Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2012 April ; 12(2): 79–87. doi:10.1016/j.clml.2011.12.004.

Molecular Resistance: An Early Indicator for Treatment Change?

Carmen Fava¹, Hagop Kantarjian², and Jorge Cortes²

¹University of Turin, Italy

²M. D. Anderson Cancer Center, TX, USA

Abstract

Vigilant monitoring of a patient's response to current treatment is imperative to the management of chronic myeloid leukemia. Early identification of treatment failure may increase the probability that alternative therapy will be effective. This review discusses the use of molecular monitoring in the timely detection of imatinib failure. Changes in the levels of BCR-ABL transcripts are predictive of response or relapse. Patients achieving a major molecular response within 12 months of treatment may experience longer cytogenetic remission. Accumulating evidence also suggests that lower transcript levels observed 6 months after treatment start are associated with improved patient outcomes. For patients with primary or secondary imatinib resistance (or intolerance), dasatinib or nilotinib may be prescribed. These agents have demonstrated activity in patients harboring imatinib-resistant BCR-ABL mutations, except for the T315I substitution.

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder¹ accounting for 15% of all patients with leukemia.^{2,3} A cellular marker for CML is the Philadelphia chromosome (Ph), the result of a reciprocal translocation between chromosomes 9 and 22.^{4,5} The resulting oncogene codes for the chimeric BCR-ABL protein, a constitutively active tyrosine kinase that underpins the pathophysiology of CML.^{6–8}

Most patients are diagnosed in the initial chronic phase (CP) of CML. If left untreated, the disease progresses through an accelerated phase (AP) to a terminal blast phase (BP).^{2,9} The final BP is further categorized as either myeloid or lymphoid BP. Both forms are usually refractory to treatment with conventional chemotherapy.

Current treatment of patients with CML relies on tyrosine kinase inhibitors directed against the pathogenic BCR-ABL protein. Allogeneic stem cell transplantation (aSCT) is a potentially curative approach; however, this therapy is limited to a subset of patients for whom related or unrelated donors can be found. Imatinib (Gleevec®)¹⁰ was the first BCR-ABL inhibitor approved as first-line therapy for CML.³ In the key International Randomized Study of Interferon and STI571 (IRIS) phase III clinical study, imatinib was associated with significantly longer progression-free survival (PFS) compared with the previous standard

Address for correspondence: Jorge Cortes, MD, Department of Leukemia, Box 428, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas, 77030, Phone: (713) 794-5783, Fax: (713) 794-42, jcortes@mdanderson.org.

Carmen Fava has no conflicts of interest;

treatment, interferon- α plus cytarabine.¹¹ The introduction of imatinib greatly improved the treatment of CML. However, many patients fail to benefit from this therapy because of primary (inadequate response to treatment) or secondary (loss of a previously achieved response to treatment) resistance. Many patients also may be intolerant to initial therapy. In IRIS, primary resistance, or failure to achieve a complete cytogenetic response (CCyR), was observed in at least 24% of imatinib-treated patients 18 months after the start of treatment.¹¹ After 5 years of treatment, secondary resistance or treatment relapse was observed in approximately 17% of imatinib-treated patients and progression to AP or BP was observed in 7% of all patients.¹² Furthermore, in a single-center, uncontrolled study of imatinib in the United Kingdom, the estimated probability of experiencing an ongoing major cytogenetic response (MCyR) at 5 years was only 63%.¹³

The consequence of drug resistance in CML is poor outcome. Three-year survival rates for patients who experienced imatinib failure in the CP, AP, and BP phases of CML during imatinib treatment were reported as 72%, 30%, and 7%, respectively.¹⁴ Thus, when imatinib failure is documented, a timely change in therapy is imperative. Two second-generation BCR-ABL inhibitors are available as second-line treatment with other BCR-ABL inhibitors currently under investigation.¹⁵ Dasatinib (Sprycel[®]) is indicated in patients with any-phase CML or Ph-positive acute lymphoblastic leukemia who are resistant or intolerant to prior therapy, including imatinib. Nilotinib (Tasigna[®]) is indicated for CML patients in CP or AP who are resistant or intolerant to prior therapy, including imatinib. Recent studies have shown that dasatinib and nilotinib have efficacy also in the first-line setting,^{16–20} and as of 2010, both BCR-ABL inhibitors have been approved in the United States for newly diagnosed CML-CP.^{19–21} In addition, the National Comprehensive Cancer Network (NCCN) has added to their guidelines for CML both of these compounds as first-line therapy along with imatinib for treatment of patients with newly diagnosed Ph-positive or BCR-ABL–positive CML.³

Constant and effective monitoring of a patient's response to current treatment is imperative to the management of CML. As all treatments for CML are more effective in CP than AP or BP,^{2,22–24} early identification of treatment failure may increase the probability that subsequent treatment adjustments will be effective. This review discusses the use of molecular monitoring (ie, monitoring of BCR-ABL transcript levels) for the timely detection of imatinib failure.

Treatment Monitoring, Goals, and Failure

In responding patients, imatinib progressively reduces the disease burden, characterized by the number of leukemic cells. As the number of leukemic cells decreases, the sensitivity of any effective monitoring technique must correspondingly increase. The initial level of response and the earliest monitoring point is the complete hematologic response (CHR), defined as the normalization of peripheral blood counts with absence of splenomegaly. The next monitoring points are levels of cytogenetic response (CyR), determined by bone marrow metaphase chromosome analysis (using 20 metaphases). Achievement of CCyR has become the gold standard for an optimal response. The most sensitive monitoring technique is molecular monitoring of BCR-ABL transcript levels by quantitative reverse

transcription-polymerase chain reaction (RT-PCR) assay. This technique allows for detection and monitoring of residual disease following cytogenetic remission.²² Widely accepted levels of response for hematologic, cytogenetic, and molecular monitoring techniques are given in Table 1.

