Donna Duke Morrison. *Least Bittern.* Watercolor, 22″ × 30″.

Identification of kinase domain mutations facilitates prediction of resistance to imatinib in patients with CML.

Tailoring Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia

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Background: *Research into chronic myeloid leukemia (CML) is increasingly focused on the problem of imatinib failure. Dasatinib and nilotinib are both active in chronic- and accelerated-phase CML, including patients with imatinib-resistant or intolerant disease.*
Methods: *This paper reviews advances in tailoring tyrosine kinase inhibition therapy according to patient risk profiles as well as hematologic, cytogenetic, and molecular responses, BCR-ABL mutation status, and emerging predictive factors.*
Results: *In addition to identifying specific tyrosine kinase mutations, clinical advances have allowed us to determine patients who are less likely to derive long-term survival benefits from imatinib.*
Conclusions: *Treatment for CML should be individualized and, when resistance to imatinib can be predicted, therapy should be modified so that patients do not progress beyond chronic phase and respond as promptly and deeply as required to maximally reduce risk.*

Introduction

Chronic myeloid leukemia (CML), a clonal myeloproliferative disorder of hematopoietic stem cells, progresses clinically through three phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP).[1] Imatinib (Gleevec®, Novartis Pharmaceuticals Corp, East Hanover, New Jersey), the prototype tyrosine kinase inhibitor (TKI) against the oncogenic "driver" of CML, Bcr-Abl, is the current standard first-line therapy for patients with newly diagnosed CML-CP.[2,3] Although stem cell transplantation (SCT) remains the only defined path to "cure," patients eligible for this procedure now generally receive a trial of kinase inhibitors before transplant.[4] As predicted by the considerable early morbidity of transplant pitted against the excellent tolerability and response to imatinib, a recent retrospective analysis has confirmed that the 5-year overall survival rate in patients with newly diagnosed, early CML-CP is significantly and markedly superior in those who receive imatinib (93%) compared with those who receive SCT (59%; $P < .0001$).[5]

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Abbreviations used in this paper: *CML = chronic myeloid leukemia, CP = chronic phase, AP = accelerated phase, BP = blast phase, TKI = tyrosine kinase inhibitor, SCT = stem cell transplantation, CHR = complete hematologic response, MCyR = major cytogenetic response, CCyR = complete cytogenetic response, MMR = major molecular response, ELN = European LeukemiaNet, ALL = acute lymphoblastic leukemia.*

Although imatinib induces sustained responses in a majority of treated patients, it has become clear that a substantial proportion fail to derive adequate or lasting clinical benefit because of intolerance and/or resistance. A large European survey of "real-life" usage of imatinib in the clinic (the Unmet Needs in CML study) reported that 45% of those receiving this compound exhibited either resistance or intolerance.[6] In a further uncensored survey, 49% of patients experienced imatinib failure following resistance to this drug.[7] In a recently reported long-term study of patients with CML treated in a single institution, the 5-year probability of remaining in major cytogenetic response while still receiving imatinib was 62.7%, meaning that roughly a third of patients require more effective therapy.[8]

The arrival of second-generation TKIs for use in clinical practice provides significant new options to manage imatinib failure across the spectrum of CML.[3] Dasatinib (Sprycel® Bristol-Myers Squibb Co, Princeton, New Jersey), the first TKI approved by the US Food and Drug Administration (FDA) for the treatment of imatinib-resistant or -intolerant CML patients in any phase, is a novel, oral, multitargeted kinase inhibitor of BCR-ABL and also SRC family kinases (SRKs), ephrin receptor kinases (EPHs), platelet-derived growth factor receptor (PDGFR), and c-Kit.[9] In vitro, dasatinib demonstrated 325-fold greater potency than imatinib against native BCR-ABL and was active against nearly all imatinib-resistant BCR-ABL mutants, with predicted intermediate sensitivity to a select few mutations and resistance to the T315I mutation.[10] Nilotinib (Tasigna®, Novartis Pharmaceuticals Corp) is an analog of imatinib with similar tyrosine kinase targets, including BCR-ABL, PDGFR, c-Kit, SFKs, and EPHB4.[10-12] Nilotinib is approximately 20-fold more potent against native BCR-ABL; however, in vitro data demonstrated activity against most imatinib-resistant mutants, with similar prediction of reduced activity against certain mutations (P-loop) and resistance to T315I.[10,11] Nilotinib was also approved by the FDA for the treatment of patients with CML who are resistant to or intolerant of prior therapy (including imatinib), limited to those with CML-CP or -AP (Table 1).[13-15]

With the sequential advances of imatinib, followed by dasatinib and nilotinib, the treatment approach for CML has been completely rewritten and continues to evolve in the current era of kinase inhibitors. Practice guidelines are evolving in tandem with the emergence of new data for second-generation TKIs and long-term follow-up data for imatinib.[1-3,16,17] It is essential that clinical management of CML reflects both the latest recommendations and the clinical data to ensure patients have optimal response and thus maximal likelihood of long-term survival.[18] For practical purposes, patients may be divided into two groups: those who respond well to and tolerate imatinib treatment and those who do not. As discussed below, patients with poor response may exhibit any of several resistance mechanisms; progression is far more likely and generally occurs early in such patients. Therefore, to optimize outcome, treatment strategies should be individualized according to responsiveness and tolerance of TKIs, with an emphasis on early decision-making. Such strategies depend on promptly detecting inadequate response rather than simply identifying developing resistance and relapse. Adequate and accurate monitoring is essential to identify patients as early as possible who may benefit from a change in strat-

