Monitoring, Treatment Resistance, and Treatment Failure in CML: Breaking Barriers to Improved Outcomes

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Abstract

Despite the dramatic success seen with tyrosine kinase inhibitors (TKIs) in most patients with chronic myeloid leukemia (CML), some patients still develop resistance or intolerance and need alternative therapies. Monitoring response to TKI therapy via hematologic, cytogenetic, and molecular analysis is a critical component of managing CML. Thus, uniform response definitions, response criteria, and monitoring recommendations have been developed to aid in early recognition of resistance to TKI therapy, allowing timely changes in management strategy. However, differences exist between these recommendations, and questions regarding how best to assess response, including how to define treatment failure and how monitoring should be conducted, remain. Several new drugs in late-stage development may help overcome resistance and provide additional options for patients with CML. As members of a coordinated multidisciplinary care team, advanced practitioners play a key role in the management of CML. Key to this process are incorporation of strategies to improve outcome by addressing nonadherence, managing side effects, and addressing other factors that can contribute to resistance. Along with improved survival with TKI therapy, family planning has become an important aspect of patient management. By providing education and support, advanced practitioners can assist patients and their partners in navigating this challenging situation.

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Chronic myeloid leukemia (CML) is a rare hematologic cancer characterized by the presence of the Philadelphia (Ph) chromosome, the result of a reciprocal translocation between chromosomes 9 and 22. The National Cancer Institute estimates that more than 5,400 new cases of CML will be diagnosed in the United States in 2012 (Howlader et al., 2012). The CML landscape dramatically changed following the approval of the tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec) by the US Food and Drug Administration in 2001. We now have

long-term data on its efficacy and safety, with an overall survival (OS) rate of 85% reported with 8 years of treatment (Deininger et al., 2009). With this improved survival, CML can now in most cases be managed more like a chronic disease. As members of a coordinated multidisciplinary care team, advanced practitioners play a key role in this process (Holloway et al., 2012).

Not all patients respond optimally to imatinib therapy, and some of those who initially do respond eventually develop resistance. The introduction of the second-generation TKIs dasatinib (Sprycel) and nilotinib (Tasigna) in 2006 and 2007, respectively, has provided additional treatment options for these patients, but resistance is often seen while using these agents as well, most frequently in patients who did not respond well to imatinib. Indeed, in an important minority of cases, TKI resistance remains a barrier to successful CML treatment. Uniform response definitions, response criteria, and monitoring recommendations have been developed to aid early recognition of resistance to TKI therapy, allowing timely change in management strategy (NCCN, 2012; Baccarani et al., 2009). This article provides advanced practitioners with a review of recommendations for patient monitoring and addressing suboptimal response and treatment failure. It also provides practical strategies for improving outcome by addressing nonadherence and other factors that can contribute to resistance.

MONITORING RESPONSE TO TKI THERAPY

Disease monitoring to assess response to TKI therapy and to detect treatment failure early is a critical component of CML patient management (National Comprehensive Cancer Network [NCCN], 2012). Monitoring also plays an important role in recognizing poor treatment adherence. Specific advice for monitoring response to therapy is included in both NCCN Clinical Practice Guidelines and European LeukemiaNet (ELN) CML treatment recommendations (NCCN, 2012; Baccarani et al., 2009). These recommendations include response definitions, suggested monitoring intervals, and key response milestones. Although these defined parameters are similar in both recommendations, some differences are noted.

Response to TKI therapy is assessed via three methods used in sequence: first hematologic, then cytogenetic, and eventually molecular, with each method being able to detect a progressively deeper response or reduction in leukemic cell burden. The advanced practitioner plays a key role in helping patients understand the differing sensitivities of these three methods.

Hematologic response is determined by peripheral blood and platelet counts, whereas cytogenetic response is determined by measuring the percentage of Ph chromosome–positive metaphases in bone marrow aspirates. Conventional karyotyping of bone marrow cells is still the preferred technique for monitoring cytogenetic response in patients with CML, and efficacy analyses in clinical trials are most often based on cytogenetic responses (NCCN, 2012; Baccarani et al., 2009). However, once a complete cytogenetic response (CCyR) is achieved, fluorescence in situ hybridization (FISH) can be used to confirm that the patient is still in a CCyR (Baccarani et al., 2009). FISH can also detect the Ph chromosome in peripheral blood specimens, so it allows for more convenient monitoring. However, FISH is limited in that it detects only the Ph chromosome, so conventional cytogenetics remains important in cytogenetic monitoring and is an important tool for detecting the presence of additional chromosomal abnormalities indicating clonal evolution (Baccarani et al., 2009). Molecular responses are assessed by measuring the level of *BCR-ABL* transcripts in the peripheral blood or bone marrow using real-time quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR). Serial monitoring of the blood is recommended (NCCN, 2012).

Definitions for defined levels of hematologic, cytogenetic, and molecular responses are provided in Table 1 (Baccarani et al., 2009; NCCN, 2012), and recommended monitoring intervals are summarized in Table 2. European LeukemiaNet recommendations state that patients with suboptimal response or warning features may require more frequent monitoring than outlined here (Baccarani et al., 2009).

Molecular Monitoring

Because TKI therapy reduces the leukemic cell burden below the level detected by conventional cytogenetics, molecular monitoring is the most appropriate method for detecting minimal residual disease (MRD). Because increasing *BCR-ABL*

Table 1. Response Definitions

Response	Definition	
	ELN[a]	NCCN[b]
Hematologic		
Complete (CHR)	Leukocyte count < 10 × 10^9/L Platelet count < 450 × 10^9/L No immature granulocytes Nonpalpable spleen Basophils < 5%	Leukocyte count < 10 × 10^9/L Platelet count < 450 × 10^9/L No immature granulocytes Nonpalpable spleen Complete normalization of peripheral blood counts No signs and symptoms of disease
Cytogenetic		
Complete (CCyR)	No Ph+ metaphases	No Ph+ metaphases
Partial (PCyR)	1%–35% Ph+ metaphases	1%–35% Ph+ metaphases
Major	NA	0%–35% Ph+ metaphases
Minor	36%–65% Ph+ metaphases	> 35% Ph+ metaphases
Minimal	66%–95% Ph+ metaphases	NA
None	> 95% Ph+ metaphases	NA
Molecular		
Complete (CMR)	Undetectable *BCR-ABL* by qRT-PCR in two consecutive samples	Undetectable *BCR-ABL* by qRT-PCR (IS) using an assay with a sensitivity ≥ 4.5 logs below the standardized baseline
Major (MMR)	Ratio of *BCR-ABL* to *ABL* ≤ 0.1% on the International Scale (≥ 3-log reduction)	Ratio of *BCR-ABL* to *ABL* ≤ 0.1% on the International Scale (≥ 3-log reduction)

Note. ELN = European LeukemiaNet; NCCN = National Comprehensive Cancer Network; NA = not applicable; qRT-PCR = real-time quantitative reverse-transcriptase polymerase chain reaction; IS = International Scale.
[a]Information from Baccarani et al. (2009).
[b]Information from NCCN (2012).

transcript levels identify patients most likely to relapse (Marin et al., 2009), many centers rely more heavily on molecular monitoring, rather than cytogenetic monitoring, for their CML patients once their patients have achieved a CCyR. However, it is important that cytogenetic studies be performed if a major molecular response (MMR) is lost or if cytopenia develops.