The European LeukemiaNet (ELN) has published internationally accepted clinical practice recommendations, including monitoring practice and formal definitions of optimal responses, warning signs, suboptimal responses, and treatment failure using hematologic, cytogenetic, and molecular criteria.^{25,26} The value of the ELN clinical practice recommendations in predicting the outcome of patients with CML in early CP has been demonstrated.^{27,28} Commonly used time-based landmarks of optimal and suboptimal responses and treatment failure are shown in Table 2. The NCCN offers another widely recognized set of guidelines but does not include time-based molecular response landmarks in their assessment of clinical response to imatinib.³

Treatment failure is considered to represent that imatinib treatment at the current schedule is no longer appropriate for a patient and a change in therapy is indicated; a suboptimal response indicates that although a patient may continue to receive a benefit from imatinib treatment with the present schedule, long-term outcome may improve with another treatment strategy.²⁵ Failure to achieve a major molecular response (MMR) within 18 months of start of treatment or loss of MMR at any time is regarded as a suboptimal response (Table 2).²⁵ Failure to achieve MMR within 18 months of treatment initiation was shown to be associated with a decreased probability of event-free survival (EFS) and survival free from progression to AP or BP in a 7-year follow-up study of IRIS.²⁹ No association between failure to achieve MMR within 18 months of treatment initiation and overall survival (OS) was seen.²⁹ Loss of an MMR has been associated with a less durable CCyR ($P=0.0003$),³⁰ whereas an increase in BCR-ABL transcript levels without outright loss of MMR is considered a warning sign.²⁵ Patients with warning signs are much less likely to experience loss of CyR or disease progression than those who exhibit a loss of MMR.³¹

The significance of a complete molecular response (CMR) is controversial. First, the rate of such a response, defined by the absence of a detectable BCR-ABL transcript, is dependent on the sensitivity of the molecular assay used. Second, imatinib is unable to totally eradicate quiescent primary CML stem cells, which are known to persist in patients even after achieving durable CCyRs with imatinib^{32,33} and which pose the constant threat of disease relapse. Achievement of a CMR has been associated with higher probability of maintaining CCyR or MMR and a very low risk of events^{34–36}; however, a 5-year follow-up report from a study in patients with CML in late CP previously treated with interferon- α showed that molecular response with imatinib was not correlated with duration of remission or survival.³⁷ In addition, there has been no report of an improvement in EFS, survival free from transformation to AP or BP, or OS for patients achieving CMR versus those with MMR or CCyR but no CMR. Perhaps the greatest potential benefit of achieving CMR is the possibility of treatment discontinuation. A study by Mahon and colleagues³⁸ has shown that approximately 40% of patients who discontinued therapy with imatinib after a sustained CMR for at least 2 years remained in remission after a median follow-up of 17 months.

While this is an interesting study result, treatment discontinuation should be considered presently only in the context of clinical trials.

Molecular Responses to Imatinib

Rates of molecular response have been examined in multiple trials since the introduction of imatinib. In the IRIS trial, CCyR was achieved in 68% of patients 1 year after commencing imatinib treatment, and MMR was detected in 57% of these patients.³⁹ Given the 1-year CCyR rate of 68% and assuming that patients without CCyR did not achieve MMR, the estimated MMR rate for imatinib-treated patients was 39% at 1 year.

MMR rates have been suggested to increase with length of treatment. For newly treated Australasian patients enrolled in IRIS, the cumulative probability of MMR at a median follow-up of 81 months was 87%.³⁵ Notably, this analysis only included patients still on trial at the time of follow-up; thus, 87% could be an overestimate of the rate of MMR. Intention-to-treat rates would be expected to be lower. For example, in an intent-to-treat analysis, de Lavallade and colleagues found that patients receiving imatinib had a cumulative MMR rate of 50% at 5 years.¹³

As for hematologic and CyR rates, the probability of achieving a molecular response decreases for patients who failed prior therapy. A study of patients who had achieved CCyR with imatinib showed that after a median follow-up of 31 months, MMR rates were 67% in previously untreated patients with CML-CP in early CP and 55% in patients with CML-CP who had failed interferon treatment previously.⁴⁰

Molecular Response as a Prognostic Indicator

The use of MMR as a treatment goal is controversial, but some studies have shown that BCR-ABL transcript levels at the time of CCyR predict duration of cytogenetic remission. In one study, patients with a stable CCyR had significantly lower BCR-ABL transcript levels at the time of achieving CCyR compared with patients who eventually experienced cytogenetic relapse.⁴¹ Furthermore, patients who achieved MMR (defined as a BCR-ABL/ β 2-microglobulin transcript ratio < 0.0005 or a 3-log reduction in BCR-ABL transcript levels from the median baseline value) at the time of the first CCyR had cytogenetic remissions of significantly longer duration than those who did not achieve MMR.⁴¹ Achieving MMR at 12 or 18 months has been suggested to be associated with more durable cytogenetic remission compared with failure to achieve this goal.^{27,40}

Achieving MMR also has been suggested to affect survival outcomes. In IRIS, no patient with both CCyR and MMR at 12 months progressed to advanced disease over 5 years.¹² In addition, the probability of remaining event free (defined as any one of the following: transformation to AP or BP disease, death while on study, increased white blood cell count, loss of CHR, or loss of MCyR) was 100% for patients who achieved CCyR with MMR at 24 months and 95% for patients who achieved CCyR without MMR at 12 months ($P=0.007$).³⁹ Unfortunately, at the 7-year follow-up, the EFS benefit of achieving MMR at 12 months was no longer detectable when compared with achieving CCyR (inferred from a 2-fold log reduction in BCR-ABL) with no MMR (91% vs 92%).²⁹ However, achievement of MMR

versus only CCyR at 18 months was associated with a modest but statistically significant increase in EFS rate at 7 years (95% vs 86%; $P=0.014$) and a trend toward improved PFS (99% vs 96%; $P=0.054$), but had no effect on OS rates (95% vs 96%; not significant). These data suggest that there is no significant incremental benefit in EFS associated with achieving MMR over CCyR by 12 months, whereas there is a small but statistically significant incremental benefit in EFS associated with achieving MMR at 18 months. This benefit in EFS does not translate into an overall survival advantage after 7 years of follow-up.²⁹ Variable results have been found by other investigators. A 6-year follow-up study assessing imatinib treatment in patients with CML-CP previously treated with interferon showed that achieving MMR was associated with a significantly higher EFS rate versus not achieving MMR (100% vs 44%; $P=0.0001$).⁴² Press and colleagues⁴³ showed that a 2-log reduction in BCR-ABL at, or 3-log reduction after, the time of CCyR was a significant and independent prognostic marker of PFS. Results of a retrospective study of 276 patients with CML in CP on imatinib therapy showed that durable MMRs documented for 12 months were associated with longer PFS but not OS.⁴⁴ However, Marin and colleagues,²⁷ evaluating imatinib treatment in newly diagnosed CML patients in early CP, found that achievement of MMR at 12 or 18 months had no significant effect on 5-year PFS or OS and de Lavallade and colleagues found that achieving CCyR at one year correlated with PFS and OS at 5 years, but achieving MMR at one year conferred no additional benefits in terms of PFS or OS at 5 years.¹³

