The "Hit Hard and Hit Early" Approach to the Treatment of Chronic Myeloid Leukemia: Implications of the Updated National Comprehensive Cancer Network Clinical Practice Guidelines for Routine Practice

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Keywords
Early molecular response, tyrosine kinase inhibitor

Abstract: In July 2012, the National Comprehensive Cancer Network (NCCN) updated its clinical practice guidelines in chronic myeloid leukemia (CML) with perhaps the most sweeping changes in a decade. These changes are expected to affect routine practice in CML, particularly with respect to criteria for early molecular response at 3 months and minimum specifications for molecular monitoring assays. Viewed as a whole, these updates signal an important shift in the recommendations for managing patients with CML. These updates support the wider use of standardized molecular monitoring assays, which should improve data consistency, reliability, and reproducibility. They also implicitly recommend that treating physicians strive for deeper levels of response early in the treatment course, in recognition of the effectiveness of current standard therapy. Most importantly, these updates reinforce the increasingly common perception that CML in its early chronic phase can be managed as a chronic disease in the majority of newly diagnosed patients. In this review, we outline the major updates to the guidelines, discuss the rationale behind these updates, and provide our perspectives on how they affect patient management in CML, including a preference for the use of newer tyrosine kinase inhibitors in the first-line setting.

Introduction

The approval of the first BCR-ABL1 tyrosine kinase inhibitor (TKI) for the treatment of Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) more than a decade ago represented a major advancement in the management of patients with CML. For most patients with CML in the chronic phase (CML-CP), BCR-ABL1 TKIs can reduce disease burden to extremely low, sometimes undetectable, levels. The effectiveness of BCR-ABL1 TKIs has had far-reaching effects on CML management, affecting methods of disease monitoring, expectations for treatment response,[1] and clinical study design.[2]

The National Comprehensive Cancer Network (NCCN) has kept up with the rapid pace of research in CML, issuing updates and revisions to the NCCN Clinical Practice Guidelines in Oncology for CML (NCCN Guidelines) biannually to reflect current, evidence-based, best practices. The guidelines were updated in July 2012 (version 1.2013).[3] Additional updates were made in September and November 2012 and in February 2013 in order to fine-tune version 1.2013 and include 3 newly approved compounds: the BCR-ABL1 TKIs bosutinib (Bosulif, Pfizer) and ponatinib (Iclusig, ARIAD Pharmaceuticals), as well as the protein synthesis inhibitor omacetaxine (Synribo, Teva Pharmaceutical Industries).[4] The majority of these recent updates relate to specifications for the timing and methodology used to monitor disease. Notably, the NCCN Guidelines (v4.2013)[4] now include recommendations for deeper responses to first-line TKI therapy, a change that will affect treatment response goals.

Because these revisions represent arguably the most substantive changes to practice guidelines in a decade, clinicians may have questions about the clinical evidence supporting the new guidelines. This review outlines the more substantive changes to the NCCN Guidelines, describes clinical data that support these changes, and provides an overview of the implications of these changes for routine clinical practice that might not be covered by these new guidelines.

Rationale Behind the Major Changes to the NCCN Guidelines

The major changes in the NCCN Guidelines v1.2013 (carried over in v2.2013, v3.2013, and v4.2013) are summarized in Table 1.

The International Scale (IS)

The IS was established in the IRIS (International Randomized Study of Interferon and STI571) trial to facilitate the direct comparison of quantitative reverse-transcription polymerase chain reaction (QPCR) data generated from the 3 investigating laboratories.[5] Each laboratory calculated a median value of *BCR-ABL1* level for a common set of 30 pretreatment samples, and independently set that median value to 100% on the IS. Then, subsequent log reductions in *BCR-ABL1* level were expressed as a reduction in percent on the IS (eg, 1-log reduction is equivalent to 10% IS). Since the IRIS study, there has been a global effort to promote the adoption of the IS,[6-9] including the development and validation by the World Health Organization (WHO) of a set of reference materials consisting of a freeze-dried panel of 4 dilution levels of K562 cells diluted in HL60 cells that laboratories can use to align themselves to the IS. Unfortunately, only a limited supply of these reference materials is available. It was envisioned that these materials would be furnished to manufacturers of secondary reference materials, thus maintaining a chain of traceability to the original WHO IS-standardized materials.[9] Recently, several commercial laboratories have developed tests that use reference materials standardized to the IS. Some of these laboratories have developed kits or are developing compact testing systems that can rapidly evaluate *BCR-ABL1* levels (IS). It is hoped that these new products will be evaluated and approved by the US Food and Drug Administration (FDA) to allow wider access and routine use of IS-standardized testing for all patients with CML.

Some laboratories have found it difficult to convert to the IS because the conversion process is labor-intensive and the currently available IS-calibrated tests are labeled for research use only. In the absence of IS standardization, these laboratories may establish their own standardized baseline against which subsequent *BCR-ABL1* values can be compared. Although the use of laboratory-specific baselines can serve the purpose of standardization, unless the standardization is validated against IS-approved materials, the test results from such laboratories may be difficult to interpret.