Table 1. — TKIs Approved for the Treatment of CML

Compound	CML Indications (not including Ph+ acute lymphoblastic leukemia)	Recommended Dose	Administration Requirements	Main Side Effects
Imatinib (Gleevec®)	Newly diagnosed adult patients with Ph+ CML-CP Patients with Ph+ CML (all phases) after failure of interferon-α Pediatric patients with Ph+ CML-CP who are newly diagnosed or whose disease has recurred after SCT or who are resistant to interferon-α therapy	CML-CP: 400 mg once daily CML-AP/-BP: 600 mg once daily	Doses should be taken with a meal and a large glass of water	Myelosuppression, elevated liver enzymes, edema/fluid retention, congestive heart failure/LV dysfunction, bullous dermatologic reactions, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, fatigue, abdominal pain
Dasatinib (Sprycel®)	For the treatment of adults with any phase CML with resistance or intolerance to prior therapy including imatinib	CML-CP: 100 mg once daily CML-AP/-BP: 70 mg twice daily	None	Myelosuppression, pleural effusions, bleeding, QT prolongation, diarrhea, headache, nausea, rash, fatigue, dyspnea
Nilotinib (Tasigna®)	For the treatment of Ph+ CML-CP/-AP in adult patients resistant to or intolerant to prior therapy that included imatinib	CML-CP/-AP: 400 mg twice daily	Avoid food 2 hours before and 1 hour after consumption	Myelosuppression, elevated liver enzymes, elevated serum lipase, electrolyte abnormalities, QT prolongation (black box warning), rash, pruritus, nausea, fatigue headache, constipation, diarrhea, vomiting

Data from Bristol-Myers Squibb Company Sprycel® (dasatinib) prescribing information and Novartis Pharmaceuticals Corporation Gleevec® (imatinib) and Tasigna® (nilotinib) prescribing information.

egy such as escalating imatinib dose, transitioning to a second-generation TKI[19] or, in select cases, abandoning TKIs for SCT. Early identification of resistance and potentially suboptimal response to imatinib is preferred as it allows change to be effected before transformation to AP or BP. This is consistent with the historical aim of delaying such progression as long as possible since long-term responses to TKI therapy might be unlikely in advanced disease.[19]

These same principles apply if SCT therapy is strongly being considered or becomes the clear choice of treatment. Although previous information on the implications of prior imatinib use and resistance on the outcome of SCT were limited,[20,21] the data from a recent, large retrospective survey indicate that pre-SCT imatinib confers a survival benefit only in patients with early-stage CML (CML-CP).[22] The authors concluded that it is imperative that patients undergo SCT before disease progression for SCT to be most successful, and research to date has not demonstrated augmentation of transplant risk based in pretransplant TKI exposure. The logical notion that SCT is optimal prior to transformation has remained true from earlier decades of initial use of SCT for CML prior to imatinib; in the era of TKIs, holding to this notion is imperative lest a vital therapeutic window may be lost.

In addition to identifying poor responders during therapy, distinguishing such patients before resistance itself is clinically apparent is becoming increasingly possible using pretherapy or early predictive factors. It may be possible that such factors could be used to identify those who require higher doses of imatinib or a more potent TKI upfront.[19] This article reviews the latest clinical and experimental data useful in tailoring TKI therapy for CML patients according to risk profile as well as hematologic, cytogenetic, and molecular response, BCR-ABL mutation status, and emerging predictive factors.

Monitoring and Assessing Response of First-Line Imatinib Therapy

Vigilant monitoring of response and toxicity to treatment is the foundation of effective patient care in CML-CP. Using formalized guidelines ensures that patients receive the optimum treatment throughout the course of their disease and that prompt changes are made when necessary. Frequent and regular monitoring of response in patients with CML is most critical during the first 1 to 2 years of therapy, when most cases of primary and secondary resistance to imatinib are detected.[17,19] Patients may be classified in a fairly straightforward manner according to hematologic, cytogenetic, and molecular response landmarks to imatinib (Table 2).

Hematologic testing, the earliest form of testing used, detects the highest and rarest level of primary resistance to treatment, and it continues throughout treatment to monitor for toxicity and not as the first indicator of relapse. The relevant landmark is the complete hematologic response (CHR). Hematologic testing should occur regularly (every 1 to 2 weeks) until this landmark is reached, and it should continue early in CML treatment due to early peak incidence (0 to 18 months) of hematologic toxicity.[23]

Given that most patients achieve a CHR, cytogenetic testing of the bone marrow is then used to follow deepening response. Marrow-based cytogenetic testing remains the gold standard due to its broad availability, consistent evaluation, and significant differences in long-term survival outcomes between patients experiencing cytogenetic response and those who do not. Data regarding efficacy of all the kinase inhibitors are based in marrow karyotype, and most authoritative guidelines, such as those of the National Comprehensive Cancer Network (NCCN)[2] and the European LeukemiaNet (ELN),[3] are centered on marrow cytogenetic landmarks. Table 2 presents several levels of cytogenetic response, but the most widely used are major and complete cytogenetic responses (MCyRs and CCyRs), with the MCyR category including patients in both CCyR and partial cytogenetic response. A CCyR was historically (in the era of interferon therapy) the most significant independent predictor of survival and the most important prognostic factor, and it remains so today in the TKI era. Thus it is considered a critical goal

Table 2. — Landmark Responses to First-Line Imatinib

Form of Testing	Response Landmark	Criteria
Hematologic	Complete	White blood cell counts < 10 × 10⁹/L with normal differential, platelet count < 450 × 10⁹/L, nonpalpable spleen
Cytogenetic	None Minimal Minor Partial Complete	Ph+ metaphases > 95% Ph+ metaphases = 66% to 95% Ph+ metaphases = 36% to 65% Ph+ metaphases = 1% to 35% Ph+ metaphases = 0%
Molecular	Major	BCR-ABL/ABL ratio ≤ .10% on the International Scale (IS) or > 3-log ↓ from baseline

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of therapy.[3,24,25] A partial cytogenetic response is considered an important step in achieving this goal and represents a critical threshold of reduction in disease burden. Cytogenetic testing is recommended at baseline for diagnostics and examination for additional clonal changes, then every 6 months thereafter until CCyR is reached, and then only as clinically indicated.[2] A general morphologic review of the percentage of bone marrow blasts and basophils is also recommended at baseline[2] to properly stage patients and rule out occult progression of disease beyond chronic phase. Most commonly, a bone marrow analysis at diagnosis and 1 to 2 subsequent bone marrow analyses are necessary to follow the typical patient into cytogenetic remission. In the absence of significant blood abnormalities or antecedent clonal or pathologic changes requiring monitoring, subsequent marrow testing may be deferred.