The NCCN recommends that a baseline *BCR-ABL* transcript level be measured in the bone marrow at diagnosis (NCCN, 2012). Afterward, *BCR-ABL* transcript levels in the peripheral blood are typically monitored, particularly after CCyR is achieved and bone marrow aspirates are done less frequently (Baccarani et al., 2009).

Unfortunately, there are wide variations in methods used to quantify *BCR-ABL* transcripts and how qRT-PCR results are reported (Hughes et al., 2006; Müller et al., 2009). Due to these variations, PCR should always be performed by the same laboratory, if possible, so that results can be accurately interpreted. In light of the clinical importance of assessing MRD, there is an ongoing international effort to standardize qRT-PCR results via the use of the International Scale (IS; Hughes et al., 2006; Müller et al., 2009). Such a scale provides a means of standard reporting across laboratories to optimize clinical management and allow comparison of measurements from clinical studies. To develop the IS, a standardized baseline value was first defined based on the *BCR-ABL*:*BCR* ratios in samples from patients in the IRIS (International Randomized Study of Interferon versus STI571) study and set at 100% (Müller et al., 2009). Then, MMR was defined as at least a 3-log reduction from that baseline (0.1%). This definition of MMR is found in both ELN and NCCN recommendations (Baccarani et al., 2009; NCCN, 2012). Laboratories can adopt the IS by establishing a laboratory-specific conversion factor, which is then multiplied by the local result to obtain an IS value (Müller et al., 2009). Obtaining a conversion factor involves a process of exchanging samples with a reference laboratory over a period of time. However, few laboratories in the United States have adopted

Table 2. Recommended Intervals for Monitoring Response to TKI Therapy in Chronic-Phase CML

Response	Recommended monitoring interval	
	ELN[a]	NCCN[b]
Hematologic	• At diagnosis • Every 15 days until CHR has been achieved • Then every 3 mo or as required	• At diagnosis
Cytogenetic	• At diagnosis • 3 mo • 6 mo • Then every 6 mo until CCyR achieved • Then every 12 mo if regular molecular monitoring cannot be assured • If treatment failure • For unexplained anemia, leukopenia, or thrombocytopenia	• At diagnosis • 3 mo if qRT-PCR (IS) not available • 12 mo if CCyR or MMR is not achieved • 18 mo if not in MMR and CCyR not achieved at 12 mo • If 1-log increase in *BCR-ABL* without an MMR
Molecular[c]	• Every 3 mo until MMR achieved • Then every 6 mo	• At diagnosis to establish baseline • Every 3 mo • When CCyR is reached, every 3 mo for 3 yr, then every 3–6 mo thereafter • If 1-log increase in *BCR-ABL* with a MMR, repeat in 1–3 mo
Mutational analysis	• If suboptimal response or failure • Before changing to other TKIs or other therapies	• If failure to achieve PCyR or *BCR-ABL/ABL* ≤ 10% (IS) at 3 mo, or CCyR at 12 mo and 18 mo • Any sign of loss of response (hematologic or cytogenetic relapse, or 1-log increase in *BCR-ABL* and loss of MMR) • Progression to accelerated phase or blast phase

Note. TKI = tyrosine kinase inhibitor; CML = chronic myeloid leukemia; ELN = European LeukemiaNet; NCCN = National Comprehensive Cancer Network; CHR = complete hematologic response; qRT-PCR = real-time quantitative reverse-transcriptase polymerase chain reaction; CCyR = complete cytogenetic response; IS = International Scale; MMR = major molecular response; PCyR = partial cytogenetic response.
[a]Information from Baccarani et al. (2009).
[b]Information from NCCN (2012).
[c]The NCCN specifies use of International Scale for molecular monitoring.

the IS to date, and they typically use their own laboratory-specific standard. The advanced practitioner plays an important role in helping patients understand reasons for potential variations in their results that might occur as a result of differing molecular assay methods or reporting.

RESPONSE MILESTONES

Response milestones at predetermined time points have been defined by both the NCCN and the ELN to assess a patient's response to frontline treatment and assist in determining when a change in therapy may be needed; see Table 3 (NCCN 2012, Baccarani et al., 2009). These response milestones were based largely on landmark studies of response outcomes according to the molecular response at certain time points observed in IRIS and other studies, as well as clinical experience (Baccarani et al., 2009).

The ELN specifically defines milestones for optimal response, suboptimal response, and failure, and includes warnings as an additional category (Baccarani et al., 2009). Achievement of an optimal response means that there is no indication that a change of therapy may improve on a survival that is currently projected to be close to 100% after 6 to 7 years (Baccarani et al., 2009). Suboptimal response means that the patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced, such that they may be eligible for an alternative approach. Failure indicates that a favorable outcome is unlikely and that the patient should receive an alternate treatment whenever available/applicable. A warning is a

Table 3. Response Criteria in Patients With Chronic-Phase Ph+ CML as Defined by the ELN[a] and the NCCN[b]

Time	Optimal response	Suboptimal response	Failure	Warnings
3 mo	CHR and at least minor CyR	No CyR	Less than CHR	NL
	BCR-ABL ≤ 10% by qRT-PCR (IS) *or* PCyR[c]	NL	*BCR-ABL* > 10% by qRT-PCR (IS) *or* < PCyR[c]	
6 mo	At least PCyR	Less than PCyR	No CyR	NL
	NL	NL	NL	
12 mo	CCyR	PCyR	Less than PCyR	Less than MMR
				NL
18 mo	MMR	Less than MMR	Less than CCyR	NL
	CCyR	NL		
Any time during treatment[d]	Stable or improving MMR	Loss of MMR BCR-ABL KD mutations (still sensitive to imatinib)	Loss of CHR Loss of CCyR BCR-ABL KD mutations (poorly sensitive to imatinib) CCA/Ph+[e]	Increase in transcript levels CCA/Ph-