It is becoming apparent that the dynamics of BCR-ABL transcript levels vary among patients with CCyR and that this may affect their long-term outcomes. For example, Pavlovsky and colleagues described how transcript levels in patients who have achieved CCyR may either progressively decline, plateau, or rise.⁴⁵ Findings from a study by Palandri et al⁴⁶ suggest that the prognostic significance of MMR increases if the response is confirmed and stable. Patients with a stable MMR (defined as a persistent BCR-ABL transcript ratio $<0.05\%$ after achievement of CCyR) had longer durations of CCyR and significantly greater PFS rates than patients without a stable MMR (ie, intermittent loss of MMR) or no MMR (ie, never achieved MMR).⁴⁶

Some studies have suggested that early molecular responses (ie, within the first 6 months of therapy) have prognostic significance. In a retrospective study of 120 patients with CML in CP receiving imatinib after prior interferon failure, the probability of MCyR at 6 months (ELN optimum response; Table 2) was significantly higher in patients with a BCR-ABL/ABL mRNA ratio $<20\%$ after 2 months of imatinib therapy than for those with a BCR-ABL/ABL mRNA ratio $\geq 20\%$.⁴⁷ Results of a study of 47 patients with CML found that the probability of achieving MCyR after 6 months of therapy was significantly higher for patients whose BCR-ABL/ABL transcript ratio had decreased to $<50\%$ of the baseline value after 4 weeks of imatinib treatment than for those who did not achieve this reduction ($P<0.001$).⁴⁸ A decrease in the BCR-ABL/ABL transcript ratio at 3 months to $<10\%$ of the baseline value was associated with a greater probability of achieving MCyR at 6 months compared with failure to achieve this decrease ($P<0.001$). Furthermore, patients who achieved these reductions in the BCR-ABL/ABL transcript ratio at 4 weeks or 3 months had superior PFS rates ($P=0.01$ and $P=0.003$, respectively) at a median follow-up of 16.5 months.⁴⁸ In another study, patients with CML-CP who had a BCR-ABL/ABL ratio of 1%

to 10% after three months of imatinib therapy had a 92% probability of achieving CCyR with continued therapy, similar to that of patients with a BCR-ABL/ABL ratio of 1% (98%). By contrast, risk of progression was nearly three times greater in patients with a BCR-ABL/ABL ratio of >1% to 10% compared with patients with a BCR-ABL/ABL ratio of 1% (11% vs 4%) and similar to that of patients with a BCR-ABL/ABL ratio of >10% (13%).⁴⁹ This inverse association between early molecular response and disease progression also was observed in Australasian patients enrolled in IRIS.⁵⁰ Here, the incidence of hematologic, cytogenetic, or molecular progression was significantly higher in imatinib-treated patients who failed to achieve a 1-log reduction by 3 months or a 2-log reduction by 6 months ($P=0.002$). In the most recent update of this study, the risk of an event was significantly lower in patients who achieved MMR by 6 months compared with those who achieved MMR after this time ($P=0.04$).³⁶ In essence, these studies suggest that patients with deeper treatment responses tend to have better long-term outcomes. However, despite suggestions that lower transcript levels at early time points may be associated with improved outcomes, no study has demonstrated that earlier changes in therapy would alter outcomes in “slower” responders. Given the considerably faster responses that may be achieved with a second-generation BCR-ABL inhibitor as initial therapy compared with imatinib, long-term results of such clinical studies may provide a clearer view of whether improvement in long-term outcomes can be expected with deeper declines with transcript levels at early timepoints. It remains to be seen whether the shift of slower imatinib responders to faster responders with these agents would alter long-term outcomes or provide only temporary benefits where these patients would still be destined to progress at a higher rate and/or faster than the slow responders. Interestingly, the overall results of the IRIS study showed no statistical difference in EFS, PFS, or OS by the level of molecular response at 6 months. The 7-year probability of EFS for those with a BCR-ABL ratio (IS) 0.1% at 6 months was 85% compared with 84% for those with a ratio 0.1.²⁹ Thus, although treatment options that give deeper responses at earlier time points may be desirable, changes in therapy for reasons other than treatment failure as defined by the ELN²⁵ currently are not recommended outside the context of clinical trials.

Point Mutations in Developing Resistance

The mechanisms underlying imatinib resistance are multifactorial (reviewed by Kantarjian et al.⁵¹). Such mechanisms include increased production of BCR-ABL (through gene amplification or overexpression), decreased intracellular levels of imatinib following changes in the expression of drug efflux or influx genes, or the involvement of other pathways (eg, SRC family kinases).

Secondary imatinib resistance most frequently occurs as a result of BCR-ABL point mutations, which may inhibit the binding of imatinib. In a study of CML patients, imatinib-resistant BCR-ABL mutations were detectable in 61% of patients who developed a 2- to 5-fold increase in transcripts during imatinib therapy.⁵² In key studies of dasatinib and nilotinib in patients with CML in CP who had previously failed imatinib therapy, baseline BCR-ABL mutations were detectable in 34%-42% of evaluated patients.⁵³⁻⁵⁵ The appearance of a BCR-ABL mutation with high insensitivity to imatinib is included in the definition of treatment failure by the ELN, whereas the appearance of a mutation that is still