Fluorescence in situ hybridization (FISH) techniques may be used to complement conventional testing at diagnosis and are well suited to confirm cytogenetic complete remission.[26] An advantage of FISH is that it may be used on peripheral blood samples and can serve as an alternative if marrow aspirates are unfeasible at any time. However, it does not detect the development of secondary chromosomal abnormalities (clonal evolution), has relatively low sensitivity and high false positivity, and has not been correlated with evolving cytogenetic response in TKI trials. Therefore, it should not be used to replace conventional marrow karyotyping to monitor early response.[19]

Molecular testing, namely quantitative polymerase chain reaction (PCR) for Bcr-Abl, is mainly used to detect minimal residual disease. With the increasing effectiveness of kinase inhibitor therapy, it has become increasingly prominent in the management of CML patients. The landmark response of quantitative PCR is the major molecular response (MMR) (Table 2). Attempts to define a complete molecular response (CMR) are controversial as extremely low levels of CML cells, which may cause future relapse, are likely to lie below current detection limits (thus confounding the notion of "complete"). More importantly, the threshold of detection is more assay- and laboratory-based and may be difficult or impossible to standardize adequately. Large-scale attempts to ensure uniformity in evaluating molecular response are underway.[27] As most patients receiving imatinib achieve a CCyR, molecular testing has become an early and regularly used tool necessary for proper monitoring, despite the fact that the achievement of an MMR has not been formalized in NCCN guidelines.[2] Molecular testing in general is recommended at baseline and every 3 months until CCyR is reached, and then every 3 to 6 months while the patient is responding.[2]

Defining an Optimal Response to First-Line Imatinib Treatment

Response outcomes to imatinib therapy can also be classified in a straightforward manner as optimal, suboptimal, and failure according to when and whether the patient reaches accepted response landmarks. Such time-based frameworks have been proposed and recommended in several published national and international guidelines, two of the most widely used being those of the NCCN[2] and the ELN[3] (Table 3). Optimal responses proposed by the NCCN and ELN correspond closely. With regard to the two key landmark responses, patients should achieve a CHR after 3 months of therapy and a CCyR after 12 months. The importance of these targets is reflected in follow-up data from the pivotal phase III imatinib study (International Randomized Study of Interferon vs STI571 [IRIS]). Achieving a hematologic response was found to be a prerequisite for consequent cytogenetic responses and long-term survival.[19] Therefore, a CHR within 3 months is a vital component of the optimum response. Similarly, CCyR was found to be an independent predictor of survival and a key prognostic indicator in imatinib-treated CML.[3,24,25]

The NCCN guidelines differ somewhat from those of the ELN. They stipulate that a CCyR should be achieved at 6 months,[2] whereas the ELN guidelines require only an MCyR at this time point.[3] The NCCN guidelines are therefore more stringent and may be more sensitive

Table 3. — Time-Based Landmarks for Evaluation of Response

Class of Response	Guidelines	3 Months	6 Months	12 Months	18 Months
Optimal	NCCN	CHR	CCyR	CCyR	CCyR
	ELN	CHR	MCyR*	CCyR	MMR
Suboptimal	NCCN	–	No CCyR	No CCyR	No CCyR
	ELN	No CHR	No MCyR*	No CCyR	No MMR
Failure	NCCN	No CHR, or hematologic relapse	No CyR	No MCyR,* or cytogenetic relapse	No MCyR,* or cytogenetic relapse
	ELN	No HR	No CHR, no CyR	No MCyR*	No CCyR

* Major cytogenetic response (complete or partial cytogenetic response). Data from Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood.* 2006;108(6): 1809-1820. Epub 2006 May 18. Data from National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia v2.2009.

with regard to early identification of imatinib-resistant patients. This introduces the concept of suboptimal response, indicating that long-term outcome may be improved if treatment is changed, even though the patient may continue to benefit from the current imatinib schedule.[3] A recent retrospective study showed that failure to achieve an MCyR by 6 months predicts decreased overall survival.[28] A recent analysis of the outcomes of CML-CP patients on imatinib with suboptimal response as defined by the ELN guidelines at 6 and 12 months noted outcomes for such patients to be more similar to those defined as failure at the same time points and suggested combining these categories of risk.[29] This was not the case for suboptimal molecular response (defined at the 18-month time point) and suggests clear differences between "suboptimal" cytogenetic and molecular response and that it is less likely that patients are "slow responders" regarding cytogenetic remission in contrast to achieving threshold molecular response (MMR).

Although an MMR is not included as a response milestone according to the NCCN guidelines,[2] achieving such a response by 12 months is considered a target response in the ELN guidelines[3] and should be considered optimal. It is important to note that the largest gains in risk reduction occur with the achievement of a CCyR, but achieving an MMR by 12 months does provide further protection from disease progression. In the pivotal phase III study of imatinib in patients with CML-CP, after 5 years of follow-up 97% of patients who achieved a CCyR within 12 months had not suffered disease progression compared with 81% of patients who did not achieve an MCyR within this time period ($P < .001$).[30] However, patients who had both a CCyR and an MMR at 12 months had a 100% probability of remaining progression-free at 5 years.[31]

Patients achieving an optimal response to imatinib should be maintained at the same dose, if tolerable.[2] Dose modification or treatment discontinuation may be required for persistent adverse events. With the availability of alternative therapies, patients who exhibit unresolvable or unrelenting nonhematologic toxicity, even at moderate levels, should be switched, or considered for a switch, to dasatinib or nilotinib treatment, or they may potentially be enrolled in a clinical trial.[2]

Definitive Signs of First-Line Treatment Failure

Imatinib resistance may be either primary or secondary. Primary resistance appears inherent and prevents patients from securing adequate or optimal response. Secondary resistance is acquired and leads to loss of response or disease progression. The consequence of imatinib resistance, primary or secondary, is either treatment failure or suboptimal response. Despite the notion that disease progression may seem less of a "threat" than in the past because of the availability of salvage treatments, as well as the expectation that gaining further response with imatinib must be balanced with the risk of trying a new therapy, treatment failure or identification of suboptimal (particularly cytogenetic) response indicates an urgent need to reassess treatment strategy since the risk of progression to AP or BP may be mounting or high.[2]

Treatment failure indicates that the current imatinib schedule is no longer appropriate and a change in treatment is necessary.[3] In the IRIS study, the median time to a CHR was 1 month; failure to achieve this landmark by 3 months is considered treatment failure by the NCCN.[2] Treatment should also be changed if cytogenetic response of any kind (eg, > 95% Ph+) is lacking after 6 months of therapy or if an MCyR and a CCyR are not present after 12 and 18 months of therapy, respectively.[2] This is supported by IRIS trial data: if no CCyR was observed at 6 months, the probability of achieving a subsequent CCyR was only 15%; if the response after 12 months of treatment was less than an MCyR, the probability of achieving a CCyR at 2 years was less than 20%.[3] Furthermore, a retrospective analysis of outcomes of patients treated with imatinib in the IRIS trial and those treated with interferon-α plus cytarabine in the CML91 trial showed a significant survival advantage for patients who achieved an MCyR at 12 months regardless of the specific treatment.[24]