IS-standardized QPCR is the preferred method of measuring treatment response and monitoring residual disease in CML. In the absence of access to IS-standardized QPCR assays, the NCCN Guidelines recommend the use of bone marrow cytogenetic testing to assess response to TKI therapy. Although cytogenetic testing is less sensitive than QPCR, the use of non-IS–standardized QPCR assays, as mentioned, yields results that may be difficult to interpret and not suitable for making decisions regarding treatment.

Minimum Sensitivity Threshold of QPCR Assay for Undetectable BCR-ABL1 *Levels*

The NCCN Guidelines (v4.2013) now defines the term *complete molecular response* (CMR) as undetectable *BCR-ABL1* levels by measurement using QPCR assays that have a sensitivity threshold of 4.5 log or higher.[4] This specification acknowledges that CMR, by itself, is an imprecise term that varies by assay (ie, method, technology, and limit of detection). This specification of assay sensitivity in the NCCN Guidelines is also consistent with a recent shift in the way molecular response (MR) is reported in the literature—that is, MR labeled with the limit of detection of the assay (eg, MR4=detectable *BCR-ABL1* level of ≤0.01% [IS] or ≥4-log reduction; CMR4=undetectable *BCR-ABL1* transcripts with ≥10,000 control transcripts detected). Note that when *BCR-ABL1* transcripts are undetectable, the control gene copy number should be reported[1] as an indication that the QPCR assay was not technically flawed, and that *BCR-ABL1* transcripts would have been detected had they been present in the sample.

Table 1. Summary of Changes to the NCCN Guidelines in CML[4,69]

Previous Recommendation (v2.2012)	Current Recommendation (v4.2013)	Change in Practice
Work-Up		
CBC	CBC with differential	Order CBC with blood differential test
QPCR	QPCR (IS) using blood or bone marrow	Use either blood or bone marrow sample for QPCR (IS)
3-Month Evaluation		
Satisfactory response level: CHR Unsatisfactory response level: less than CHR	Satisfactory response level: *BCR-ABL1* transcript level ≤10% by QPCR (IS) or PCyR by bone marrow evaluation if QPCR (IS) is not available Unsatisfactory response level: *BCR-ABL1* transcript level >10% by QPCR (IS) or less than PCyR by bone marrow evaluation if QPCR (IS) is not available	Strive for deeper levels of response to first-line TKI therapy Conduct QPCR during work-up Conduct QPCR in accordance with the IS
Consider bone marrow cytogenetic testing at 3 months after start of TKI therapy if less than CHR	Conduct bone marrow cytogenetic testing if QPCR (IS) is not available to assess response to TKI therapy	If QPCR (IS) is not available, then bone marrow cytogenetic testing is recommended
6-Month Evaluation		
Treatment response evaluation recommended at 6 months after start of TKI therapy	6-month evaluation eliminated; QPCR (IS) is recommended at this time	Guidelines no longer provided for treatment response evaluation at 6 months
12-Month Evaluation		
Conduct bone marrow cytogenetic testing	Conduct bone marrow cytogenetic testing if neither CCyR nor MMR is achieved	Conduct bone marrow cytogenetic testing in patients who have not achieved CCyR or MMR by 12 months
18-Month Evaluation		
Conduct bone marrow cytogenetic testing	Conduct bone marrow cytogenetic testing if not in MMR and lack of CCyR at 12 months	Conduct bone marrow cytogenetic testing in patients who have not achieved MMR at 18 months and had not achieved CCyR at 12 months
Criteria for Complete Molecular Response		
CMR: *BCR-ABL1* mRNA undetectable by RT-PCR	CMR: no detectable *BCR-ABL1* mRNA by QPCR (IS) using an assay with a sensitivity of ≥4.5-log below the standardized baseline	Conduct QPCR testing using an assay with adequate level of sensitivity
Rare But Serious Toxicities		
TKI therapy-related rare but serious toxicities not described	Nilotinib: peripheral arterial occlusive disease (PAOD) Dasatinib: pulmonary arterial hypertension (PAH) Ponatinib: arterial thrombosis, venous thromboembolism, congestive heart failure or left ventricular dysfunction, hemorrhage, cardiac arrhythmias, tumor lysis syndrome	Nilotinib: Evaluate patients for preexisting PAOD and vascular risk factors prior to and during treatment. If PAOD is confirmed, nilotinib should be discontinued permanently Dasatinib: Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to and during treatment. If PAH is confirmed, dasatinib should be discontinued permanently Ponatinib: If rare but serious adverse events occur, consider dose interruption, dose adjustment, and/or discontinuation of ponatinib. For tumor lysis syndrome, ensure adequate hydration and correct high uric acid levels prior to ponatinib treatment in patients with advanced-phase CML

CBC=complete blood count; CCyR=complete cytogenetic response; CHR=complete hematologic response; CML=chronic myeloid leukemia; CMR=complete molecular response; IS=international scale; MMR=major molecular response; NCCN=National Comprehensive Cancer Network; PCyR=partial cytogenetic response; QPCR=quantitative RT-PCR; RT-PCR=reverse transcription polymerase chain reaction; TKI=tyrosine kinase inhibitor.

Acceptable Samples for QPCR Molecular Monitoring

The NCCN Guidelines (v4.2013) now indicate that the use of either peripheral blood or bone marrow samples for QPCR assay is acceptable.[4] Bone marrow sampling is considered an invasive procedure, which may pose a barrier to performing monitoring every 3 months, as recommended in the NCCN Guidelines. Allowing the use of peripheral blood samples for QPCR assays could alleviate some of the burden of performing quarterly molecular monitoring of response.