Note. CML = chronic myeloid leukemia; ELN = European LeukemiaNet; NCCN = National Comprehensive Cancer Network; CHR = complete hematologic response; CyR = cytogenetic response; NL = not listed; qRT-PCR = real-time quantitative reverse-transcriptive polymerase chain reaction; IS = International Scale; PCyR = partial cytogenetic response; CCyR = complete cytogenetic response; MMR = major molecular response; KD = kinase domain; CCA = clonal chromosome abnormalities. ELN criteria refer to previously untreated patients with early chronic-phase CML who are treated with imatinib 400 mg daily. NCCN criteria refer to previously untreated patients with chronic-phase Ph+ or *BCR-ABL*+ CML who are treated with imatinib 400 mg daily, nilotinib 300 mg twice daily, or dasatinib 100 mg daily.
[a]Information from Baccarani et al. (2009).
[b]Information from NCCN (2012). NCCN treatment response criteria that differ from ELN criteria are noted in shaded cells.
[c]As assessed on bone marrow cytogenetics.
[d]Refers only to ELN recommendations.
[e]Occurrence of CCA/Ph+ during treatment (i.e., clonal progression) is a marker of treatment failure. Confirmation requires two consecutive cytogenetic tests, and the same CCA must be demonstrated in at least two Ph+ cells.

coexisting prognostic factor that may modulate each of these responses. The presence of such a warning may affect the response to therapy, and thus necessitate more careful monitoring (Baccarani et al., 2009).

The NCCN defines target responses at specific time points, and failure to achieve these target responses can be considered treatment failure, as shown in Table 3 (NCCN, 2012). The NCCN recently updated its treatment algorithm (with an updated discussion to follow), showing a divergence in response criteria definitions between the two professional organizations at the earlier time points. However, revised recommendations from the ELN are expected shortly, so comparisons may not be valid at this time.

Familiarity with recommendations for assessing treatment responses and response milestones will enable advanced practitioners to facilitate patients' understanding of their test results and help convey to their patients throughout their CML journey the importance of monitoring in achieving optimal outcome. By doing these things, advanced practitioners will help patients become active participants in the management of their CML.

Clinical Implications of Suboptimal Response

The long-term prognostic significance of suboptimal response to imatinib therapy as defined using ELN criteria has been determined in a number of studies. For example, compared with patients who achieved an optimal response, patients with a suboptimal response at 6 and 12 months (ELN criteria) have been shown to have a lower probability of achieving a CCyR and lower survival rates (Marin et al., 2008). Likewise, Alvarado et al. (2009) demonstrated that patients

with suboptimal responses at these early time points also had significantly worse survival than those achieving an optimal response. Thus, utilizing response evaluation criteria early to identify patients experiencing suboptimal response or resistance to imatinib may lead to improved outcomes (Bixby & Talpaz, 2011).

However, the definition of suboptimal response remains controversial. In both of the studies just discussed, similar poor outcomes were seen in patients characterized as failures and suboptimal responders at 6 and 12 months (ELN criteria; Marin et al., 2008; Alvarado et al., 2009). Marin et al. (2008) went so far as to propose combining some of the criteria in both categories. Others have proposed that the suboptimal response category be dropped completely. Response definitions continue to evolve, and at present, there is only one instance in the NCCN Guidelines (i.e., a partial cytogenetic response [PCyR] at the 12-month evaluation) for which a response is included that is neither optimal nor a failure (NCCN, 2012). As such, revised recommendations from the ELN are eagerly anticipated.

THE IMPORTANCE OF MOLECULAR RESPONSE

Long-term data from IRIS show that achievement of MMR is an important milestone for predicting long-term outcome. In this study, patients with CCyR who attained MMR (*BCR-ABL* transcripts ≤ 0.1% using the IS) by 18 months were much less likely to lose their CCyR than patients not achieving this milestone (Hughes et al., 2010). In addition, patients attaining MMR by 18 months had no progression to advanced disease (accelerated phase or blast crisis) and a 95% event-free survival (EFS) at 7 years. Conversely, patients with *BCR-ABL* transcript levels > 10% at 6 months and > 1% at 12 months had inferior EFS and a higher rate of progression to advanced disease than patients with lower transcript levels (Hughes et al., 2010).

More recently, the predictive value of early molecular response in patients receiving TKIs has been confirmed by multiple groups worldwide, thus shifting the focus toward earlier testing (Marin et al., 2012a; Marin et al., 2012b; Shah et al., 2012; Branford et al., 2010). For example, Marin et al. (2012b) reported that *BCR-ABL* transcript measurements performed at 3, 6, or 12 months could identify patients with inferior outcomes to imatinib, and of these, the 3-month assessment was the most strongly predictive and may be the only one required. Patients who had *BCR-ABL* transcript levels > 9.84% (IS) at 3 months had worse long-term outcome with regard to survival and achievement of CCyR and complete molecular response (CMR) than those with lower transcript levels. Similarly, transcript levels > 1.67% at 6 months and > 0.53% at 12 months also identified high-risk patients (Marin et al., 2012b). Because these transcript cutoff values were based on observed outcomes, some may prefer them over the standard log reductions from baseline as definitions for molecular responses (Marin et al., 2012b).

Similarly, the predictive value of early molecular response was also demonstrated in patients treated with first-line dasatinib (Marin et al., 2012a). Patients with transcripts > 10% at 3 months were significantly less likely to obtain CCyR and MMR than patients with lower transcript levels. In addition, the predictive value of the 3-month transcript level could be improved using a set of cutoff values for each specific outcome (CCyR and CMR) that are specific to dasatinib. These values are lower than those for imatinib, highlighting the different response kinetics between the two TKIs.

Taken together, the results of these studies support the use of earlier molecular testing to assess response to TKIs in patients with CML. As a result, the 3-month ≤ 10% *BCR-ABL* (IS) response cutoff was recently incorporated into the NCCN treatment algorithm, replacing the achievement of complete hematologic response (CHR) as a criterion for optimal response (NCCN, 2012). However, cytogenetic analysis remains an important component of patient monitoring, because the achievement of an early CCyR remains a major determinant of outcome in CML regardless of whether MMR is achieved (Jabbour et al., 2011b).