The above criteria address the presence of primary resistance, but guidelines also address the scenario of secondary resistance by stipulating treatment change in case of relapse or progressive disease.[2,3] In such cases, it is implied that the biology of the disease has likely changed, given that there is proliferation or transformation in the face of ongoing therapy. Patient care must change to reflect the management of transforming disease. Patients with true transformation to CML-AC or -BP should be monitored more vigilantly for both response and basis of resistance (eg, mutation analysis over time), and treatment should be changed to dasatinib (for patients with CML-AP or CML-BP) or nilotinib (for patients with CML-AP only), followed by SCT when feasible.[2]

Baseline Prognostic Indicators for Initial Treatment

Since imatinib was introduced, identification of a number of prognostic "tools" have helped to more accurately predict whether a patient will respond optimally to standard-dose imatinib.[19] Some indicators are "historical" (associated with the pre-imatinib era) and are supported with conclusive evidence. Other putative indicators have been suggested by more recent evidence and require further confirmation. All such indicators can be used to individualize initial treatment in order to optimize patient response. Among historical indicators, the phase of disease at the time of diagnosis is a major determinant of response. The likelihood of achieving a response is far greater for patients in CP compared to those with advanced-phase disease. For example, prolonged CCyRs are achieved in approximately 70% of patients with CML-CP compared with less than 30% of patients with advanced-phase disease.[32] This is a major reason why patients should receive optimum treatment as early as possible, with the aim of delaying or preventing progression. Disease phase is currently the only prognostic indicator used to individualize initial imatinib treatment. The Sokal score[33] and, to a lesser degree, the Hasford CML score[34,35] developed in the pre-imatinib era have retained value in predicting response to imatinib. Studies have shown a correlation between Sokal score and the rates of CCyR and MMR.[36,37] However, among patients who achieve a CCyR, there is no correlation between Sokal score and risk of relapse.[30]

Cytogenetic clonal evolution is another negative prognostic factor that predates the imatinib era.[38-40] The effect on response to therapy is not clear, particularly when seen in isolation; however, when observed with other criteria for acceleration, clonal evolution predicts for a reduction in efficacy outcomes.[41]

One common form of secondary chromosomal abnormality is chromosome 9 [der(9)] deletion. Some studies have found that this deletion had a negative impact on imatinib response and patient outcome, but others have reported that imatinib apparently overcomes this historically negative prognostic factor.[41-46] Further studies controlling for imatinib schedule and disease stage are warranted. Among other factors present and part of routine diagnostics at diagnosis, imatinib resistance may also be predicted by assessing levels of BCR-ABL overexpression, which could cause resistance to standard-dose imatinib.[47]

Newer potential predictors of imatinib response include trough plasma imatinib levels, in vitro sensitivity to imatinib, expression of transport proteins, and baseline genetic profiling. In the case of serum imatinib levels, two clinical studies have reported an association between trough plasma levels of imatinib and response, suggesting that monitoring plasma imatinib levels may be a potential tool for optimizing treatment outcome.[48,49] However, a more recent study has failed to replicate this finding.[37] The authors suggested that length of follow-up, timing of the trough level from treatment start, and patient characteristics may obscure any effect of serum level on response,[37] perhaps limiting the usefulness of this prognostic indicator.

The evidence for measuring in vitro sensitivity of cell samples from patients with CML appears to be more clear-cut. White et al[50] showed that in vitro IC_{50} values for imatinib-induced inhibition of ABL kinase activity correlated with clinical sensitivity: 12-month MMR rates were 47% and 23% for patients with low and high in vitro IC_{50} values, respectively. In a further study, 100% of patients who showed > 50% kinase inhibition in vitro achieved an MMR by 24 months compared with 56% of patients without 50% in vitro kinase inhibition ($P < .001$). Patients with < 50% kinase inhibition were also more likely to have suboptimal responses.[51] Studies have also suggested that increased expression of the influx protein, OCT-1, correlates with higher response rates.[52] Rapid throughput methods for testing in vitro sensitivity to imatinib and expression of OCT-1 could therefore prove useful in predicting response and tailoring treatment.[19] However, the accuracy of these methods for predicting response has not been adequately confirmed, and such techniques may be impractical for most clinical settings due to the sensitivity and specificity required. Lastly, microarray genetic profiling is currently in its infancy, but in the future it may be used to identify patients less likely to respond to imatinib by identifying disrupted pathways and genes in individual patients.[53-57]

The Effect of BCR-ABL Mutations on Response

An indicator associated uniquely with TKI therapy is the presence of BCR-ABL mutations with variable degrees of predicted treatment-insensitivity, believed to be the cause of most cases of acquired resistance to imatinib.[1,58-61] The cumulative data demonstrating the involvement of such mutations in resistance to TKI treatments are now substantial. Mutations that retain some sensitivity to imatinib may respond to imatinib dose escalation.[62] However, mutations regarded as imatinib-insensitive ($IC_{50} \geq 5$ times wild-type) require a change to a second-generation TKI. Mutations in the P-loop (including Y253H/F and E255K/V), a common site of mutations,[63] are sensitive to dasatinib but are often clinically insensitive to high-dose imatinib or nilotinib.[10,64-68] The T315I contact point mutation, however, is insensitive to all commercially available TKIs,[10] and alternative strategies such as SCT are required for patients carrying this mutation.[21] As with the P-loop mutations and nilotinib, a select number of mutations are unlikely to be sensitive to dasatinib, such as V317L (which retains sensitivity to nilotinib).[10]