In a recent study by Lima and associates, a significant correlation was found between QPCR results using paired bone marrow samples versus peripheral blood samples (n=64 paired samples; r=0.869; $P<.0001$) from patients with CML (all stages) treated with a TKI or with omacetaxine mepesuccinate.[10] Similarly, a post-hoc analysis of the RIGHT (Rationale and Insight for Gleevec High-Dose Therapy) study also found a significant correlation between peripheral blood and bone marrow QPCR results (n=170 paired samples; r=0.9256; $P<10^{-4}$).[11] Lima and colleagues further determined that the costs associated with bone marrow biopsies (including professional and technical costs, and fees associated with conscious sedation) in the first 18 months after diagnosis of CML were more than 4 times those associated with peripheral blood drawings (including professional and technical costs, and fees associated with phlebotomies).[10]

The 3-Month Treatment Response Milestone

In the current NCCN Guidelines (v4.2013), criteria for satisfactory response to TKI therapy at 3 months were changed from achievement of complete hematologic response (CHR) to *BCR-ABL1* transcript level of 10% or less (IS) (≥1-log reduction) or partial cytogenetic response (PCyR; 1–35% Ph+).[4] There is considerable clinical evidence that TKIs elicit significantly higher rates of molecular response than pre-TKI standard treatment modalities, such as interferon alfa. In the IRIS study, the rate of major molecular response (MMR) at 1 year (*BCR-ABL1* ≤0.1% [IS] or ≥3-log reduction from baseline; 39% vs 2%, $P<.001$) was significantly higher with imatinib (Gleevec, Novartis) than with the control regimen of interferon alfa plus cytarabine.[5] Likewise, the newer BCR-ABL1 TKIs have improved rates of MMR over imatinib. In the phase III randomized ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients) study, the rate of MMR at 1 year (44% vs 22%; $P<.001$),[12] and the rates of MR4 and MR$^{4.5}$ at 1, 2, and 3 years were significantly higher with nilotinib (Tasigna, Novartis) 300 mg twice daily than with imatinib.[13,14] In the DASISION (Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients) trial, the rate of MMR at 1 year (46% vs 28%; $P<.0001$),[15] and the rates of MR$^{4.5}$ at 2 and 3 years were significantly higher with dasatinib (Sprycel, Bristol-Myers Squibb) than with imatinib.[16,17] In the BELA (Bosutinib Efficacy and Safety in Newly Diagnosed CML) study, the rate of MMR at 12 months was higher with bosutinib than with imatinib (41% vs 27%; $P<.001$), although the rate of complete cytogenetic response (CCyR) at 12 months was similar with either TKI.[18] This change in treatment response expected at 3 months recognizes that the previous criterion of CHR at 3 months was neither sufficiently sensitive nor specific in distinguishing patients who might need closer evaluation or follow-up from those with satisfactory response to first-line treatment, because nearly all patients treated with TKI therapy achieve CHR at 3 months (eg, median time to CHR with imatinib in the IRIS study was 1 month[19]). The updated response criteria at 3 months, namely *BCR-ABL1* levels of 10% or less (IS; ≥1-log reduction) or partial cytogenetic response (PCyR), should identify a greater proportion of patients who do not respond adequately to first-line TKI therapy, compared with the previous 3-month response criterion of CHR.

The new response criteria are based on findings of landmark analyses linking early cytogenetic or molecular responses with long-term outcomes. In the IRIS study, achievement of cytogenetic response at 3 months predicted durable response at 8 years.[20] Furthermore, the achievement of cytogenetic responses has been associated with fewer CML-related events and longer survival without disease progression to accelerated phase (AP) or blast crisis (BC) in the IRIS study,[20,21] as well as in other studies of first-line imatinib.[22-24] Similarly, other studies have shown that the achievement of CCyR at 3, 6, and 12 months is associated with improved event-free survival (EFS) and overall survival (OS),[25] and the achievement of at least PCyR at 3 months predicts significantly better 5-year OS than lower levels of cytogenetic response.[26]

The update of the NCCN Guidelines for expected treatment response at 3 months also reflects a considerable body of clinical research showing that the achievement of *BCR-ABL1* levels of 10% or less (IS; ≥1-log reduction) at 3 months significantly predicts favorable long-term outcome[27-34] (Table 2). The first of these studies to show a significant correlation between molecular response at 3 months and prolonged OS was a landmark analysis conducted by Marin and colleagues, in which unselected patients treated at a single center with first-line imatinib who achieved *BCR-ABL1* up to 9.84% (IS) at 3 months had significantly higher rates of CCyR, MMR, and CMR, as well as higher rates of OS, progression-free survival (PFS), and EFS at 8 years than patients with higher *BCR-ABL1* levels at 3 months.[31] In addition, multivariate analysis identified the *BCR-ABL1* level at 3 months (≤9.84% vs >9.84%) to be the only independent predictor of OS, PFS, EFS, and current CCyR survival (the probability of

Table 2. Long-Term Outcomes of Patients at 3 Months After Initiation of TKI Therapy

