. Hughes TP, Hochhaus A, Saglio G, et al. ENESTnd update: Continued superiority of nilotinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML–CP) (Abstract). *Blood* 2010;116(21):207.
27. Larson RA, Kim D, Rosti G, et al. Comparison of nilotinib and imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML–CP): ENESTnd 24-month follow-up (Abstract). *J Clin Oncol* 2011;29:6511.
28. Saglio G, LeCoutre PD, Pasquini R, et al. Nilotinib versus imatinib in patients (pts) with newly diagnosed Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia in chronic phase (CML–CP): ENESTnd 36-month (mo) follow-up (Abstract). *Blood* 2011;118(21):452.
29. Shah N, Kantarjian H, Hochhaus A, et al. Dasatinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML–CP) in the DASISION trial: 18-month follow-up (Abstract). *Blood* 2010;116(21):206.
30. Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION).

Guidelines for Chronic Myeloid Leukemia

- Blood* 2012;119(5):1123–1129.
31. Shah NP, Kim D-W, Kantarjian H, et al. Potent, transient inhibition of BCR–ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response, or intolerance to imatinib. *Haematologica* 2010;95(2):232–240.
 32. 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.
 33. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007;109(6):2303–2309.
 34. Soverini S, Hochhaus A, Nicolini FE, et al. BCR–ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: Recommendations from an expert panel on behalf of European LeukemiaNet. *Blood* 2011;118(5):1208–1215.
 35. Soverini S, Gnani A, De Benedittis C, et al. Validation of the new European LeukemiaNet (ELN) recommendations for Bcr–Abl kinase domain mutation analysis in chronic myeloid leukemia: An analysis of the GIMEMA CML Working Party studies (Abstract). *Blood* 2011;118(21):112.
 36. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon- α in newly diagnosed chronic myeloid leukemia. *J Clin Oncol* 2011;29(12):1634–1642.
 37. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: An analysis from the international randomized study of interferon versus STI571 (IRIS). *Blood* 2010;116(19):3758–3765.
 38. Müller MC, Hochhaus A, Lauseker M, et al. Molecular response <1% BCR–ABL IS at 12 months is associated with improved overall and progression-free survival: The randomized German CML Study IV (Abstract). *Blood* 2010;116(21):669.
 39. 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.
 40. 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.
 41. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for CML patients on long term therapy. *Blood* 2011;117(14):3733–3736.
 42. 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.
 43. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Curr Med Res Opin* 2010;26(1):61–69.
 44. Kim DH, Sriharsha L, Jung CW, et al. Comprehensive evaluation of time-to-response parameter as a predictor of treatment failure following imatinib therapy in chronic phase chronic myeloid leukemia: Which parameter at which time-point does matter? *Am J Hematol* 2010;85(11):856–862.
 45. Hanfstein B, Muller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia* 2012;26(9):2096–2102.
 46. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR–ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol* 2012;30(3):232–238.
 47. Hochhaus A, Saglio G, Chuah C, et al. Dasatinib and imatinib-induced reductions in BCR–ABL transcript levels below 10% at 3 months are associated with improved responses in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML–CP): Analysis of molecular response kinetics in the DASISION trial (Abstract). *Blood* 2011;118(21):2767.
 48. Latagliata R, Breccia M, Carmosino I, et al. Complete cytogenetic response after 3 months is a very early indicator of good response to imatinib as first-line treatment in chronic myelogenous leukemia (Abstract). *Blood* 2011;118(21):3783.
 49. Ohm A-C, Barbany G, Arvidsson I, et al. Landmark analysis of imatinib treatment in CML chronic phase: ES–FISH <10% Ph+ at 3 months associated with better cytogenetic response and improved long-term event-free survival (Abstract). *Blood* 2011;118(21):1702.
 50. Ross DM, Branford S, Seymour JF, et al. Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. *Leukemia* 2010;24(10):1719–1724.
 51. Goh HG, Lin M, Fukushima T, et al. Sensitive quantitation of minimal residual disease in chronic myeloid leukemia using nano-fluidic digital polymerase chain reaction assay. *Leuk Lymphoma* 2011;52(5):896–904.
 52. Mahon FX, Rea D, Guilhot J, et al. 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.
 53. Mahon F-X, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular response: Updated results of the STIM study (Abstract). *Blood* 2011;118(21):603.
 54. Rea D, Rousselot P, Nicolini FE, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia (CML) patients (pts) with stable undetectable Bcr–Abl transcripts: Results from the French CML Group (FILMC) (Abstract). *Blood* 2011;118(21):604.
 55. Goh H-G, Choi S-Y, Bang J-H, et al. Discontinuation of imatinib therapy in chronic myeloid leukemia patients with sustained complete molecular response^{4,5} (CMR^{4,5}) (Abstract). *Blood* 2011;118(21):2763.
 56. Matsuki E, Ono Y, Sakurai M, et al. Discontinuation of imatinib in patients with CML and sustained complete molecular response (CMR) for over 2 years in the Japanese population: An interim analysis of KEIO STIM study (Abstract). *Blood* 2011;118(21):3765.
 57. Rousselot P, Makhoul PC, Rea D, et al. Fluctuating values of molecular residual disease (MRD) without molecular progression after imatinib discontinuation in patients (pts) with chronic myeloid leukemia (CML) who have maintained complete molecular response: Implications for re-treatment criteria and role of prior interferon therapy: A pilot study of the French CML Group (FILMC) (Abstract). *Blood* 2011;118(21):3781.
 58. Takahashi N, Kyo T, Maeda Y, et al. Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia (Abstract). *Blood* 2011;118(21):3759.
 59. Benson AB, Brown E. Role of NCCN in integrating cancer clinical practice guidelines into the healthcare debate. *Am Health Drug Benefits* 2008;1(1):28–33.
 60. Hoyle M, Rogers G, Moxham T, et al. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. *Value Health* 2011;14(8):1057–1067.
 61. Wu EQ, Guerin A, Yu AP, et al. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. *Curr Med Res Opin* 2010;26(12):2861–2869.
 62. Stephens J, Carpiuc KT, Botteman M. The burden of managing pleural effusions in patients with chronic myelogenous leukemia post-imatinib failure: A literature-based economic analysis. *Int J Gen Med* 2010;3:31–36. ■