The frequency of BCR-ABL mutations increases with more advanced phases of disease. Therefore, if imatinib resistance is confirmed, there is impetus to change treatment as early as possible to potentially avoid genesis of mutant clones resistant to alternative therapies.[17,69,70] Mutation screening should be performed in patients with CML-CP and evidence of emerging resistance as well as in all patients with advanced-phase CML.[17] In the majority of patients who achieve a CCyR, frequent molecular monitoring (every 3 months) should be ongoing to detect potential loss of response to imatinib. In patients who have significant and confirmed rising levels of BCR-ABL, the frequency of measurement may be increased and mutation analysis performed if transcript levels are above a threshold level to detect mutations.[17] However, such tests have limited value at baseline. Studies have shown that baseline mutation screening cannot predict the future emergence of an aggressive mutant clone or decreased responses to imatinib, event-free survival, and overall survival.[71] In addition, baseline levels of circulating BCR-ABL do not predict subsequent responses.[72] Instead, other measures, such as the measurement of in vivo kinase inhibition using a crkl phosphorylation assay (a substrate that is phosphorylated by Bcr-Abl), may help to determine if BCR-ABL is being inhibited, but its use is currently experimental.[50]

Table 4. — Association Between Early Achievement of CCyR and Probability of Subsequent CCyR or Progression in Patients With CML-CP Treated With Imatinib

Months of Treatment	No. of Patients Not in CCyR	Probability of Outcome (%)		*P* Value
		CCyR	Progression	
3	104	74	16	.04
6	47	60	26	
12	26	62	31	

This research was originally published in *Blood*. Quintas-Cardama A, Kantarjian HM, Jones D, et al. Delayed achievement of molecular responses is associated with increased risk of progression among patients (pts) with chronic myelogenous leukemia (CML) in chronic phase (CP) treated with imatinib (IM). *Blood (ASH Annu Meet Abstracts)*. 2006;108:432. Abstract. © American Society of Hematology.

Early Response Signs of Patients Who May Need a Change in Therapy

The time-based landmarks of response used to formally identify treatment failure or suboptimal responses to imatinib, as discussed above, may be complemented by utilizing additional early response indicators that are not currently recognized in treatment guidelines but are able to define populations in need of alteration in treatment strategy. Molecular testing is the most sensitive monitoring technique; it therefore may detect signs of primary resistance earlier than other techniques can. Early incorporation of transcript level measurement has been extensively studied. Branford et al[73] reported that patients who fail to achieve a 1-log reduction in BCR-ABL transcripts at 3 months or a > 2-log reduction by 6 months, are unlikely to achieve a significant response and are at high risk for disease progression. In a study of 55 patients with newly diagnosed CML-CP, those who achieved at least a > 2-log reduction in BCR-ABL transcript levels after either 3 or 6 months had probabilities of achieving an MMR by 24 months of 100% and 86%, respectively. Among patients who failed to achieve a > 2-log reduction by 6 months, none achieved an MMR at 24 months. Furthermore, only 13% of patients who failed to achieve at least a 1-log reduction in BCR-ABL transcripts by 3 months achieved an MMR at 30 months. Similarly, a study by Quintás-Cardama et al[74] showed that failure to achieve a BCR-ABL/ABL level of ≤ 1% within 3 to 6 months is associated with subsequent lack of response as well as disease progression. For example, the risk of long-term progression rose from 2% in patients with BCR-ABL/ABL levels of ≤ 1% at 3 months to 13% in patients with BCR-ABL/ABL levels of > 10%. Molecular monitoring can also be used to detect secondary resistance. Real-time quantitative PCR for measuring BCR-ABL levels in peripheral blood is particularly valuable for monitoring patients on imatinib, and a rise in BCR-ABL transcripts can track the development of resistance.[72,75,76] In particular, a 2- to 5-fold rise in BCR-ABL levels over a 1-month interval is a key indicator of resistance and is often associated with the emergence of imatinib-resistant mutations.[17]

Apparent changes or expectations regarding BCR-ABL transcript levels may be difficult to interpret and may differ from traditional cellular assays (karyotype) in the case of various mechanisms of resistance (for example, overexpression). The threshold for such changes is still being defined. Changes in BCR-ABL transcript levels may reflect corresponding changes in disease burden and might imply resistance due to presumed proliferation, but they may be caused to some degree by assay variability. Furthermore, BCR-ABL levels may naturally fluctuate within the disease itself, much like the white blood cell count would historically in many patients who were treated with hydrea only. Thus, defining relevant changes and threshold changes in BCR-ABL transcript levels remains difficult, especially at low levels of disease burden.

Applying more stringent demands on early cytogenetic response may also provide prognostic information. Studies have demonstrated that overall survival and progression-free survival (PFS) are improved in patients who achieve a cytogenetic response at 3 or 6 months.[77-79] In the IRIS trial, risks of disease progression were significantly lower in patients who had achieved a CCyR with imatinib by 6 or 12 months than in patients without these responses, thereby supporting the use of these yardsticks as optimum landmark responses.[2,74] Patients not in CCyR within the first year of starting imatinib face the competing probabilities of disease progression vs achieving a CCyR with continued therapy (Table 4). These data drive the need to manage such risk with patients through discovery, disclosure/discussion, and decisive and often difficult decision-making.

Current TKI-Based Treatment Options for Patients Following Imatinib Failure or Suboptimal Response

Approved second-line treatment options for patients with CML failing first-line imatinib treatment include high-dose imatinib, dasatinib, and nilotinib. Response and toxicity should be reassessed and continually modified if required. Such an approach is needed, given the availability of multiple therapies, the greater potential for disease instability in the setting of imatinib resistance, and the continued uncertainty (relative to imatinib) of response duration and long-term safety of salvage approaches.

Imatinib Dose Escalation

High-dose imatinib is included as a treatment option by both the ELN and the NCCN for patients with less than optimal responses to first-line imatinib.[2,23] Schedules of 600 mg/day and 800 mg/day are recommended for patients with CML-CP and advanced-phase disease, respectively. The use of high-dose imatinib following failure of standard-dose imatinib is controversial; it is an appropriate strategy for some patients, but clinical benefit is not achieved by all. Reported CCyR rates have been in the range of approximately 10% to 40%.[78,80-84] Responses achieved are also frequently transient.[78,83] Furthermore, studies show that patients with CML-CP who do not achieve any cytogenetic response from standard-dose imatinib fail to benefit from high-dose imatinib.[78,80,81]

High-dose imatinib at 800 mg/day was compared with dasatinib 70 mg twice daily in a randomized phase II study of patients with CML-CP who were resistant to imatinib at 400 to 600 mg/day.[81] The study had some limitations. Patients who did not achieve MCyR by 3 months in the high-dose imatinib were allowed to cross over to receive dasatinib, but the same option was not available to patients receiving dasatinib. Also, dose increase of imatinib from 600 mg/day to 800 mg/day may be viewed as a modest intervention in comparison to a switch in therapy. After 24 months of follow-up, dasatinib was superior to high-dose imatinib with regard to rates of MCyR (53% vs 33%; $P = .017$), CCyR (44% vs 18%; $P = .003$), MMR (29% vs 12%; $P = .028$), and PFS (86% vs 65%; $P = .001$).[85] Rates of MCyR were also higher with dasatinib in patients who had received prior imatinib therapy at a dose of 400 mg/day (dasatinib 58%; high-dose imatinib 53%), but the difference was not significant.[81] However, the percentages of patients retaining MCyR at 18 months (90% vs 74%) and without failure at 24 months (59% vs 18%; $P < .001$) were greater for those taking dasatinib.