There currently are no trial data available to assess whether early treatment modification for early failure improves outcomes. However, achieving an early molecular response of *BCR-ABL* transcript level ≤ 10% (IS) at 1 and 3 months was associated with improved outcomes in imatinib-resistant or -intolerant patients who were switched to dasatinib (Shah et al., 2012). Similar findings were seen in patients receiving nilotinib following imatinib

failure who achieved an early molecular response (≤ 10% IS) at 1 month (Branford et al., 2010).

MECHANISMS OF RESISTANCE

It is estimated that approximately 20% to 30% of patients will eventually develop resistance to imatinib (Quintas-Cardama, Kantarjian, & Cortes, 2009). Patients who fail to achieve the preset milestones defined by the ELN and NCCN are described as having primary resistance to therapy, whereas patients who lose previously obtained responses are considered to have secondary resistance (Bixby & Talpaz, 2011).

Resistance to TKIs is thought to be multifactorial (Quintas-Cardama et al., 2009). Potential mechanisms of resistance may be categorized as being pharmacologic, leukemia cell–related, or patient-related, as shown in Table 4. Because continuous and adequate dosing of TKIs is essential to achieve optimal therapeutic effect, several of these mechanisms of resistance can be attributed to failure to deliver effective concentrations of the agent to inhibit the BCR-ABL kinase. This can occur via pharmacologic mechanisms as well as mechanisms related to influx and efflux of TKI at the cellular level (Quintas-Cardama et al., 2009). Leukemia cell–related mechanisms are major contributors to resistance. Resistance to imatinib may be related to the heterogeneity of the disease in different patients, as well as the presence of quiescent stem cells that are intrinsically resistant to imatinib therapy and thus prevent disease eradication (Quintas-Cardama et al., 2009). Amplification of *BCR-ABL* can lead to resistance because there are increased levels of the target protein needed to be inhibited by a therapeutic dose of imatinib. CML cells that overexpress *BCR-ABL* have been shown to be less sensitive to imatinib, to yield mutant subclones that are resistant to imatinib, and to acquire mutations at a faster rate than cells with low *BCR-ABL* expression (Barnes et al., 2005). Importantly, mutations in the kinase domain (KD) of BCR-ABL are a common cause of secondary resistance in CML; they may also be a cause of primary resistance in some cases, though they may simply be markers of increased genomic instability in others (Soverini et al., 2011). Lastly, nonadherence can both mimic and increase the risk of resistance.

Table 4. Potential Mechanisms of Resistance to TKIs

Type	Examples
Pharmacologic	Poor intestinal absorption Drug-drug interactions Binding with plasma components
Leukemia cell-related	Heterogeneity of CML cells Stem cell quiescence Amplification/increased expression of *BCR-ABL* Drug influx (i.e., reduced levels of drug transporters, e.g., OCT-1) Drug efflux (i.e., increased levels of drug exporters, e.g., MDR1) BCR-ABL kinase domain mutations Clonal evolution
Patient-related	Poor adherence

Note. TKI = tyrosine kinase inhibitor; CML = chronic myeloid leukemia.

Drug-Drug Interactions

Drug-drug interactions are a possible cause of treatment resistance because they may result in reduced plasma TKI levels (Quintas-Cardama et al., 2009). However, some drug-drug interactions can increase plasma levels of TKIs, as well as increase the risk of adverse events (NCCN, 2012). The NCCN states that potential drug interactions should be evaluated in all patients with an inadequate response to TKI therapy and in those who experience cytogenetic relapse at 12 or 18 months (NCCN, 2012).

BCR-ABL KD Mutations

More than 100 distinct point mutations responsible for single amino acid substitutions in the BCR-ABL KD have been detected in patients with CML that is resistant to imatinib therapy (Quintas-Cardama et al., 2009). These point mutations disrupt critical contact points between TKIs and BCR-ABL, thus reducing the TKI's ability to bind to and inhibit the protein. The T315I mutation is one of the most frequently reported KD mutations, being identified in about 15% of imatinib-resistant patients who harbor mutations (Cortes et al., 2007). T315I has been termed the "gatekeeper mutation" because the resultant conformational change confers resistance to imatinib, dasatinib, nilotinib, and bosutinib (Bosulif).

BCR-ABL KD mutations are more commonly identified in cases of secondary resistance,

but they have also been identified in primary resistance (Soverini et al., 2011). The reported frequency of BCR-ABL KD mutations in imatinib-resistant disease is somewhat variable. Soverini et al. (2011) estimated that about 29% of chronic-phase CML patients who fail imatinib harbor a BCR-ABL KD mutation, with these mutations also being found in about 16% of patients with suboptimal response. Hughes et al. (2009) reported that over 55% of imatinib-resistant patients had BCR-ABL KD mutations. Not surprisingly, the presence of KD mutations has been associated with poorer prognosis. (Soverini et al., 2005).

Mutational analysis is critical in guiding choice of subsequent treatment in cases of treatment failure or suboptimal response and is recommended in these instances by both the ELN and the NCCN (Table 2; Baccarani et al., 2009; NCCN, 2012). Mutational analysis is also recommended any time that a switch in therapy is warranted (ELN) and in cases in which response is lost or there is progressive disease (NCCN).

NONADHERENCE

Nonadherence has been associated with a number of undesirable clinical outcomes, including suboptimal response, loss of response, and treatment failure. In a study reported by Marin et al. (2010), adherence was identified as the critical factor for achievement of both major and complete molecular response in patients who had already achieved CCyR, thus confirming the importance of investigating noncompliance as a cause of suboptimal response. Poor adherence has also been identified as the main reason for loss of CCyR and imatinib failure in patients on long-term therapy (Ibrahim et al., 2011). Nonadherence to imatinib therapy also significantly increases inpatient resource utilization and overall costs (Wu et al., 2010). These include increased costs for both inpatient and outpatient care, as well as non-imatinib pharmacy costs, which are not offset by lower imatinib drug costs.

Nonadherence to TKI therapy is more prevalent than many patients, physicians, and family members believe it to be, with up to 40% of patients being reported as nonadherent to imatinib in some studies (Noens et al., 2009; Marin et al., 2010; St Charles et al., 2009). Patients who achieve optimal responses may be tempted to discontinue treatment because they are responding well, or they may become complacent. In addition, treatment side effects have been shown to be an important factor in imatinib adherence (Marin et al., 2010). Other factors that have been associated with imatinib nonadherence include older patient age, shorter time between CML diagnosis and prescription fill, longer duration on treatment, higher starting imatinib dose, good functional status/positive disease perception, and lower percentage of drug copayment (Noens et al., 2009; St Charles et al., 2009).