TKI	Study	Parameter	*BCR-ABL1*% (IS) at 3 Months	*P* Value	
Imatinib	German CML Study IV[26]		≤10% (n=501)	>10% (n=191)	
		5-year OS	95.2%	87.0%	<.001
			>1% to 10% (n=283)	>10% (n=191)	
		5-year PFS	92%	87%	.037
	Hammersmith Hospital[31]		≤9.84% (n=211)	>9.84% (n=68)	
		8-year OS	93.3%	56.9%	<.001
			≤9.54% (n=208)	>9.54% (n=71)	
		8-year PFS	92.8%	57.0%	<.001
			≤8.58% (n=169)	>8.58% (n=79)	
		8-year CCyR	99.4%	21.7%	<.001
			≤2.81% (n=141)	>2.81% (n=137)	
		8-year MMR	82.5%	21.1%	<.001
	ENESTnd[36]*		≤10% (n=176)	>10% (n=88)	
		MMR by 2 years	58%	21%	NR
		PFS at 3 years	97.7%	83.8%	
		OS at 3 years	98.9%	84.8%	
	DASISION[33]*		≤10% (n=154)	>10% (n=85)	
		AP/BC by 3 years	2.6%	12.9%	NR
		PFS at 3 years	95.9%	75.3%	<.0001
		OS at 3 years	96.0%	88.0%	.0036
	BELA[35]*		≤10% (n=146)	>10% (n=77)	
		MMR by 24 months	69%	17%	<.001
		CCyR by 12 months	95%	65%	<.001
		OS at 24 months	99%	95%	NS
Nilotinib	ENESTnd[36]		≤10% (n=234)	>10% (n=24)	
		MMR by 2 years	80%	29%	NR
		PFS at 3 years	95.9%	82.9%	
		OS at 3 years	97.6%	86.7%	
Dasatinib	DASISION[33]		≤10% (n=198)	>10% (n=37)	
		AP/BC by 3 years	3.0%	13.5%	NR
		PFS at 3 years	93.1%	68.2%	.0003
		OS at 3 years	95.9%	85.9%	.0348
Bosutinib	BELA[35]		≤10% (n=179)	>10% (n=29)	
		MMR by 24 months	74%	21%	<.001
		CCyR by 12 months	96%	48%	<.001
		OS at 24 months	99%	88%	.004

*Data for the imatinib arm of the study.

AP=accelerated phase; BC=blast crisis; CCyR=complete cytogenetic response; MMR=major molecular response; NR=not reported; NS=not significant; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

being alive and in CCyR at a given time) at 8 years. In a landmark analysis of the randomized, controlled German CML IV study, achievement of early molecular response (*BCR-ABL1* ≤10% [IS] at 3 months and *BCR-ABL1* ≤1% [IS] at 6 months) was associated with significantly higher rates of PFS and OS at 5 years.[26] Independent validation of the prognostic significance of early molecular response to imatinib was conducted in a group of patients who were treated with imatinib in the IRIS study. In agreement with the findings of the German CML IV landmark analysis, IRIS patients with *BCR-ABL1* levels up to 10% (IS) at 3 months had a higher rate of OS at 8 years than patients with *BCR-ABL1* levels greater than 10% (IS) at 3 months (93% vs 81%).[26] Because their data predicted poorer prognosis for patients without early molecular response, the German CML Study Group considers an early switch in TKI therapy in these so-called "slow-responding" patients to be justified.

Although not as mature as the imatinib data, landmark analyses of the ENESTnd, DASISION, and BELA studies show that early response to nilotinib, dasatinib, and bosutinib, respectively, correlate with higher rates of future response,[33,35,36] higher rates of OS[35,36] and PFS,[33] and lower incidences of disease progression to AP/BC.[33,36] Notably, half of the progression events occurring in patients in the ENESTnd study with *BCR-ABL1* levels above 10% (IS) occurred between 3 and 6 months,[36] which further supports the concept that the 3-month mark is an important decision point. Some of the landmark analyses—particularly those of imatinib—have followed patients for many years and have shown significant survival differences. The more recent analyses have demonstrated a higher likelihood of attaining CCyR and MMR for early responders, and a higher likelihood of reaching the 3-month molecular target with the newer TKIs than with imatinib. As a whole, the findings of these landmark analyses point to the importance of achieving rapid response to first-line TKI therapy for improving long-term outcome.

Practical Considerations of the Updated NCCN Guidelines

Goals of Therapy

The new 3-month treatment response milestone—*BCR-ABL1* levels less than or equal to 10% (IS; ≥1-log reduction)—underscores the importance of achieving rapid response to first-line TKI therapy, based on the significant prognostic link between rapid response and improved long-term OS. The NCCN Guidelines have consistently recommended regular monitoring of treatment response and minimal residual disease, acknowledging the need for constant vigilance in detecting potential signs of disease progression. Preventing the progression of CML to advanced stages (CML-AP and CML-BC) is an important goal of therapy. First-line TKI therapy significantly reduces the frequency of disease progression relative to previous standard treatment modalities. In the IRIS study, patients treated with imatinib had a significantly higher rate of freedom from progression at 12 months than patients treated with interferon alfa plus cytarabine (98.5% vs 93.1%; $P<.001$).[19] In the ENESTnd study, the time to progression to CML-AP/BC was significantly longer with nilotinib (either dose) than with imatinib at 1 year,[12] and the rate of freedom from progression was significantly higher at 2 years[13] and at 3 years.[14] In both the DASISION[15,17] and BELA[18] studies, the number of patients who progressed to CML-AP/BC while on treatment was lower with dasatinib and bosutinib than with imatinib. Given the relatively poor prognosis of patients with advanced CML—especially CML-BC[37,38]—and the dearth of effective treatment options for patients with CML-BC, delaying disease progression may ultimately improve EFS and OS; however, longer-term follow-up of clinical studies involving TKIs is needed.