Dose escalation of imatinib may be a more feasible option for patients with suboptimal responses.[84] Dose escalation may be associated with increased frequency and severity of adverse events.[77,86] In clinical studies, imatinib discontinuation or dose interruption/reduction was necessary in approximately 30% to 60% of patients, mostly in response to grade 3/4 hematologic adverse events.[80,81,83] This highlighted the fact that hematologic toxicity may be augmented in patients with more refractory disease and may reflect disease biology.

Dasatinib

Dasatinib is approved for the treatment of patients with CML in any phase as well as Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to imatinib. Its clinical efficacy and safety were demonstrated through large clinical trials across these disease subtypes.[81,87-91] Rapid and deep responses have been observed with dasatinib as a single agent in all phases of CML and in Ph+ ALL. After 8 months of treatment, 52% of patients with CML-CP achieved an MCyR.[89] High hematologic and cytogenetic response rates were maintained after 2 years of follow-up (Table 5).[92-95] In addition, a high MMR rate (47%) was recorded among responding patients with CML-CP after 2 years,[92] and PFS was maintained in 80% of patients at this time point. Also, mutational analyses have demonstrated that dasatinib is able to elicit CCyR among patients with P-loop mutations.[96]

Dasatinib has a distinct but manageable safety profile. Cytopenias and pleural effusions increased in frequency with dasatinib. Higher-grade neutropenia and thrombocytopenia were noted in nearly half of initial patients in CP treated with dasatinib 70 mg twice daily, and dose interruptions and reduction were required for the majority of these patients. Pleural effusions and, to a lesser degree, pericardial effusions were recognized as rare complications of imatinib. During early clinical studies of dasatinib, it became apparent that the potential was greater and vigilance/screening for effusions increased. Despite the incidence of approximately 5% to 15% across all phases of disease, early recognition and proper management can minimize morbidity of this complication. Diuretic and/or corticosteroid therapy can also be used to manage pleural effusions if necessary,[2,97] but they are usually managed effectively with simple dose interruption or reduction.[13]

Bleeding events (due to induced platelet dysfunction) were increased with dasatinib use to a modest degree, were generally associated with thrombocytopenia, and were mainly gastrointestinal in location. Based

Table 5. — Response of Imatinib-Resistant CML to Dasatinib and Nilotinib

Agent	Follow-up (mos)	CHR Achieved	MCyR Achieved	CCyR Achieved
Dasatinib	24	86%	55%	45%
Nilotinib	14	77%	56%	39%

Data from Mauro MJ, Baccarani M, Cervantes F, et al. Dasatinib 2-year efficacy in patients with chronic-phase chronic myelogenous leukemia (CML-CP) with resistance or intolerance to imatinib (START-C). *J Clin Oncol.* 2008;26(May 20 suppl):7009. Abstract. Data from Kantarjian H, Hochhaus A, Cortes J, et al. Nilotinib is highly active and safe in chronic phase chronic myelogenous leukemia (CML-CP) patients with imatinib-resistance or intolerance. *Blood (ASH Annu Meet Abstracts).* 2007;110:735. Abstract.

on recent data with a dose of 100 mg once daily, which demonstrated an improved overall risk-benefit profile compared with the previous schedule of 70 mg twice daily,[98] the recommended starting dose for patients with CML-CP is now 100 mg once daily. Efficacy is unchanged with dasatinib 100 mg once daily, but rates of grade 3/4 thrombocytopenia (22% vs 37%; P = .004) and all-grade pleural effusion (7% vs 16%; P = .028) are significantly lower than those seen on the previous schedule. The recommended starting dose for patients with advanced-phase disease or Ph+ ALL, however, remains 70 mg twice daily.

Nilotinib

Nilotinib is approved for the treatment of patients with CML-CP or CML-AP who are resistant to or intolerant of prior therapy, including imatinib. A broad set of phase I/II studies explored the efficacy and safety of nilotinib.[99-103]

The activity of nilotinib is also rapid and marked. In one study, after a median of 8 months of follow-up in patients with CML-CP, the MCyR rate was 48%; however, 16% of patients who had achieved an MCyR experienced loss of response over the follow-up period.[104] Of note, trials in CP with nilotinib required all patients, even those entering a trial for imatinib intolerance, to exhibit a degree of clinical resistance, whereas trials with dasatinib had a fraction of intolerant patients in whom clinical resistance was not required for treatment. At the most recent follow-up (18 months), overall rates of MCyR and CCyR were similar to dasatinib at 56% and 40%, respectively (Table 5).[105]

Nilotinib is also active in advanced-phase disease. In patients with CML-AP, 31% achieved an MCyR and 19% achieved a CCyR after a follow-up of 7 months.[106] Studies are ongoing in patients with BP and Ph+ ALL. Early results have shown significant clinical activity.[107]

As mentioned above, the activity of nilotinib is reduced against P-loop mutations, up to 39-fold in biochemical assays and 35-fold in cell proliferation assays.[10] In phase II clinical studies, nilotinib showed diminished responses among patients harboring P-loop mutations. Only 10% of evaluable patients with CML-CP and P-loop mutations achieved a CCyR at 9 months compared with 37% patients with non–P-loop mutations and 47% with no mutation.[108] This may explain in part the 18-month time-to-progression rate of 64%, which is somewhat inferior to comparable data for dasatinib CP studies.[92,105]

Nilotinib was well tolerated in clinical trials. Cytopenias are common, occurring with subsequent nilotinib treatment at a greater frequency than that observed with primary imatinib therapy. They are generally reversible and managed with temporary treatment interruption and dose reduction.[15] Electrolyte disturbances are common, and there is potential for an increase in pancreatic enzymes, albeit with only rare cases of clinical pancreatitis; however, both toxicities are reversible and generally self-limited. Nilotinib carries a black box warning in its prescribing information that relates to the potential to prolong the QT interval. These risks should be avoidable with pre-therapy ECG screening, regular monitoring of patients on therapy, and avoidance of aggravating factors and concomitant medications that may compound the risk of arrhythmia and sudden death.