The NCCN states that nonadherence should be evaluated in all patients with an inadequate response to TKI therapy (NCCN, 2012). Advanced practitioners can investigate the myriad factors that can contribute to nonadherence as part of their ongoing assessment of patients. Of particular importance are assessing the potential impact of side effects and educating patients on the importance of adherence to achieve optimal outcome.

ADDRESSING SUBOPTIMAL RESPONSE AND TREATMENT FAILURE

Before suboptimal response or treatment failure can be addressed, one must first identify the cause of the lack of response. As noted earlier, clinicians must first evaluate the possible role of nonadherence in suboptimal response before considering a change in treatment. Next, mutational analysis should be performed, because it is critical in guiding the choice of subsequent treatment (NCCN, 2012). When a BCR-ABL KD mutation is identified, the treatment strategy should be tailored based on patient mutation data. Both the NCCN and ELN have made treatment recommendations for cases of specific KD mutations (Table 5; NCCN, 2012; Baccarani et al., 2009). Treatment should also be tailored to patient comorbidities and take into account the side-effect profiles of the TKIs being considered. Both the ELN and NCCN provide recommendations for suboptimal response and treatment failure to front-line and second-line therapy.

Suboptimal Response to Front-Line Therapy

The optimal treatment strategy for patients with suboptimal response has yet to be defined because there is no confirmatory evidence that a change in treatment will improve the response (Baccarani et al., 2009). For patients who have a suboptimal response to imatinib as front-line therapy, the ELN recommends a number of options,

Table 5. Treatment Recommendations Based on BCR-ABL KD Mutation Status[a]

Mutation	Treatment recommendation
T315I	Allo-HSCT or investigational agent
V229L, T315A, F317L/V/I/C	Consider nilotinib rather than dasatinib
Y253H, E255K/V, F359V/C/I	Consider dasatinib rather than nilotinib
Any other mutation	Consider high-dose imatinib or dasatinib or nilotinib[b]

Note. KD = kinase domain; Allo-HSCT = allogeneic hematopoietic stem cell transplantation.
[a]Information from Soverini et al. (2011) and NCCN (2012).
[b]Dose-escalation data are lacking to determine whether mutations with lower 50% inhibitory concentration values are sensitive to high-dose imatinib.

including continuing imatinib at the same dose, testing dose escalation of imatinib to 800 mg, or switching to dasatinib or nilotinib (Baccarani et al., 2009). The updated NCCN recommendations for patients achieving only a partial cytogenetic response to front-line TKI therapy at 12 months include changing to an alternate second-generation TKI (preferred), continuation of front-line dasatinib or nilotinib, or imatinib dose escalation, as tolerated, if not a candidate for dasatinib or nilotinib (NCCN, 2012).

Failure on Front-Line Therapy

Addressing failure on front-line imatinib is somewhat more straightforward than addressing suboptimal response. The ELN recommends that patients failing front-line imatinib be switched to a second-generation TKI (Baccarani et al., 2009). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recommended in patients who have progressed to accelerated phase or blast phase and in those who carry the T315I mutation. NCCN recommendations mirror those of the ELN, with the added guidance that patients not responding to first-line therapy with a second-generation TKI be switched to an alternate second-generation TKI, and that clinical trial participation be considered for patients who carry the T315I mutation (NCCN, 2012).

Suboptimal Response to Second-Line Therapy

Provisional definitions developed by the ELN for response to second-generation TKIs when used as second-line therapy in imatinib-resistant disease include definitions for suboptimal response (see Table 6; Baccarani et al., 2009). ELN treatment recommendations for patients having a suboptimal response to second-line dasatinib or nilotinib include continuation of the agents, with an option for allo-HSCT in patients with warning features and in those with a European Group for Blood and Marrow Transplantation (EBMT) risk score ≤ 2.

Failure on Second-Line Therapy

The provisional definitions developed by the ELN for response to second-generation TKIs when used as second-line therapy include definitions for failure (Table 6; Baccarani et al., 2009). In these patients, allo-HSCT is recommended as a third-line treatment option. NCCN recommendations concur but also include investigational therapies as an option for this patient population (NCCN, 2012).

The Role of Allo-HSCT

With the excellent long-term efficacy of TKIs, allo-HSCT is now second- or third-line therapy, and as such, plays a minor role in the treatment of CML. Its use is confined to patients who fail or relapse on therapy, patients who progress to accelerated phase or blast phase, and those with the T315I mutation (NCCN, 2012). However, allo-HSCT is a viable option for patients experiencing TKI failure and resistance. For example, a recent study of allo-HSCT following imatinib failure in patients with chronic-phase CML demonstrated a 3-year OS rate of 91% with transplantation (Saussele et al., 2010). In a study of patients with imatinib-resistant CML for whom mutation data were available, allo-HSCT resulted in 2-year OS rates of 44% and 76% in patients with and without BCR-ABL mutations, respectively (Jabbour et al., 2011a).

The following vignette illustrates how appropriate monitoring and mutational analysis was used to guide a patient through second-line therapy and beyond:

A 54-year-old woman with chronic-phase CML was started on imatinib 400 mg daily.

Monitoring at 3 months showed she had achieved a complete hematologic response (CHR), but at 6 months she had 55% Ph+ marrow metaphases, indicating a minor cytogenetic response, which was considered a suboptimal response to imatinib (< PCyR) according to NCCN and ELN criteria at that time. Her imatinib dose was increased to 800 mg daily, which was tolerated well. The patient remained in CHR, but at 12 months, her Ph+ metaphases increased to 70% (minimal cytogenetic response). Mutational analysis showed evidence of the BCR-ABL KD mutations, G250E and F317L. The presence of the F317L mutation led to the choice of nilotinib, rather than dasatinib, for second-line therapy. With nilotinib, the patient achieved a PCyR after 3 months, a CCyR after 6 months, and a MMR after 18 months. Follow-up mutational analysis at that time showed persistence of the two preexisting mutations, plus the T315I mutation. Nilotinib was continued, and as the patient had no sibling donors, a search for an unrelated donor was initiated. Despite the presence of these mutations, the patient maintained a CCyR for 1 year before loss of first MMR, then CCyR. Mutational analysis at that time showed T315I as the only detectable mutation, so the patient was enrolled in a trial of ponatinib (AP24534), an investigational agent shown to be effective against the T315I mutation (discussed in the next section). The patient responded with a minor cytogenetic response (CyR) after 3 months and PCyR after 6 months of therapy.