First-Line TKI Treatment Choice

At present, there are 3 BCR-ABL1 TKIs approved for the treatment of patients with newly diagnosed Ph+ CML-CP: imatinib, nilotinib, and dasatinib. (Bosutinib and ponatinib were approved in 2012 for treatment after TKI failure.) The NCCN Guidelines characterize each first-line–approved TKI as a valid treatment option and do not recommend one over the others in the first-line setting. The only exception is for patients who are classified as intermediate- or high-risk by the Sokal and Hasford models. Then, the NCCN Guidelines suggest that nilotinib or dasatinib may be preferred over imatinib as initial therapy, based on observations that most patients in the imatinib arms of the ENESTnd and DASISION studies who progressed to CML-AP/BC had intermediate- or high-risk scores. In addition, the acknowledged importance of achieving rapid response to first-line therapy could highlight nilotinib or dasatinib as potentially more suitable options than imatinib. In the landmark analysis of the ENESTnd study,[36] 9% of evaluable patients on nilotinib 300 mg twice daily versus 33% of patients on imatinib had *BCR-ABL1* levels above 10% (<1-log reduction) at 3 months. In the DASISION study,[33] 16% of evaluable patients on dasatinib versus 36% of patients on imatinib had *BCR-ABL1* levels above 10% (<1-log reduction) at 3 months (Table 2). These observations indicate that considerably fewer patients treated with nilotinib or dasatinib versus imatinib experienced responses considered unsatisfactory by the updated NCCN criteria for the 3-month point. Thus far, there have been no significant differences in EFS or OS with nilotinib and imatinib in the ENESTnd study,[14] or in PFS or OS with dasatinib and imatinib in the DASISION[17] study.

Management of Patients With BCR-ABL1 *Levels Above 10% (<1-Log Reduction) at 3 Months*

For patients with *BCR-ABL1* levels above 10% (<1-log reduction) at 3 months, the current NCCN Guidelines recommend first evaluating for adherence to therapy and drug-drug interactions and conducting *BCR-ABL1* mutational analysis before considering a switch in TKI treatment, evaluating for hematopoietic stem cell transplant, or enrolling in a clinical study.[4] There are currently no published studies evaluating the effect of second-line TKIs in patients who do not achieve *BCR-ABL1* levels of 10% or less (≥1-log reduction) at 3 months with first-line imatinib. None of the studies shown in Table 2 had included in their protocols any provision to switch therapy during the first year of treatment upon failure to achieve specific molecular targets. Instead, the patients in these studies switched treatment based on study parameters that typically included failure to achieve hematologic or cytogenetic response, or relapse after achievement of response. These studies thus reflect the outcomes of patients who had a delayed (rather than early) switch in treatment following inadequate response to first-line TKI therapy. It remains to be determined whether switching therapy early, at the time of the 3-month evaluation, would result in better outcome. Instead, there are clinical studies of second-line nilotinib, dasatinib, and bosutinib that might provide clues to the likely outcomes of patients who require second-line TKI therapy. First, clinical studies in patients with resistance to or intolerance of first-line imatinib show that roughly half of patients achieve cytogenetic and molecular response with second-line TKIs, and high rates of long-term PFS and OS are achievable.[39-53] In general, these studies suggest that the second-line TKI therapy elicited higher response rates in patients with intolerance to imatinib than with resistance to imatinib, which implies that an earlier switch in TKI therapy may lead to improved outcomes.

Second, there are a small number of clinical studies that have compared outcomes of patients who were switched sooner versus later to second-line therapy. In a retrospective pooled analysis comparing outcomes of patients who were switched to second-line dasatinib after the loss of cytogenetic response versus after the loss of both cytogenetic and hematologic response to first-line imatinib, the group that was switched sooner had higher cumulative rates of CHR, CCyR, and MMR, as well as higher rates of 24-month EFS, transformation-free survival, and OS compared to the group that was switched later.[50] In the TIDEL-II (Therapeutic Intensification in De Novo) study,[54] patients with newly diagnosed CML-CP on first-line imatinib who failed to meet specific treatment response milestones were either switched to nilotinib directly or given high-dose imatinib for 3 months before switching to nilotinib. Patients switched to nilotinib directly had a higher rate of MR$^{4.5}$ at 12 months, but not at 24 months, than patients who were switched later. In aggregate, these observations suggest favorable odds that patients with unsatisfactory response to first-line imatinib who are switched to second-line nilotinib or dasatinib will have good long-term prognosis.