Minimizing Competing Risks

Formalized measures of treatment failure and suboptimal response, and negative prognostic indicators discussed above, can be viewed as competing risks. Given the high degree of success with TKI therapy, it is reasonable to increasingly focus the management of CML patients on the need to lower the likelihood of such competing risks. This can be achieved primarily by optimizing the rapidity and duration of response, thereby reducing the risk of progression and anticipating the development of resistance. This needs to be done within reason, driven by data supporting the merit of intervention and also in balance with the risk (albeit low) of toxicity of alternate TKIs.

As discussed above, shorter time to cytogenetic responses to imatinib have been associated with improved patient outcome. However, a 6-year follow-up analysis of the IRIS study has failed to confirm this principle.[109] In this report, estimated 6-year overall survival rates for patients who achieved a CCyR within 6, 12, and 18 months and after 18 months were 94%, 95%, 91%, and 98%, respectively (P = .55). However, these data were based on a cohort with attrition of failing patients and where competing risk of failure continually increased. Data from phase II clinical trials reviewed earlier prove that second-generation TKIs are most effective in extending survival when administered in CML-CP rather than advanced-phase CML. While intuitive, in the setting of relapsing disease, earlier change to second-line TKIs (at the onset of cytogenetic relapse rather than hematologic relapse) has been demonstrated to be advantageous. An analysis of patients with CML-CP treated in clinical trials of dasatinib showed that markedly higher rates of CCyR were achieved in patients who had experienced cytogenetic relapse (72%) compared with those who had also suffered hematologic relapse (42%).[110] Currently, treatment guidelines use a conservative approach and do not recommend a change in therapy for patients who have not experienced outright treatment failure up to the first 18 months of therapy.[2,3] Suboptimal responders may eventually achieve a response with imatinib. However, the proportion of patients with impending treatment failure may outweigh the proportion of "slow responders." With multiple second-line treatment options available, more aggressive treatment targets may be warranted.[2,16] For example, first-line imatinib may be reassessed if patients fail to achieve a cytogenetic response after 3 months, a CCyR after 6 months, or an MMR after 12 to 18 months. Studies have been designed and launched to evaluate whether second-line TKIs should be used following suboptimal responses to first-line imatinib treatment rather than after subsequent treatment failure. Unfortunately, a trial of dasatinib vs high-dose imatinib and a trial of nilotinib vs high-dose imatinib both closed due to insufficient accrual.

A further putative trigger for the early introduction of second-line therapy is the detection of imatinib-resistant BCR-ABL mutations. While a 2- to 5-fold rise in BCR-ABL transcripts is associated with the emergence of a BCR-ABL mutation and may be an early indicator of loss of response,[17,72] no guidelines are currently available for changing therapy based on rising BCR-ABL transcripts alone. However, as the emergence of mutations in the BCR-ABL kinase domain during treatment is tantamount to a diagnosis of imatinib resistance and should prompt a change in therapy,[64,65] an increase in transcript levels should prompt cytogenetic evaluation, mutational monitoring, and continuous monitoring of peripheral blood BCR-ABL.

Potential Changes in First-Line Treatment

Current standard practice is to treat newly diagnosed CML-CP initially with imatinib at the standard dose of 400 mg/day. However, a higher starting dose may be selected to treat patients with poor prognostic features or to achieve a more rapid response. Higher doses of imatinib are effective in patients with advanced-phase CML and are recommended in such cases.[1-3,16,17] Early studies of initial therapy in CML-CP with imatinib 800 mg/day revealed increased rapidity and proportion of responses.[77,111] For example, 90% of newly diagnosed patients with CML-CP achieved a CCyR within 15 months of follow-up.[77] More importantly, long-term follow-up from single-arm studies suggested a reduction in progression risk with the use of high-dose imatinib at diagnosis. Data from these small studies led to a major study of high-dose imatinib in the front-line setting.[112] In the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) Study, 476 patients with newly diagnosed CML-CP were randomized to receive imatinib at either 400 mg/day or 800 mg/day. Although patients in the high-dose arm achieved MMRs significantly faster than those in the standard-dose arm, the trial failed in its primary endpoint of showing statistically significant superiority in MMR rates at 12 months (46% vs 40%, respectively; $P < .05$). There was also no statistical difference in CCyR rates between these treatments at this time point (70% vs 66%, respectively; $P = .347$).[112] Moreover, the high-dose regimen was also associated with a greater frequency of adverse events as well as discontinuation rates due to adverse events (1.3% vs 5.6%, respectively).

The TOPS data therefore do not support the universal use of high-dose imatinib in the first-line setting. Interim data from a different study also show no advantage for the use high-dose imatinib over standard dosing in Sokal high-risk patients.[113] Caveats to such conclusions include the following: (1) with further analysis of later time points and long-term outcome, survival advantage from reduction in progression risk may become evident, and (2) the selective effect of more-intense therapy was the goal of comparison in the Sokal high-risk study, and for those patients who maintained high-dose imatinib without significant reduction or interruption, clear benefit was derived. As dasatinib also has a clear efficacy advantage over high-dose imatinib in the second-line setting (and if data were available, nilotinib might possess a similar advantage), the goal of delivering more therapy early in the disease course with minimal toxicity may be achieved a number of ways. In a study of pretreated patients with CML-CP, high-dose imatinib (800 mg/day) "induction" over a fixed 6-month period followed by "maintenance" at 400 mg/day is being compared with imatinib 400 mg/day throughout.[114] Interim data, similar to the conclusions of the TOPS trial, suggest that although significantly higher response rates were achieved during the first 6 months of treatment in the induction arm, rates of CCyR (48% vs 37%, respectively) and MMR (21% vs 16%, respectively) were not significantly superior ($P < .05$) at 12 months. Longer follow-up is required to assess this approach conclusively.