Table 6. ELN Provisional Definitions of Response to Second-Generation TKIs as Second-Line Therapy in Imatinib-Resistant Disease[a]

Time	Suboptimal response	Failure	Warnings
At diagnosis	NA	NA	Hematologic resistance to imatinib CCA/Ph+ (i.e., clonal progression) Mutations[a]
3 mo	Minor CyR	No CyR New mutations[b]	Minimal CyR
6 mo	PCyR	Minimal CyR New mutations[b]	Minor CyR
12 mo	Less than MMR	Less than PCyR New mutations[b]	

Note. ELN = European LeukemiaNet; TKI = tyrosine kinase inhibitor; NA = not applicable; CCA = clonal chromosome abnormalities; CyR = cytogenetic response; PCyR = partial cytogenetic response; MMR = major molecular response.
[a]Information from Baccarani et al. (2009).
[b]BCR-ABL kinase domain mutations that are poorly sensitive to imatinib.

NEW AGENTS TO OVERCOME DRUG RESISTANCE

Several therapies are being evaluated as a means of overcoming or avoiding resistance to current TKIs. The investigational drug ponatinib (AP24534) is in late-stage clinical trials; omacetaxine mepesuccinate (Synribo) was approved in October 2102 for the treatment of adults with chronic or accelerated phase CML with resistance to two or more TKIs, and bosutinib (Bosulif) was approved in September 2012 as a treatment option for adult patients with Ph+ CML who are resistant or intolerant to prior therapy.

Ponatinib is an oral multikinase inhibitor that was developed using a structure-based design platform (O'Hare et al., 2009). It inhibits BCR-ABL as well as its isoforms that carry the T315I and other mutations. Ponatinib is currently being evaluated in the PACE (Ponatinib Ph+ ALL and CML Evaluation) trial in patients with chronic-, accelerated-, or blast-phase CML with resistance or intolerance to dasatinib or nilotinib, or who carry the T315I mutation (Cortes et al., 2011a; 2012a). Updated interim results from this trial presented at the 2012 annual meeting of the American Society of Clinical Oncology (ASCO) demonstrated that of 271 patients with chronic phase CML, 45% of patients with resistance or intolerance to dasatinib or nilotinib and 62% of patients with the T315I mutation achieved a MCyR, the primary endpoint of this study. Demonstrating substantial activity in heavily pretreated resistant or intolerant patients and those with refractory T315I, 36% and 57% achieved a CCyR and 20% and 47% achieved a MMR, respectively (Cortes et al., 2012).

A phase II trial designed to evaluate ponatinib as front-line therapy in patients with Ph+ or BCR-ABL–positive CML in early chronic-phase disease is currently enrolling patients (ClinicalTrials.gov identifier: NCT01570868). A new drug application (NDA) for use of ponatinib in patients with resistant or intolerant CML and Ph+ acute lymphoblastic leukemia was submitted to the FDA in July 2012 as part of a rolling submission process.

Omacetaxine (formerly called homoharringtonine) is an agent derived from an evergreen tree native to China (Chen et al., 2009). It has a mechanism of action that is different from TKIs and its activity appears to be independent of BCR-ABL mutation status. For example, in phase II studies, subcutaneously administered omacetaxine induced hematologic and cytogenetic responses in patients with the T3151 mutation who had failed imatinib (Cortes et al., 2009) and in patients who were intolerant or whose disease was resistant to two or more TKIs (Wetzler et al., 2009). Interim results of a trial of 62 patients with imatinib-resistant, chronic-phase CML that was positive for the T315I mutation indicated that 76% of patients experienced a complete hematologic response and 24% achieved a MCyR at a median follow-up of 19.1 months (Nanda et al., 2011).

Bosutinib is a small-molecule dual inhibitor of both Src and ABL kinases (Golas et al., 2003). A phase I/II study evaluated bosutinib in three patient cohorts: (1) patients with chronic-phase CML who failed imatinib, (2) patients with chronic-phase CML who failed imatinib plus dasatinib and/or nilotinib, and (3) patients with accelerated-phase CML who failed any TKI. Patients without BCR-ABL mutations experienced CHR rates of 90%, 77%, and 39% in each of the cohorts, respectively, whereas CHR rates in patients with BCR-ABL mutations were lower at 83%, 67%, and 17%, respectively (Khoury et al., 2011). An analysis of patients in the second cohort revealed a 32% MCyR rate, 24% CCyR rate, and 73% CHR rate, and responses were observed across all mutations except T315I (Khoury et al., 2012). The BELA (Bosutinib Efficacy and safety in chronic myeloid LeukemiA) trial compared bosutinib with imatinib as front-line therapy in newly diagnosed chronic-phase CML. Although efficacy was comparable in both groups, the trial did not meet its primary endpoint of CCyR at 12 months, most likely due to the high early discontinuation rate in the bosutinib arm due to adverse events (Cortes et al., 2011b). At 24 months, cumulative CCyR rates were equivalent (79% and 80% for bosutinib and imatinib, respectively) and bosutinib treatment was associated with a significantly higher MMR rate (59% vs. 49%; $p = .019$) (Gambacorti-Passerini et al., 2012).