sensitive to imatinib is included in the definition of suboptimal response.²⁵ Recently it has been suggested that the detection of a BCR-ABL mutation, without any other sign of imatinib resistance, is highly predictive of loss of CCyR and progression to AP or BP CML.⁵⁶ However, although the presence of a mutation predicted progression to AP or BP, only 10 of 37 patients with mutations had this detected before achieving or while still in CCyR; as a result, the significance of detecting mutations in patients remaining in CCyR is unclear. The median time from detection of a mutation to loss of CCyR was 20.7 months. There was no indication that intervention at the time a mutation was detected instead of the time CCyR was lost would have changed outcomes. A recent analysis of patients included in the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study—where mutations were investigated routinely at different time points—indicated that a mutation could be detected in 13%–41% of patients with a loss of response and in 21% of those who progressed to advanced disease, but was rarely detected in patients not meeting the ELN definition of failure.⁵⁷ Currently, a mutational analysis is recommended for patients with failure, always before a change in BCR-ABL inhibitor or other treatment, and in some instances of suboptimal response, particularly if this outcome is documented at 6 months from the start of therapy.²⁵ To date, more than 100 imatinib-resistant mutations have been identified.⁹ However, just 15 amino acid substitutions are responsible for 85% of those detected,⁵⁸ with the phosphate-binding loop (P-loop) being the most common mutation site (~40% of detected mutations).⁵⁹ The most common mutations are described in Table 3.

The T315I contact point mutation is insensitive to all clinically available BCR-ABL inhibitors (Table 3).^{51,58} Outcomes in patients with this mutation appear largely to be determined by stage of disease. Patients with CML in CP at the time of detection often have an indolent disease course; in one retrospective study, 87% of such patients remained alive for 2 years after detection.⁶⁰ However, outcomes in advanced disease were worse, with median survival times of 14 and 4 months following detection in patients with CML in AP and BP, respectively. In this study, the presence of T315I following treatment failure did not confer worse survival compared with the presence of other or no BCR-ABL mutations.⁶⁰ However, in another retrospective study, the presence of T315I was associated with poor prognostic features, including a low CCyR rate in response to imatinib (59%) and disease progression.⁶¹ Differences between these two studies may be attributable to small sample sizes as well as differences in patient selection and type of intervention after detection of mutation. However, both studies demonstrated that the presence of T315I was associated with lack of response to second-generation BCR-ABL inhibitors.^{60,61} According to ELN guidelines, the appearance of a T315I mutation is a sign of treatment failure for all available BCR-ABL inhibitors²⁵; patients who harbor this mutation should be considered for aSCT or participation in clinical trials of novel agents (eg, ponatinib, DCC2036, omacetaxine).

Certain mutations within the ATP P-loop of the BCR-ABL kinase domain, including Y253F/H and E255K/V, are highly resistant to imatinib (Table 3).^{62–64} Two studies, in which patients were treated with imatinib alone (no crossover to second-line treatment), demonstrated that patients harboring P-loop mutations had particularly poor outcomes.^{62,64} In contrast, a study in which second-generation BCR-ABL inhibitors were available did not show worse outcomes in patients with P-loop mutations, confirming the higher activity of these compounds against these mutations (Table 3).⁶⁵ In total, 46% of patients with P-loop

mutations in this study received either dasatinib or nilotinib. More recently, it was confirmed that mutations in the P-loop (excluding those at residue 244) are associated with a higher risk of disease progression than those located elsewhere.⁵⁶ However, not all P-loop mutations are associated with the same level of sensitivity to imatinib or other BCR-ABL inhibitors (Table 3) or provide the same level of proliferative advantage, and this may confound the interpretation of study results. Despite the historical convenience of discussing geographical groupings of mutations, it is more valuable to discuss the frequency and resistance to BCR-ABL inhibitors of individual mutations. Detection of highly resistant mutations, such as the Y253F/H and E255K/V mutations, should be regarded as treatment failure in line with ELN guidelines,²⁵ and imatinib therapy should be halted accordingly.

Nilotinib exhibits activity against most imatinib-resistant mutations, except T315I, and is relatively ineffective in vitro to a few commonly occurring mutations, including Y253F/H, E255K/V, and F359V (Table 3). In the pivotal phase II study of nilotinib in patients resistant to imatinib, no CCyR was observed in patients with Y253F/H or E255K/V mutations.^{54,66} These mutations develop relatively often during nilotinib therapy and are associated with disease progression.⁶⁷ Nilotinib treatment failure has been shown to be associated most frequently with mutations in residues 253, 255, 359, and 311.⁶⁸

Dasatinib also has activity against most imatinib-resistant mutations tested, except T315I.^{53,69–71} Dasatinib is less active against E255K/V than against other common mutations, but its activity against these mutations generally is higher than that of imatinib or nilotinib (Table 3).²⁵ One exception is that dasatinib has less activity against V299L or F317L than imatinib or nilotinib; clinical resistance to dasatinib has been linked to mutations at residue 315 and, less commonly, residues 299 and 317.^{68,72,73}

Molecular Monitoring and Treatment Guidelines

Vigilant monitoring aids in the proper follow-up of patients and identification of optimal response, and ensures that patients receive the most suitable therapy as early in the disease course as possible (Table 1). ELN guidelines recommend measuring BCR-ABL transcript levels using RT-PCR during treatment every 3 months until achievement of MMR, and every 6 months thereafter.²⁵ Molecular data provide prognostic information, because patients who achieve MMR have a very low incidence of relapse. In contrast, failure to achieve MMR by 18 months or loss of MMR at any time is evidence of a suboptimal response and should lead to a reassessment of treatment options.²⁵ Increases in BCR-ABL transcript level also should prompt an inquiry into adherence. Moreover, RT-PCR data may vary by approximately 0.5- to 1-log depending on the analyzing laboratory. Thus, small variations in BCR-ABL transcript level, particularly those less than 1-log, should be interpreted with caution and confirmed by repeated testing before a change in therapy is considered.