At this time, whether patients who receive first-line nilotinib or dasatinib have long-term clinical outcomes as favorable as patients who receive second-line TKI therapy after first-line imatinib failure is not known, although the findings of the ENESTnd extension study might provide some insight. In that study, patients with resistance (not intolerance) to first-line nilotinib 300 mg twice daily or imatinib 400 mg (once or twice daily) were eligible to receive nilotinib 400 mg twice daily.[45] It is important to note that resistance was defined by the European LeukemiaNet (ELN) criteria for suboptimal response or treatment failure at 6, 12, and 18 months,[55] not by the NCCN criterion of *BCR-ABL1* levels above 10% (<1-log reduction) at 3 months. By the ELN criteria, 18 patients (6.4%) on nilotinib 300 mg twice daily and 31 patients (11.0%) on imatinib had suboptimal response or treatment failure. Of the 31 imatinib-resistant patients, 7 patients achieved MMR on nilotinib 400 mg twice daily in the extension study. Thus, there remained 24 patients (8.5% of patients in the imatinib arm of the ENESTnd study) without molecular response following 2 lines of therapy, a proportion similar to the proportion of patients with resistance to first-line nilotinib (6.4%). This suggests that patients who received a first-line, second-generation TKI may have outcomes at least as favorable as patients who received a second-line, second-generation TKI after failure of first-line imatinib. These findings are provocative, although follow-up of the ENESTnd extension study is ongoing and final results are not yet available. A new clinical study to be conducted in the United Kingdom, in which newly diagnosed patients will start on first-line imatinib and switch to a different TKI treatment if their *BCR-ABL1* levels are greater than 10% (IS) at 3 months, should address this clinical question.

Applying the updated 3-month treatment response milestone in the NCCN Guidelines, would patients with unsatisfactory response to first-line imatinib have fared better (or at least as well) if nilotinib or dasatinib had been given in the first-line setting? Table 2 summarizes the available 3-month molecular response data for more than 1,600 imatinib-treated patients and more than 900 patients treated with a newer TKI. Based on these data, the number of patients treated with first-line imatinib who failed to meet the 3-month response target was approximately 31%, and the number treated with a first-line, second-generation TKI (considered as a single group) was approximately 13% (Figure 1). For patients

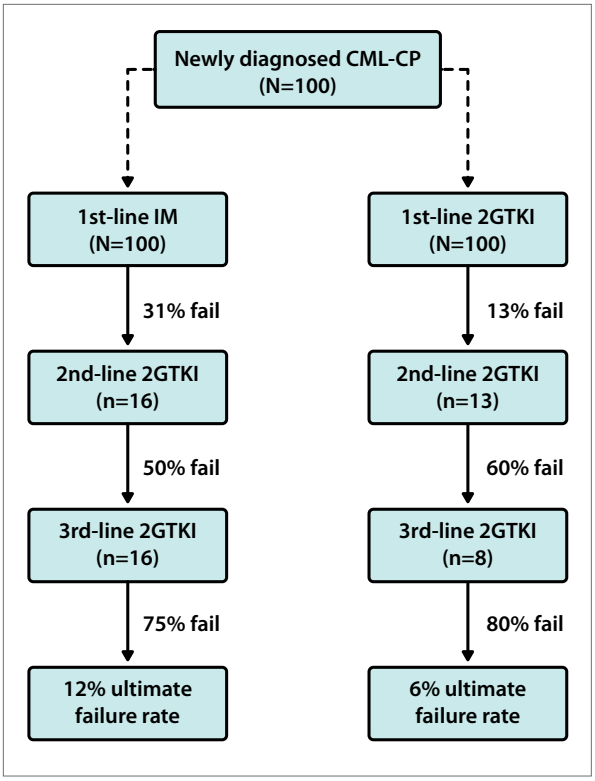

Figure 1. Ultimate failure rates after successive lines of tyrosine kinase inhibitor (TKI) therapy for a hypothetical set of 100 patients with chronic myeloid leukemia in the chronic phase (CML-CP) who received imatinib (IM [left]) or a second-generation TKI (2GTKI [right]) in the first-line setting.

with inadequate imatinib response who are switched to second-line TKI therapy to achieve the same degree of response as patients who received a second-generation TKI in the first-line setting, 58% of patients switched would need to respond to second-line therapy. Data show, however, that for patients who switch from imatinib to a newer TKI because of imatinib resistance, only approximately 50% achieve CCyR. There are very few data on the response to second-line therapy in patients who are switched at 3 months for *BCR-ABL1* levels above 10% (IS; <1-log reduction). The TIDEL-II study did include a group of patients who switched from imatinib to nilotinib at 3 months for *BCR-ABL1* levels greater than 10% (IS; <1-log reduction), and only 27% of patients achieved MMR at 12 months after the switch.[56] Based on these preliminary calculations, patients who are switched to second-line TKI therapy are unlikely to achieve the same degree of overall response as patients who are treated with a newer TKI as first-line therapy.