PRACTICAL CONSIDERATIONS

Addressing Nonadherence

Advanced practitioners can implement a number of strategies to improve adherence. Most importantly, adherence behavior should be assessed routinely throughout the care continuum of CML (Noens et al., 2009). Being more knowledgeable about CML and its treatment is associated with adherence, pointing to the need for education to be an integral component of ongoing communications with patients. Increased time spent with patients at diagnosis and during follow-up visits has also been associated with improved adherence. A combination of strategies is likely to be of greater benefit than any one alone. In cases of suspected nonadherence that is denied by the patient, additional direct or indirect methods (e.g., pill counts, third-person questioning, prescription refills) may be helpful in investigating adherence. The following vignette illustrates this point:

> *An 18-year-old male patient initially started on imatinib 400 mg daily but was switched to nilotinib (400 mg twice daily) at 1 month due to a severe skin rash. The patient developed severe headaches, so the nilotinib dose was modified to 300 mg twice daily at 3 months; the headaches improved. With this regimen, the patient achieved a rapid reduction in BCR-ABL to the level of 10% (IS) by 3 months and 0.01% at 6 months, with an undetectable level by 9 months. His transcript levels began to rise at 12 months, reaching 0.1% at 15 months, but had declined back to 0.01% at 18 months. By 21 months, his BCR-ABL level had rapidly risen to 10%. Cytogenetic analysis showed 8/20 Ph+ cells, but no BCR-ABL KD mutations were detected. Before considering a change in therapy, both the patient and his mother were questioned about adherence. The patient's mother stated that her son had frequently missed doses over the past few months. The patient denied this, but*

admitted that he stopped his medication for 1 week recently. After additional counseling, the patient more fully understood the risk he was taking by missing/stopping his medication, and by 24 months, his BCR-ABL transcript levels had again rapidly declined. This unusual rapid rise and fall of transcript levels seen in this case is typical of that seen with intermittent nonadherence.

Managing Side Effects

Patients who experience TKI-related side effects, even low-grade effects, may be more inclined to miss or decrease dosages or to discontinue treatment, all of which can increase the risk of suboptimal response, loss of milestone responses, acquiring drug resistance, or disease progression (Ault & Allen-Bard, 2012). Thus, side-effect monitoring and management, as well as ongoing adverse-event counseling, can aid in improving patient adherence to therapy.

Each of the three approved TKIs has unique toxicities in addition to toxicities that are a class effect. It is important to recognize that the intensity and frequency of these adverse events may differ in the first- and subsequent-line setting. Because of the critical importance of adverse-event management in ensuring optimal treatment and patient quality of life, NCCN Guidelines include comprehensive recommendations for managing adverse events related to imatinib, dasatinib, and nilotinib, which are summarized in Table 7.

Drug-Drug Interactions

By routinely reviewing patients' medication and supplement usage, advanced practitioners play an important role in minimizing potential drug-drug interactions. Patients should be reminded to consult with their health-care team before taking any new prescription or over-the-counter medications, as well as vitamins, minerals, and herbal supplements.

Imatinib, dasatinib, and nilotinib are primarily metabolized by the cytochrome P450 (CYP) 3A4 pathway (Novartis, 2012a; Bristol-Myers Squibb, 2011; Novartis, 2012b). Thus, patients need to be aware of potential interactions of TKIs with drugs or foods that affect the CYP system. Patients should be advised to avoid concomitant administration with strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, certain antiretroviral agents, and grapefruit products, because these can increase plasma concentrations of TKIs. In addition, they should also be advised to avoid concomitant treatment with strong CYP3A4 inducers such as rifampin, certain antiepileptic drugs (e.g., carbamazepine, phenytoin), and St. John's wort, because these may reduce TKI plasma levels. Conversely, TKIs also inhibit CYP3A4 and certain other CYP isoenzymes, so caution is recommended when TKIs are administered with substrates that have a narrow therapeutic window (e.g., astemizole, cyclosporine, fentanyl, sirolimus, tacrolimus; Novartis, 2012a; Bristol-Myers Squibb, 2011; Novartis, 2012b).

The solubilities of both dasatinib and nilotinib are pH-dependent (Bristol-Myers Squibb, 2011; Novartis, 2012b). Therefore, patients receiving these agents should be advised to avoid concomitant treatment with a proton pump inhibitor or histamine H_2 antagonist due to the potential for reduced drug exposure with reduced gastric acid secretion. Instead, antacids administered at least 2 hours prior to or 2 hours after dasatinib or nilotinib administration should be considered if needed. Tasigna product labeling contains a black box warning regarding QT prolongation with nilotinib; thus, the administration of nilotinib with agents that may prolong the QT interval, such as antiarrhythmic agents, should be avoided (Novartis, 2012b). Caution is also warranted when administering antiarrhythmic agents with dasatinib (Bristol-Myers Squibb, 2011).

Effect of Food

As noted above, while taking their medication, patients who are receiving TKI therapy should avoid eating grapefruit or other foods that are known to inhibit CYP3A4 (Novartis, 2012a; Bristol-Myers Squibb, 2011; Novartis, 2012b). The effect of food in general varies among the three approved TKIs. The bioavailability of imatinib is not affected by food (van Erp, Gelderblom, & Guchelaar, 2009). However, it is suggested that imatinib be taken along with a meal and a large glass of water to minimize possible stomach upset (Novartis, 2012a). The bioavailability of dasatinib is not significantly affected by food, and it can be taken with or without a meal (Bristol-Myers Squibb, 2011). Food increases blood levels of nilotinib,

Table 7. Summary of NCCN Recommendations for Managing TKI-Related Adverse Events[a]

Adverse events	Imatinib	Dasatinib	Nilotinib
Hematologic			
Grade 3/4 neutropenia or thrombocytopenia	Drug interruption, dosage reduction	Drug interruption, dosage reduction	Drug interruption, dosage reduction
Nonhematologic[b]			
Diarrhea	Supportive care	Supportive care	Supportive care
Fluid retention events (pleural/pericardial effusion, ascites, edema)	Diuretics, supportive care, dose reduction, interruption, discontinuation; consider echocardiogram to check LVEF	Diuretics, supportive care, dose interruption; consider short course of steroids if significant symptoms	NL
Headache	NL	Supportive care	Supportive care
GI upset	Take with meal and large glass of water	Take with meal and large glass of water	NL
Muscle cramps	Calcium supplement, tonic water	NL	NL
Rash	Topical/systemic steroids, dose reduction, interruption, discontinuation	Topical/systemic steroids, dose reduction, interruption, discontinuation	Topical/systemic steroids, dose reduction, interruption, discontinuation
Hepatic	Grade 2: Hold until grade < 1; dosage reduction; evaluate for other hepatotoxic drugs Grade 3–4: Consider change to another TKI or clinical trial	NL	Elevated liver enzymes or bilirubin (grade ≥ 3): drug interruption
QT interval prolongation (QT > 480 msec)	NL	NL	Obtain ECG at baseline, 7 days after initiation, periodically, and following any dose adjustments. Hold drug; correct serum potassium and magnesium levels as needed; resume at prior or reduced dose; discontinue if QTcF returns to > 480 msec

Note. NCCN = National Comprehensive Cancer Network; TKI = tyrosine kinase inhibitor; NL = not listed in NCCN Guidelines; GI = gastrointestinal; LVEF = left ventricular ejection fraction; QTcF = QT interval corrected for heart rate using Fridericia-corrected formula; ECG = echocardiogram.
[a]Information from NCCN (2012).
[b]Unless otherwise noted, all interventions listed are suggested for grade 2–3 adverse events. If not responsive, treat as grade 4: hold drug until grade 1 or better, then consider resuming at a reduced dose; consider change to another TKI or clinical trial.

so patients should avoid eating for 2 hours before and 1 hour after taking nilotinib (Novartis, 2012b). Advanced practitioners can guide their patients in scheduling the optimal time to take their specific TKI medication in relation to meals as needed.