It is thus logical to project that higher response rates and improved patient, outcomes would be achieved if more potent, second-generation TKIs were used in the front-line setting instead of imatinib, even at high doses. Dasatinib and nilotinib are both being studied in this setting. Interim data show that first-line dasatinib (100 mg/day once daily or 50 mg twice daily) (n = 40; accrual ongoing) elicited a CCyR rate of 94% at 6 months and 100% at 12 months.[115] The activity of nilotinib 800 mg/day was similar, with CCyR rates at 6 and 12 months both being 100%.[116] Both agents were significantly ($P < .001$) more active than imatinib at these time points, as assessed from historical controls.

It is also possible that these second-generation TKIs will induce higher MMR rates than those achieved with imatinib in the first-line setting. The 12-month time point may be too early to assess such an effect based on observations in studies to date and based on the differential kinetics of disease burden reduction over time in CML. For example, MMR rates for Australasian patients in IRIS over a period of 81 months and for imatinib-intolerant patients (no resistance) treated with dasatinib over 24 months were similar (87% and 78%, respectively),[92,117] suggesting that dasatinib may be more effective than imatinib with follow-up beyond 12 months.

In summary, the goals of CML treatment are to maintain the patient in CML-CP for as long as possible, to reduce disease burden promptly, and to key threshold levels. Once the disease becomes unstable or existing unstable clones proliferate, resistance has developed and BCR-ABL mutations become common; with subsequent disease progression, the biology of the disease has transformed and thus becomes more difficult — if not impossible — to control in the same fashion as we can for the majority of responding CML-CP patients. The opportunity for stable, long-term remission is likely lost. A shorter time to cytogenetic response landmarks (more rapid disease reduction) is undoubtedly important in this respect, and, as discussed earlier, is associated with improved patient outcome. Rapidity of molecular response may also be important, but the weight and value of such response continue to be clarified. Longer follow-up of comparison trials such as the TOPS trial, which suggested there may be a ceiling to this effect as shorter time to MMR was not reflected by a subsequently higher MMR rate,[112] should yield answers. The algorithms for optimal treatment in CML continue to be written in real-time as research continues.

Ongoing Questions

Among the various questions surrounding TKI treatment of CML is how effective response benchmarks are to be defined in the second- and third-line settings. Is the same "yardstick" used for imatinib response to be used for dasatinib/nilotinib (eg, response landmarks over time)? While further studies are required before clear benchmark criteria can be established for second-line TKI treatment, it is likely that the requirements will be more stringent than first-line response criteria. Tam et al[118] suggest that failure to achieve a cytogenetic response by 3 to 6 months of second-line treatment (dasatinib or nilotinib) should prompt a change in treatment. However, similar to imatinib, their study of 113 patients treated with second-line dasatinib or nilotinib showed that achieving an MCyR by 12 months was associated with a significantly improved 1-year survival rate (97%) compared with achieving only a minor cytogenetic response or CHR (84%; $P = .02$). Less than 10% of patients with no sign of cytogenetic response by 3 to 6 months subsequently achieved an MCyR by 12 months. It is currently unclear how effective response will be defined in the third-line setting.

A second question is whether the same speed and depth of response can be achieved in the second-line setting as in the first-line setting. In IRIS, 25% of patients receiving first-line imatinib achieved an MMR after the first year of treatment.[36] Within the population of patients receiving second-line TKI treatment, there are two different subsets: imatinib-resistant and imatinib-intolerant patients. These subsets of patients will likely display different response dynamics, and expectations should be gauged appropriately. Among 202 patients with CML-CP enrolled in the START-C trial, MMRs were achieved after 12 months of treatment in 14% of imatinib-resistant patients and in 45% of imatinib-intolerant patients.[108] As discussed above, the MMR rate in imatinib-intolerant patients rose to almost 80% following 2 years of follow-up.[92] Moreover, within the imatinib-resistant population, response dynamics differ according to the various underlying mechanisms of resistance.[108]

Another area under investigation is the most appropriate treatment if second-line TKI treatment fails. It has recently been shown that both dasatinib and nilotinib have activity in patients who have failed treatment with the other drug, ie, dasatinib following nilotinib failure and nilotinib following dasatinib failure.[88,102] It has been suggested that, in theory, such patients could go back to imatinib treatment. This remains a possibility as the underlying disease may have changed, but the likely presence or rapid re-emergence of imatinib-resistant BCR-ABL mutations makes this improbable.

The role of SCT in CML treatment is also being re-evaluated. Currently, SCT should be considered in patients who have CML-CP, are younger with no limiting comorbidities and with matched related donors, and have experienced significant relapse and/or progression on first-line imatinib or overt failure on imatinib. Initial action prior to transplant would hopefully restore good disease control, and ideally CCyR and minimal residual disease remission on a second-line TKI can be achieved to minimize disease relapse risk.[5] SCT should also be considered in patients with high-risk disease who require a number of treatment adjustments to maintain an adequate response and thereby avoid disease progression. Patients who should also be considered for SCT include those who harbor the T315I mutation (or compound/multiple mutations) prior to clinical progression to advanced-stage CML, those who achieve only a partial response to second-line TKI therapy, those who experience significant toxicity precluding them from the option of second-line TKI treatments, and those who experience failure after second-line TKI therapy.

Conclusions

The introduction of novel TKIs has created the opportunity for tailored treatment of the patient with CML. While empiric imatinib is likely to remain the first choice for initial therapy in the short-term, recent advances in risk assessment, response monitoring, and availability of mutation analysis now allow early identification of individuals for whom imatinib is less likely to result in long-term remission and survival. For patients unlikely to obtain optimal benefit from imatinib, therapy should be reassessed and modified prior to progression to advanced disease. The most active therapy should be started at the earliest opportunity. Rationale algorithms are necessary to balance risk over time, with expectation of continued response. With further clarification and understanding of risk, more aggressive treatment of CML at earlier time points and in the face of suboptimal response is likely to be adopted. Dasatinib, approved for the treatment of imatinib-resistant or -intolerant patients with CML in any phase or Ph+ ALL, and nilotinib, approved for the treatment of imatinib-resistant or -intolerant patients with CML in CP or AP, offer excellent response, durability, minimal cross-intolerance with imatinib and modest intrinsic toxicity profiles. Clinical trials are currently assessing the value of these novel TKIs as primary therapy for CML.

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