The gap in overall response rates achievable in patients who start on imatinib and switch to nilotinib/dasatinib versus patients who start on nilotinib/dasatinib may be even greater, because patients who do not achieve early molecular response to first-line nilotinib or dasatinib could also switch to another TKI at 3 months. Therefore, the proportion of patients who fail both first-line nilotinib or dasatinib and second-line TKI therapy is likely to be less than 13%. At present, there are very few second-line clinical data available on patients with resistance to or intolerance of first-line nilotinib, dasatinib, or bosutinib. In a small series of patients treated at MD Anderson Cancer Center in Houston, Texas,[57] 23 of 172 patients on first-line nilotinib or dasatinib discontinued treatment, 12 of 23 patients subsequently received a second-line TKI, and 5 of 12 patients (42%) achieved MMR on second-line imatinib, nilotinib, or dasatinib. An estimate of the ultimate failure rate in patients treated with imatinib or a second-generation TKI in the first-line setting is shown in Figure 1. Starting with a second-generation TKI would be associated with fewer ultimate TKI treatment failures compared to starting with imatinib, assuming that: 1) 31% of patients fail first-line imatinib and 13% of patients fail first-line second-generation TKI; 2) 50% of patients with first-line imatinib failure and 60% of patients with first-line second-generation TKI failure will also fail second-line therapy; and 3) in the third-line setting, the rate of response is about half the rate of response in the second-line setting (ie, 25% of patients who started on imatinib and 20% of patients who started on a second-generation TKI would respond to TKI therapy in the third-line setting). For patients starting with imatinib to reach the same degree of ultimate response to TKI therapy as patients starting with a second-generation TKI, the failure rate of first-line imatinib would need to decrease to 16%, the failure rate of second-line TKI therapy would need to decrease to 26%, or the failure rate of third-line therapy would need to decrease to 38% (Figure 2). As this is highly unlikely, the provocative conclusion is that starting with second-generation TKIs as first-line treatment would result in greater long-term success. In other words, the strategy of starting with first-line imatinib and then switching to a second-generation TKI is unlikely to be superior to starting all patients on a second-generation TKI.

Patient Evaluations Between 3 and 12 Months

For patients with satisfactory response to first-line TKI therapy at 3 months, the NCCN Guidelines recommend quarterly molecular monitoring but no other specific treatment response evaluation until 12 months. For patients with an unsatisfactory response at 3 months who are subsequently switched to alternative TKI therapy, treatment evaluation before the 12-month mark is advisable. Although not addressed in the NCCN Guidelines, the ELN guidelines include provisional criteria for suboptimal response to and failure of second-line nilotinib and dasatinib.[55] These

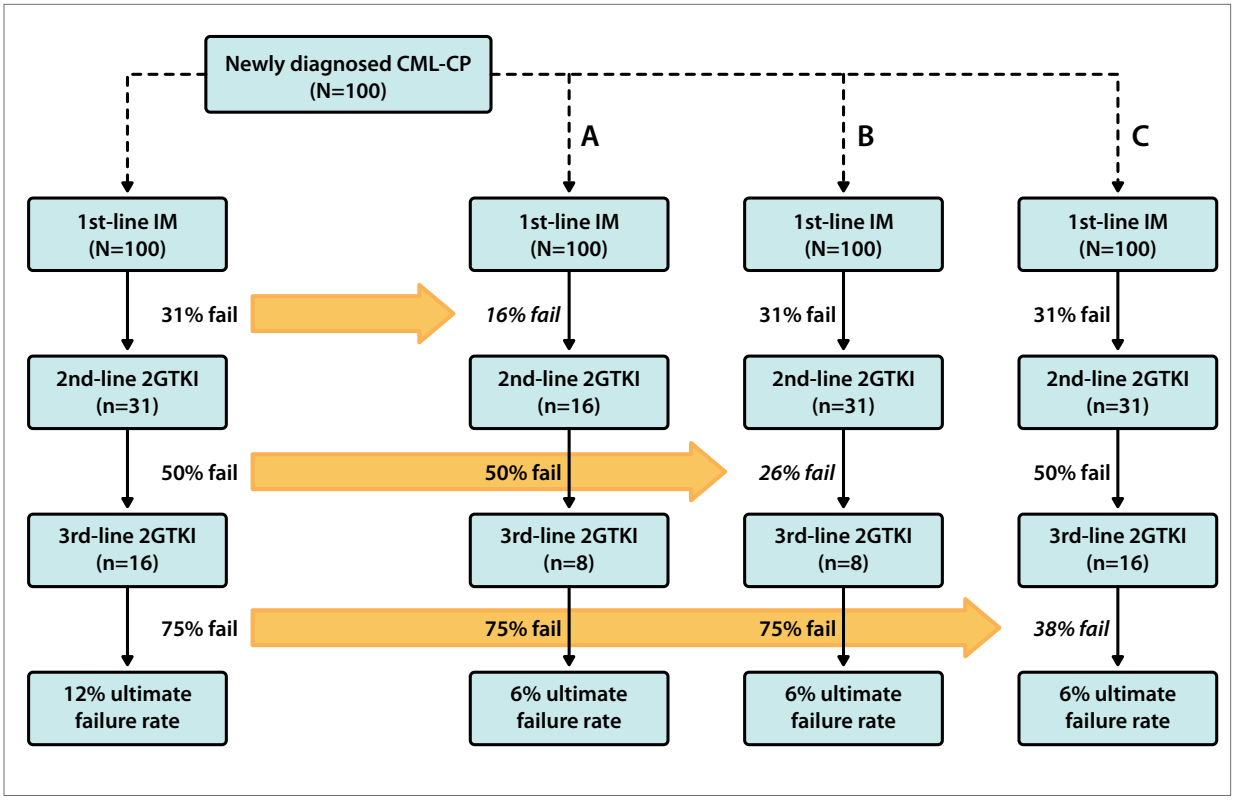

Figure 2. Theoretical improvements to failure rates of first-line (A), second-line (B), and third-line (C) tyrosine kinase inhibitor (TKI) therapy needed for patients treated with first-line imatinib (IM) in order to have an ultimate failure rate equivalent to that of patients treated with first-line, second-generation TKI (2GTKI) therapy (6%) for chronic myeloid leukemia in the chronic phase (CML-CP).