Pregnancy

With improved survival with TKI therapy, family planning has become an important aspect of patient management over the long term. By providing education and support, advanced practitioners can assist patients and their spouses

in navigating this challenging situation, which is still a matter of continued debate.

In animal studies, imatinib has been shown to be teratogenic (Novartis, 2012a), and embryo-fetal toxicities were observed with both nilotinib and dasatinib (Novartis, 2012b; Bristol-Myers Squibb, 2011). Imatinib has been shown in animal studies to impair spermatogenesis (Novartis, 2012a), but there are limited data regarding the effects in men receiving TKI therapy and their partners who became pregnant. ELN recommendations state that imatinib should not be administered at conception or during gestation (Baccarani et al, 2009). They also recommend that treatment interruption be considered for a patient in MMR to permit a safe pregnancy. However, interferon-alfa remains an option during pregnancy. NCCN Guidelines state that there is insufficient evidence to support continuation of any of the three approved TKIs during pregnancy (NCCN, 2012). In addition, the NCCN recommends that men wishing to father a child should consider sperm cryopreservation prior to starting TKI therapy. However, product labeling for these agents does not formally advise against fathering children while on therapy. Because imatinib and its metabolites can be excreted in breast milk, breastfeeding is strongly discouraged while on TKI therapy (Novartis, 2012a). It is not known if nilotinib or dasatinib are excreted in human milk (Novartis, 2012b; Bristol-Myers Squibb, 2011).

A recent review of published case reports indicates a high rate of adverse events with imatinib exposure during pregnancy (Cole, Kantarjian, Ault, & Cortes, 2009). The review identified 215 women who had a pregnancy occur in the setting of treatment with imatinib, with a total of 217 pregnancies. Among the 109 pregnancies that the women intended to carry to term with known outcome, 36 (33%) resulted in complications (i.e., 24 spontaneous abortions, 1 stillbirth, 9 with malformations, and 2 with low birth weight). In this review, one case report described a 21-year-old woman diagnosed with CML during early pregnancy. She was closely monitored without active intervention, had a healthy child, and was able to breastfeed for 3 weeks before staring dasatinib. This case demonstrates that close monitoring might be an option for selected patients in these circumstances who have minimal clinical manifestations (Cole et al., 2009).

For women who have achieved a MMR and wish to start a family, cessation of treatment is typically recommended (Baccarani et al., 2009). The following vignette illustrates a possible course of action for a patient who has not yet achieved a MMR:

> *A 30-year-old woman was started on imatinib 600 mg/day for treatment of her CML. At 18 months, she had achieved a CCyR, but not an MMR. She wishes to start a family as soon as her clinician tells her it is safe to proceed. Her physician questions if switching to a second-generation TKI would provide a greater chance of achieving a stable response prior to a period of cessation while she attempts a pregnancy. Data from the randomized ENEST CMR (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–CMR) trial of nilotinib vs. imatinib demonstrated that the rates of CMR and MMR were significantly higher in patients who switched to nilotinib compared to those who remained on imatinib (Hughes et al., 2011). Thus, it was surmised that switching to nilotinib would improve the patient's chances of achieving a CMR or deep molecular response. In addition, her chances of sustaining the CMR off-therapy may be improved with nilotinib compared with imatinib, although this remains to be established.*

Can Therapy Be Stopped?

With the increase in long-term survival among CML patients, the question arises whether TKI therapy can ever be discontinued. There are now data from two studies evaluating the outcome of patients who discontinued imatinib following achievement and maintenance of CMR for at least 2 years (Mahon et al., 2010; Mahon et al., 2011; Ross et al., 2012). In these studies, the majority of patients (55%–61%) experienced a molecular relapse, most within the first 6 to 7 months of discontinuation. However, the remaining patients, some who have been followed up to 5 years, appear to maintain their CMR following imatinib discontinuation. At this time, it is not possible to determine definitively who can safety stop TKI therapy, so clinicians are advised not to stop therapy outside of a clinical trial (NCCN, 2012).

CONCLUSION

Cytogenetic and molecular monitoring play critical roles in the early detection of treatment failure, allowing timely changes in management strategy and improved outcome. In addition, mu-

tational analysis can help tailor choice of therapy in cases of resistance and treatment failure. Although uniform response definitions, response, criteria, and monitoring recommendations have been developed by the ELN and NCCN, these are in a state of flux and differences exist between them. In addition, questions regarding best practices and definition of treatment failure remain. Clinical advances in CML continue to be made in conjunction with greater understanding of the biology of the disease.

Advanced practitioners play a key role in the management of CML. By helping to address preventable barriers, such as nonadherence and drug interactions, managing side effects, and providing education and support in family planning, advanced practitioners can help improve outcome and greatly assist patients in their CML journey.

A NURSING PERSPECTIVE

The field of CML is rapidly evolving with advances in treatment and monitoring; these advances have translated into improved long-term survival for patients. The prolonged survival offered by TKI therapy for CML creates several new considerations for disease management. With the evolution in treatment, CML has now emerged as a chronic condition, giving rise to new issues as clinical management has adapted. As CML patients live longer, oncology nurses play an increasingly influential role in educating and supporting patients over the long term. The essential practice of monitoring is of critical importance to the safety profile of TKIs and long-term patient management. Treatment-related responsibilities, monitoring treatment adherence, and patient education are essential aspects of nursing care that significantly contribute to positive outcomes. Inquiries on disease- and treatment-related symptoms and their impact on quality of life allow for early identification of issues that may necessitate a dosing modification or change in treatment.

As new therapies and monitoring techniques are evaluated, the need for education and support continue to be vital aspects of optimizing patient care. Understanding time-point testing is critical in helping to avoid less-than-optimal treatment decisions. Thus, translation of this information into the clinical arena is critical for aiding treatment decisions in patients with CML receiving TKI therapy.

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