In patients with suboptimal response, ELN recommendations consider the option of increasing the dose of imatinib to 600 or 800 mg/day or switching to a second-generation BCR-ABL inhibitor.^{25,26} To date, however, it has not been demonstrated conclusively that increasing imatinib dosage alters the long-term outcome of patients with molecular suboptimal responses compared with patients who continue treatment with standard-dose

imatinib. Results of one study suggested that low trough imatinib levels may reduce the probability of molecular responses to standard-dose imatinib⁷⁴; however, these results could not be replicated by Forrest and colleagues,⁷⁵ who found no correlation of mean plasma trough imatinib levels and CCyR or MMR. Results of a study that specifically examined the effect of dose escalation in patients with primary suboptimal molecular response found that high-dose imatinib was associated with MMR in 38% of patients,⁷⁶ but the small size of the sample (n=13) precludes drawing firm conclusions. Data are available from 2 studies investigating dose escalation in patients with suboptimal responses according to ELN criteria. In one study, MMRs were achieved in 5% of patients who received an escalated dose of imatinib.⁷⁷ In the other study, MMR was achieved in 1 of 9 patients with suboptimal response (8 of whom were unable to achieve MMR at 18 months) who received an escalated dose of imatinib.⁷⁸ Notably, the small sample size in these studies limits the interpretation of these findings. Even when BCR-ABL transcript levels were shown to decrease after dose escalation, it was not demonstrated that this affects long-term outcomes. Results from another study did not support dose escalation in response to suboptimal responses.⁷⁹ Furthermore, dose escalation to 600 mg/day may reduce patient adherence,⁸⁰ most likely due to associated toxicity.

Nilotinib treatment in patients with suboptimal cytogenetic response at 6 or 12 months has been shown to be associated with higher CHR, MCyR, and CCyR rates and faster time to CHR and MCyR versus patients with imatinib resistance.⁸¹ Nilotinib treatment has also been shown to be associated with high MMR rates in patients with prior suboptimal molecular response to imatinib.⁸² These data suggest that second-generation BCR-ABL inhibitors may provide a better benefit-risk ratio than dose-escalated imatinib in patients with suboptimal response.

As discussed above, secondary resistance is often caused by the acquisition of point mutations in the ABL kinase domain. Assessment of mutations in patients who have clinical evidence of treatment failure or suboptimal response facilitates selection of the most appropriate second-line treatment in some instances, based on the sensitivity of the specific mutation to dasatinib or nilotinib. Mutation analyses are recommended by the ELN following treatment failure or a suboptimal response.²⁵ ELN guidelines do not currently recommend mutation analyses at baseline in newly diagnosed CP patients²⁵; however, newly diagnosed patients with advanced disease may benefit from screening, as mutations occasionally antecede BCR-ABL inhibitor therapy. Studies have shown that mutations are most common in patients with secondary resistance and advanced disease.^{65,83} It has not been shown that these pre-existing mutations adversely affect outcome with BCR-ABL inhibitor therapy.⁸⁴

If an imatinib-resistant mutation suggestive of treatment failure is detected in a clinically stable patient, an appropriate second-line BCR-ABL inhibitor may be considered (unless there is a T315I mutation, in which case aSCT or a therapeutic trial of a novel agent should be considered). However, almost all clinical data on changing therapy has been obtained after clinical evidence of response failure, not by detection of mutations alone.

A second potential cause of decreased efficacy is low organic cation transporter-1 (OCT-1) activity, which reduces cellular drug influx. Recently, it was shown that patients with high OCT-1 activity had a greater MMR rate at 60 months (89% vs 55%; $P=0.007$), a higher OS (96% vs 87%; $P=0.028$), a higher EFS (74% vs 48%; $P=0.03$), and a lower BCR-ABL mutation rate (4% vs 21%; $P=0.047$).⁸⁵ It has been proposed that higher doses of imatinib may counteract such resistance, although both dasatinib and nilotinib are unaffected by OCT-1 activity.^{86–89} However, assessment of OCT-1 activity is not a clinically available test and thus cannot be used as a routine tool for clinical decision making.

Continued molecular monitoring throughout treatment is recommended even if a sustained CCyR has been achieved. For patients with early CP, IRIS data suggest a very low progression rate in patients with a stable CCyR.⁹⁰ Nevertheless, routine monitoring continues to be recommended because it allows the detection of changes that may indicate poor adherence and helps to identify development of resistance well before loss of CHR or transformation to AP or BP disease, when the probability of response to salvage therapy is much lower.

At present, there are no published data to suggest that switching treatment in response to increased BCR-ABL transcript levels in patients with CCyR improves long-term outcome. However, evidence of increasing disease burden, as manifested by increasing BCR-ABL transcript levels, may be a signal to increase vigilance, assess adherence to therapy, and optimize therapy (eg, returning to standard-dose therapy in patients with prior dose reductions, provided no further toxicity is encountered) before deciding on therapy changes. Enrollment in a clinical trial examining early detection and treatment is recommended. Treatment options in response to potentially negative molecular data, according to current ELN guidelines, are summarized in Figure 1.

Conclusion

Early identification of imatinib failure may increase the probability that alternative treatments will be effective. Therefore, vigilant and effective monitoring of a patient's response to treatment is vital. However, before earlier interventions are broadly recommended, clinical trials are needed to compare the effects on outcomes of early intervention (at the time of changes in BCR-ABL transcript levels) versus intervention when clinically evident relapse is documented. Although early treatment response and attainment of the lowest possible BCR-ABL transcript levels (undetectable if possible) are desirable therapeutic goals, MMR should be considered a measure of treatment success. At the same time, lack of MMR should not necessarily be considered a sign of treatment failure.

Acknowledgments

The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise. They also wish to acknowledge StemScientific, funded by Bristol-Myers Squibb, for providing writing and editing support. Bristol-Myers Squibb did not influence the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

Hagop Kantarjian has received research support from Bristol-Myers Squibb, Pfizer, Ariad, and Novartis, and has served as a consultant for Novartis; Jorge Cortes has received research support from Bristol-Myers Squibb, Novartis and Pfizer, and has served as a consultant for Novartis, Bristol-Myers Squibb, Chemgenex, Ariad, and Pfizer.