criteria were based on a study that found the *BCR-ABL1* level at 3 months after the start of second-line nilotinib or dasatinib to be significantly correlated with rates of MMR and MCyR at 24 months.[58] Thus, it is advisable that response to second-line treatment be evaluated at the 6-month mark, or 3 months after the start of second-line therapy following an early switch, because that would allow timely intervention if there is no response to 2 successive lines of TKI therapy (which we approximated could occur in approximately 15% of imatinib-treated patients).

Regular Molecular Monitoring of BCR-ABL1

The overarching message is the importance of regular molecular monitoring of disease burden every 3 months, and more frequently when there are signs that suggest relapse or disease progression.[59] An increase in *BCR-ABL1* transcript level of as little as 0.5 log (~3.2-fold) has been shown to significantly predict the occurrence of relapse (defined as loss of CHR, loss of CCyR, or progression to CML-AP/BC) in patients who achieved CCyR on imatinib.[60] In another study, a 1-log increase in *BCR-ABL1* level, particularly in patients who had achieved CCyR but not MMR, and in patients who had lost MMR at the time of *BCR-ABL1* increase, significantly predicts disease progression (defined as loss of CHR, loss of CCyR, transformation to CML-AP/BC, or death).[61] The NCCN Guidelines recommend that patients with MMR who experience a 1-log increase in *BCR-ABL1* level undergo repeat QPCR testing within 1–3 months, and patients who experience a 1-log increase with concomitant loss of MMR should have *BCR-ABL1* kinase domain mutational analysis performed.[4]

Despite the importance of regular molecular monitoring as a means to monitor response, and to detect minimal residual disease and potential signs of eventual disease progression, evidence shows that patients with CML are routinely monitored less frequently than recommended.[62-64] The recent updates to the NCCN Guidelines and concerted efforts to adopt the IS in QPCR testing are expected to increase awareness of the importance of regular molecular monitoring by QPCR.

Commercial Reference Laboratory Choice

At present, the majority of commercial laboratories do not use IS-standardized QPCR assays.[65] When laboratories use either their own standard baselines or no baselines, clinicians may be challenged to make sense of inconsistent, potentially confusing test results, or to compare test results reported

across laboratories. In addition, there are currently no minimum requirements for QPCR test reporting, so reports from one laboratory may differ from those of another laboratory.

The use of IS standardization in QPCR testing, as recommended in the current NCCN Guidelines, may alleviate potential problems that could complicate patient care. For example, universally interpretable data might facilitate the use of a uniform set of treatment decision criteria,[7] such as those outlined in the NCCN Guidelines, which in turn could standardize the treatment of CML across practices. Furthermore, the transfer of patients from one practice to another would be less problematic[7] because IS-standardized molecular monitoring could continue more seamlessly, even if a different testing laboratory is used. Most importantly, IS standardization allows for easier interpretation of QPCR data for individual patients (ie, reduces variability in serial monitoring in individual patients) and across patients within a practice, as well as aggregate data across clinical studies.[7]

Summary and Conclusions

The most recent set of updates to the NCCN Guidelines in CML (v1.2013, v2.2013, v3.2013, and v4.2013) includes some sweeping changes that affect routine clinical practice, particularly goals of therapy, molecular monitoring of *BCR-ABL1* level, and management of patients with unsatisfactory response to first-line TKI. Updated clinical practice guidelines issued by the ELN, which were last updated in 2009,[55] are also expected in the coming months. It is important for clinicians to be aware of both sets of guidelines, as they form the basis of response criteria used in modern CML clinical study designs, and of the recent and forthcoming updates, because they represent evidence-based best practices and reflect broader shifts in the management of CML.

The durable, deep molecular responses now possible with TKI therapy allow for the management of CML as a chronic disease, in which patients are stably maintained in CP for extended periods of time with TKI therapy. Whether patients who stably maintain undetectable *BCR-ABL1* levels on TKI therapy can safely stop treatment is the subject of current clinical research in CML. Evidence suggests that achievement and maintenance of MR^4 (IS) or better for at least 2 years may be an important criterion for safely stopping TKI therapy.[66-68] The current NCCN Guidelines with specifications for the use of QPCR assays should ease the identification of patients who meet this inclusion criterion. With a larger pool of patients potentially eligible for clinical studies of safe cessation of TKI therapy, the CML community may one day realize its ultimate goal of having as many patients as possible living in treatment-free remission.

Acknowledgments

Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. The authors would like to thank Anna Lau, PhD, and Claudette Knight, PharmD, of Percolation Communications LLC for medical editorial assistance.

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