References

1. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999; 340:1330–40. [PubMed: 10219069]
2. Alvarez RH, Kantarjian H, Cortes JE. The biology of chronic myelogenous leukemia: implications for imatinib therapy. *Semin Hematol*. 2007; 44(suppl 1):S4–14. [PubMed: 17292736]
3. National Comprehensive Cancer Network. [Accessed July 25, 2011] NCCN Clinical Practice Guidelines in Oncology™. Chronic myelogenous leukemia. Version 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdfhttp://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
4. Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science*. 1960; 132:1497.
5. Rowley JD. A new consistent abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature*. 1973; 243:290–3. [PubMed: 4126434]
6. Bartram CR, de Klein A, Hagemeijer A, et al. Translocation of c-abl oncogene correlates with the presence of a Philadelphia chromosome in chronic myelocytic leukaemia. *Nature*. 1983; 306:277–80.
7. Groffen J, Stephenson JR, Heisterkamp N, et al. Philadelphia chromosome breakpoints are clustered within a limited region, bcr, on chromosome 22. *Cell*. 1984; 36:93–9. [PubMed: 6319012]
8. Lugo TG, Pendergast AM, Muller AJ, et al. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. *Science*. 1990; 247:1079–82. [PubMed: 2408149]
9. Quintás-Cardama A, Cortes J. Molecular biology of *bcr-abl*-positive chronic myeloid leukemia. *Blood*. 2009; 113:1619–30. [PubMed: 18827185]
10. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med*. 1996; 2:561–6. [PubMed: 8616716]
11. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003; 348:994–1004. [PubMed: 12637609]
12. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006; 355:2408–17. [PubMed: 17151364]
13. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol*. 2008; 26:3358–63. [PubMed: 18519952]
14. Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. *Cancer*. 2007; 109:1556–60. [PubMed: 17342766]
15. Fullmer A, Kantarjian H, Cortes J, et al. New developments in the treatment of chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukemia. *Leuk Lymphoma*. 2011; 52(suppl 1):81–91. [PubMed: 21299461]
16. Rosti G, Palandri F, Castagnetti F, et al. Nilotinib for the frontline treatment of Ph+ chronic myeloid leukemia. *Blood*. 2009; 114:4933–8. [PubMed: 19822896]
17. Cortes JF, Jones D, O'Brien S, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol*. 2010; 28:392–7. [PubMed: 20008621]
18. Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2010; 28:398–404. [PubMed: 20008620]
19. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010; 362:2260–70. [PubMed: 20525995]
20. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010; 362:2251–9. [PubMed: 20525993]
21. Sprycel (dasatinib) tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2010.
22. Radich JP, Oehler V. Monitoring chronic myelogenous leukemia in the age of tyrosine kinase inhibitors. *J Natl Compr Canc Netw*. 2007; 5:497–504. [PubMed: 17509253]

23. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood*. 2002; 99:3530–9. [PubMed: 11986204]
24. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood*. 2002; 99:1928–37. [PubMed: 11877262]
25. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol*. 2009; 27:6041–51. [PubMed: 19884523]
26. Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukemia. *Lancet*. 2007; 370:342–50. [PubMed: 17662883]
27. Marin D, Milojkovic D, Olavarria E, et al. European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. *Blood*. 2008; 112:4437–44. [PubMed: 18716134]
28. Alvarado Y, Kantarjian H, O'Brien S, et al. Significance of suboptimal response to imatinib, as defined by the European LeukemiaNet, in the long-term outcome of patients with early chronic myeloid leukemia in chronic phase. *Cancer*. 2009; 115:3709–18. [PubMed: 19517462]
29. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the international randomized study of interferon versus STI571 (IRIS). *Blood*. 2010; 116:3758–65. [PubMed: 20679528]
30. Press RD, Galderisi C, Yang R, et al. A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. *Clin Cancer Res*. 2007; 13:6136–43. [PubMed: 17947479]
31. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. *J Clin Oncol*. 2009; 27:3659–63. [PubMed: 19487383]
32. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science*. 2001; 293:876–80. [PubMed: 11423618]
33. Bocchia M, Ippoliti M, Gozzetti A, et al. CD34+/Ph+ cells are still detectable in chronic myeloid leukemia patients with sustained and prolonged complete cytogenetic remission during treatment with imatinib mesylate. *Leukemia*. 2008; 22:426–8. [PubMed: 17690698]
34. Columbat M, Fort M-P, Chollet C, et al. Molecular remission in chronic myeloid leukemia patients with sustained complete cytogenetic remission after imatinib mesylate treatment. *Haematologica*. 2006; 91:162–8. [PubMed: 16461299]
35. Branford S, Seymour JF, Grigg A, et al. BCR-ABL messenger RNA levels continue to decline in patients with chronic phase chronic myeloid leukemia treated with imatinib for more than 5 years and approximately half of all first-line treated patients have stable undetectable BCR-ABL using strict sensitivity criteria. *Clin Cancer Res*. 2007; 13:7080–5. [PubMed: 18056186]
36. Branford S, Lawrence R, Grigg A, et al. Long term follow up of patients with CML in chronic phase treated with first-line imatinib suggests that earlier achievement of a major molecular response leads to greater stability of response [abstract]. *Blood*. 2008; 112:2113.
37. Hess G, Meyer RG, Schuch B, et al. Sustained remissions and low rate of BCR-ABL resistance mutations with imatinib treatment chronic myelogenous leukemia in patients treated in late chronic phase. *Am J Hematol*. 2008; 83:178–84. [PubMed: 17876770]
38. Mahon F-X, Rea D, Guilhot F, et al. Discontinuation of imatinib therapy after achieving a molecular response in chronic myeloid leukemia patients [abstract]. *Blood*. 2009; 114:859.
39. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003; 349:1423–32. [PubMed: 14534335]
40. Cortes J, Talpaz M, O'Brien S, et al. Molecular responses in patients with chronic myelogenous leukemia in chronic phase treated with imatinib mesylate. *Clin Cancer Res*. 2005; 11:3425–32. [PubMed: 15867244]

41. Iacobucci I, Saglio G, Rosti G, et al. Achieving a major molecular response at the time of a complete cytogenetic response (CCgR) predicts a better duration of CCgR in imatinib-treated chronic myeloid leukemia patients. *Clin Cancer Res*. 2006; 12:3037–42. [PubMed: 16707599]
42. Qin Y, Jiang B, Jiang Q, et al. Molecular responses of late chronic phase chronic myeloid leukemia patients after achieving complete cytogenetic responses with imatinib treatment: a 6-year follow-up. *Ann Hematol*. 2009; 88:37–41. [PubMed: 18651143]
43. Press RD, Love Z, Tronnes AA, et al. BCR-ABL levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. *Blood*. 2006; 107:4250–6. [PubMed: 16467199]
44. Kantarjian H, O'Brien S, Shan J, et al. Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia. *Cancer*. 2008; 112:837–45. [PubMed: 18085610]
45. Pavlovsky C, Giere I, Lombardi V, et al. Monitoring response to imatinib by quantitative real-time polymerase chain reaction (RQ-PCR) in chronic phase, chronic myeloid leukemia patients in complete cytogenetic remission [abstract]. *J Clin Oncol*. 2008; 26(suppl):18013a.
46. Palandri F, Iacobucci I, Soverini S, et al. Treatment of Philadelphia-positive chronic myeloid leukemia with imatinib: importance of a stable molecular response. *Clin Cancer Res*. 2009; 15:1059–63. [PubMed: 19188180]
47. Merx K, Müller MC, Kreil S, et al. Early reduction of BCR-ABL mRNA transcript levels predicts cytogenetic response in chronic phase CML patients treated with imatinib after failure of interferon alpha. *Leukemia*. 2002; 16:1579–83. [PubMed: 12200666]
48. Wang L, Pearson K, Ferguson JE, et al. The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia. *Br J Haematol*. 2003; 120:990–9. [PubMed: 12648069]
49. Quintás-Cardama A, Kantarjian H, Jones D, et al. Delayed achievement of cytogenetic and molecular response is associated with increased risk of progressions among patients with chronic myeloid leukemia in early chronic phase receiving high-dose or standard-dose therapy. *Blood*. 2009; 113:6315–21. [PubMed: 19369233]
50. Branford S, Rudzki Z, Harper A, et al. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Leukemia*. 2003; 17:2401–9. [PubMed: 14523461]
51. Kantarjian HM, Talpaz M, Giles F, et al. New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. *Ann Intern Med*. 2006; 145:913–23. [PubMed: 17179059]
52. Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. *Blood*. 2004; 104:2926–32. [PubMed: 15256429]
53. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood*. 2007; 109:2303–9. [PubMed: 17138817]
54. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007; 110:3540–6. [PubMed: 17715389]
55. Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib (100 mg once daily) preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2008; 226:3204–12.
56. Khorashad JS, de Lavallade H, Apperley JF, et al. Finding of kinase domain mutations in patients with chronic phase chronic myeloid leukemia responding to imatinib may identify those at high risk of disease progression. *J Clin Oncol*. 2008; 29:4806–13.
57. Branford S, Goh H, Izzo B, et al. A review of mutation analysis in the TOPS trial of standard dose versus high dose IM in CML suggests that refinements to the ELN recommendations for mutation screening may be appropriate [abstract]. *Blood*. 2010; 116:889.
58. Apperley JF. Part I: mechanisms of resistance to imatinib in chronic myeloid leukemia. *Lancet Oncol*. 2007; 8:1018–29. [PubMed: 17976612]

59. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood*. 2005; 105:2640–53. [PubMed: 15618470]
60. Jabbour E, Kantarjian H, Jones D, et al. Characteristics and outcome of patients with chronic myeloid leukemia and T315I mutation following failure of imatinib mesylate therapy. *Blood*. 2008; 112:53–5. [PubMed: 18403620]
61. Nicolini FE, Hayette S, Corm S, et al. Clinical outcome of 27 imatinib mesylate-resistant chronic myelogenous leukemia patients harboring a T315I BCR-ABL mutation. *Haematologica*. 2007; 92:1238–41. [PubMed: 17768119]
62. Branford S, Rudzki Z, Walsh S, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. *Blood*. 2003; 102:276–83. [PubMed: 12623848]
63. O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res*. 2005; 65:4500–5. [PubMed: 15930265]
64. Soverini S, Martinelli G, Rosti G, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. *J Clin Oncol*. 2005; 23:4100–9. [PubMed: 15867198]
65. Jabbour E, Kantarjian H, Jones D, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. *Leukemia*. 2006; 20:1767–73. [PubMed: 16855631]
66. Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. *J Clin Oncol*. 2009; 27:4204–10. [PubMed: 19652056]
67. Branford S, Shou Y, Lawrence R, et al. The P-loop mutations Y235H and E255K/V may develop more frequently than T315I during nilotinib therapy after imatinib failure and are associated with progression in patients with Ph-positive leukemia [abstract]. *Haematologica*. 2007; 92(suppl 1): 337–8.
68. Cortes J, Jabbour E, Kantarjian H, et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. *Blood*. 2007; 110:4005–11. [PubMed: 17785585]
69. Cortes J, Rousselot P, Kim D-W, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood*. 2007; 109:3207–13. [PubMed: 17185463]
70. Guilhot F, Apperley J, Kim DW, et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood*. 2007; 109:4143–50. [PubMed: 17264298]
71. Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance to intolerance to imatinib: Interim results of a phase II study. *Blood*. 2007; 110:2309–15. [PubMed: 17496201]
72. Soverini S, Colarossi S, Gnani A, et al. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. *Haematologica*. 2007; 92:401–4. [PubMed: 17339191]
73. Müller MC, Cortes JC, Kim D-W, et al. Dasatinib treatment of chronic phase chronic myeloid leukemia: analysis of responses according to pre-existing BCR-ABL mutations. *Blood*. 2009; 114:4944–53. [PubMed: 19779040]
74. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood*. 2007; 109:3496–9. [PubMed: 17192396]
75. Forrest DL, Trainor S, Brinkman RR, et al. Cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia are correlated with Sokal risk scores and duration of therapy but not trough imatinib plasma levels. *Leukemia Res*. 2009; 33:271–5. [PubMed: 18762338]

76. Rea D, Etienne G, Corm S, et al. Imatinib dose escalation for chronic phase-chronic myelogenous leukemia patients in primary suboptimal response to imatinib 400 mg daily standard therapy. *Leukemia*. 2009; 23:1193–6. [PubMed: 19242496]
77. Kim DY, Kim HJ, Jeong JS, et al. Efficacy of imatinib mesylate dose-escalation in CML patients showing suboptimal response to standard dose [abstract]. *Blood*. 2007; 110:2967.
78. Jabbour E, Kantarjian H, Atallah E, et al. Impact of imatinib mesylate dose escalation on resistance and sub-optimal responses to standard-dose therapy in patients (pts) with chronic myeloid leukemia (CML) [abstract]. *Blood*. 2007; 110:1035.
79. Batra U, Dasappa L, Lakshmiah KC, et al. Dose escalation of imatinib in CML patients with sub-optimal response to conventional dosage: is it worth it? [abstract]. *J Clin Oncol*. 2008; 26(suppl): 18026.
80. Sun SX, Fincher CL, Wang J, et al. Real-world adherence rates of chronic myeloid leukemia patients to higher doses of imatinib. *J Manag Care Pharm*. 2007; 13:705–6.
81. Nicolini FE, Kim D-W, Ceglarek B, et al. Impact of prior therapy and suboptimal response to imatinib on the efficacy and safety of nilotinib among 1,422 patients with imatinib-resistant or -intolerant chronic myeloid leukemia (CML) in chronic phase (CP): sub-analyses of the ENACT (Expanding Nilotinib Access in Clinical Trials) study [abstract]. *Blood*. 2009; 114:2201.
82. Yang AS, Jillella A, Miller CB, et al. Nilotinib-associated molecular responses achieved in chronic myeloid leukemia in chronic phase (CML-CP) patients with a suboptimal molecular response to imatinib [abstract]. *Blood*. 2009; 114:2206.
83. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. *Clin Cancer Res*. 2006; 12:7374–9. [PubMed: 17189410]
84. Willis SG, Lange T, Demehri S, et al. High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naïve patients: correlation with clonal cytogenetic evolution but not response to therapy. *Blood*. 2005; 106:2128–37. [PubMed: 15914554]
85. White DL, Dang P, Engler J, et al. Functional activity of the OCT-1 protein is predictive of long-term outcome in patients with chronic-phase chronic myeloid leukemia treated with imatinib. *J Clin Oncol*. 2010; 28:2761–7. [PubMed: 20421539]
86. White DL, Saunders VA, Dang P, et al. OCT-1-mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN107): reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. *Blood*. 2006; 108:697–704. [PubMed: 16597591]
87. White DL, Saunders VA, Dang P, et al. Most CML patients who have a suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity. *Blood*. 2007; 110:4064–72. [PubMed: 17761829]
88. Hiwase DK, Saunders V, Hewett D, et al. Dasatinib cellular uptake and efflux in chronic myeloid leukemia cells: therapeutic implications. *Clin Cancer Res*. 2008; 14:3881–8. [PubMed: 18559609]
89. Giannoudis A, Davies A, Lucas CM, et al. Effective dasatinib uptake may occur without human organic cation transporter 1 (hOCT1): implications for the treatment of imatinib-resistant chronic myeloid leukemia. *Blood*. 2008; 112:3348–54. [PubMed: 18669873]
90. Hochhaus A, Druker BJ, Larson RA, et al. IRIS 6-year follow-up: sustained survival and declining annual rate of transformation in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib [abstract]. *Blood*. 2007; 110:25a.

Figure 1.
Treatment Algorithm in Response to Changes in BCR-ABL Transcript Levels in Patients With CML in CP Treated With First-Line Imatinib²⁵

Table 1Common Response Definitions and Monitoring Guidelines²⁵

Response	Definition	Monitoring
Hematologic CHR	Platelet count $<450 \times 10^9/L$; WBC count $<10 \times 10^9/L$; normal differential and with $<5\%$ basophils; nonpalpable spleen	Check at diagnosis, then every 15 days until a CHR is achieved and confirmed; subsequently every 3 months unless clinically required
Cytogenetic None Minor MCyR PCyR CCyR	Ph+ metaphases $>95\%$ Ph+ metaphases $>35\%–95\%$ Ph+ metaphases $0\%–35\%$ Ph+ metaphases $1\%–35\%$ Ph+ metaphases 0%	Check at diagnosis, then at 3 and 6 months, then every 6 months until a CCyR achieved and confirmed; subsequently every 12 months if regular molecular monitoring cannot be guaranteed
Molecular MMR	BCR-ABL/control gene ratio according to international scale 0.10	Check every 3 months until an MMR has been achieved and confirmed, then at least every 6 months; perform mutational analysis following failure or suboptimal response, and always before changing treatment

Abbreviations: CHR = complete hematologic response; CCyR = complete cytogenetic response; MCyR = major cytogenetic response; MMR = major molecular response; WBC = white blood cell

Table 2

ELN Time-Based Landmarks of Optimal and Suboptimal Responses and Treatment Failure During First-Line Imatinib Treatment <<Permission requested; to be forwarded upon receipt>>

Class of Response	Time of Assessment			
	3 months	6 months	12 months	18 months
Optimal	CHR, and at least a minor CyR	At least PCyR	CCyR	MMR
Suboptimal	No CyR	Less than PCyR	PCyR	Less than MMR
Failure	Less than CHR	No CyR	Less than PCyR	Less than CCyR

Abbreviations: CHR = complete hematologic response; CyR = cytogenetic response; CCyR = complete cytogenetic response; HR = hematologic response; MMR = major molecular response; PCyR = partial cytogenetic response

Adapted from Baccarani et al.²⁵

Table 3

The Most Commonly Occurring BCR-ABL Mutations and Their Relative Sensitivity to BCR-ABL Inhibitors⁹

Mutation	Location	Sensitivity/IC50, Fold Increase Over Native BCR-ABL		
		Imatinib	Nilotinib	Dasatinib
T315I	ATP binding region	>24.6	>153.9	>250.0
Y253F	P-loop	13.4	9.6	1.8
Y253H	P-loop	>24.6	34.6	1.6
E255K	P-loop	20.0	15.4	7.0
E255V	P-loop	>24.6	33.1	13.8
M351T	Catalytic domain	3.4	1.2	1.4
G250E	P-loop	5.2	3.7	2.3
F359V	catalytic domain	7.0	13.5	2.8
H396P	A-loop	3.3	3.1	0.8
H396R	A-loop	6.7	3.2	1.6

Mutations are shown in descending order of frequency.⁵⁸