Focus on Molecular Monitoring in CML: What You Need to Know for Clinical Practice CME/CE

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Title:

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CME Information:

Target Audience

This activity is intended for hematologists, hematologic oncologists, pathologists, oncology nurses, and other healthcare professionals involved in the diagnosis and treatment of patients with chronic myeloid leukemia (CML).

Goal

The goal of this activity is to explore hematologic, cytogenetic, and molecular monitoring to guide therapeutic decision making in patients with CML receiving tyrosine kinase inhibitor (TKI) therapy.

Learning Objectives

Upon completion of this activity, participants will be able to:

Explain the rationale, methodology, and recommended timing of hematologic, cytogenetic, and molecular monitoring in patients with CML receiving TKI therapy

Use hematologic, cytogenetic, and molecular monitoring in the management of patients with CML to assess response to TKI therapy

Interpret results of hematologic, cytogenetic, and molecular assessments to guide therapeutic decision making in patients with CML

Credits Available

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Pathophysiology

Chronic myeloid leukemia (CML) is characterized by the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 that places the upstream 5' exons of the *BCR* (breakpoint cluster region) gene from chromosome 22 in juxtaposition with the *ABL* (Abelson) gene exons from chromosome 9 that encode the tyrosine kinase domain (TKD). The resulting abnormal tyrosine kinase activity of the BCR-ABL fusion protein both drives CML pathology and represents the therapeutic target for tyrosine kinase inhibitors (TKIs). The unique t(9;22) chromosome is a specific diagnostic target for cytogenetic and molecular tests, allowing sensitive monitoring of disease burden. Three TKIs are now widely available to clinicians and their patients: imatinib mesylate and 2 second-generation TKIs, nilotinib and dasatinib.

Current State of Affairs in Chronic Myeloid Leukemia

Tyrosine Kinase Inhibitor Therapy Is Remarkably Effective

Imatinib is highly effective in chronic-phase CML. Approximately 80% of patients with chronic-phase CML will achieve complete cytogenetic remission (CCyR), and those who achieve a CCyR have excellent survival rates.[1] A 6-year follow-up of the pivotal phase 3 study in patients with chronic-phase CML (International Randomized Study of Interferon and STI571 [IRIS]) showed rates of event-free survival and freedom from progression to advanced disease of 83% and 93%, respectively[2,3]; the 8-year follow-up continues to show a stability of response, with corresponding values of 82% and 92%.[4] Patients who achieved CCyR at 12 months were less likely to progress to advanced disease (progression-free rates, 100% vs 85%; $P < .001$) than those who did not achieve CCyR.[5].

The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) have similar recommendations for the management of patients with CML.[6,7] The ELN defines CCyR at 12 months as an optimal treatment response.[7] Both the NCCN and ELN recommend that patients with chronic-phase CML start with an imatinib dose of 400 mg/day. Imatinib is considered to have failed in patients who do not obtain a complete hematologic response by 3 months, any cytogenetic response by 6 months, major cytogenetic response by 12 months, or CCyR within 18 months of the start of therapy; these patients should receive second-line treatment with a second-generation TKI.

Resistance in Chronic-Phase Disease Is Unusual, but Serious

Unfortunately, a substantial proportion of patients either cannot tolerate imatinib or are resistant to it. Using the ELN response criteria, retrospective analyses of past studies suggest that approximately 25% of patients with early chronic-phase disease had suboptimal response to imatinib or treatment failure.[7] An additional 5% to 10% of patients are intolerant of imatinib.

Imatinib-Resistant Disease Can Be Treated, but Progression Is a Problem

There are various approaches to treating patients with imatinib-resistant disease, all of which focus on delivering more ABL inhibition. Increasing the imatinib dose can occasionally be effective but has become less attractive with the introduction of dasatinib and nilotinib, 2 second-generation TKIs approved by the US Food and Drug Administration for the treatment of patients with imatinib-resistant CML or who cannot tolerate imatinib.[8] Both agents are effective in patients with resistant disease, yielding CCyR in approximately 50% of cases of chronic-phase CML; in patients who discontinue imatinib because of drug intolerance, CCyR rates are greater than 70%.[9]

Molecular Monitoring Can Predict Response to Therapy and Disease Progression

CCyR is a treatment endpoint highly correlated with long-term outcome. Molecular monitoring using polymerase chain reaction (PCR) is a sensitive assay that can measure disease burden in CCyR cases and may identify patients at higher risk of resistance or relapse.[10-13]

Clinicians who care for patients with CML are fortunate to have highly effective initial therapy, good secondary therapy, and a way to monitor patients carefully to shape optimal therapy. How should monitoring be approached in the real world, apart from the relative order of the clinical trial?

Methods of Determining Response

There are several tests to measure disease state and burden, and, as one might expect, greater complexity is required to gain sensitivity. Widely available clinical tests are shown in Table 1,[14] and sensitivity in the clinical context is shown in Figure 1.[14]

Table 1. Methods to Detect Minimal Residual Disease in Chronic Myelogenous Leukemia

Method	Target	Sensitivity	Advantages	Disadvantages
Morphology	Cellular morphology	5%	Standard	Poor sensitivity
Cytogenetics	Chromosome structure	1%-5%	Widely available	Low sensitivity Bone marrow only
FISH*	Specific genetic markers	0.1%-5%	Fast (1-2 days)	Does not detect other clonal events
Quantitative PCR	RNA sequence	0.001%-0.01%	Very sensitive	Poor standardization Laboratory intensive

CML = chronic myeloid leukemia; FISH = fluorescence in situ hybridization; PCR = polymerase chain reaction

[a]Depends on disease, number of probes, used and number of nuclei scored

From Radich JP. *Blood*. 2009;114:3376-3381.[14]

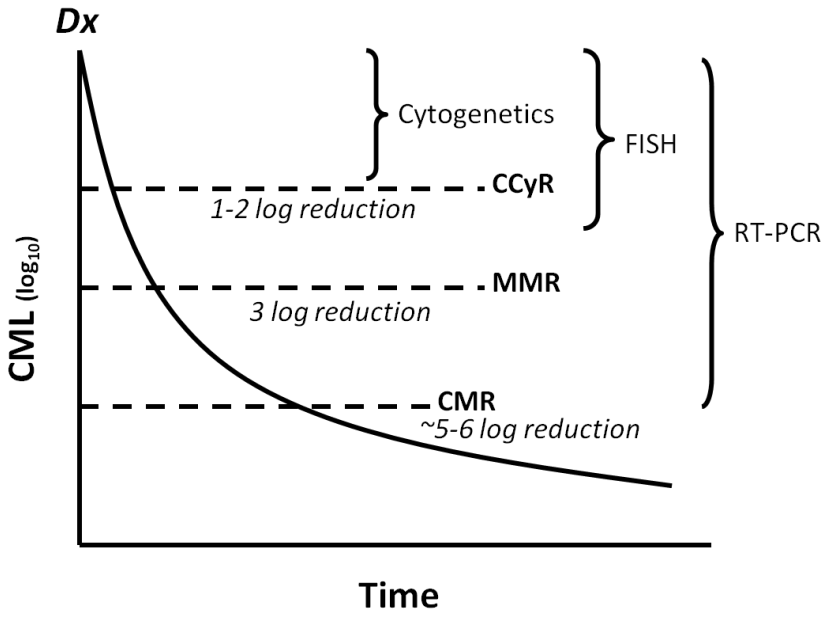

Figure 1. Disease burden and tests. The figure shows the reduction of CML burden and the sensitivity of assays (plot not to scale).Routine cytogenetic analysis will fail to detect the Philadelphia chromosome (CCyR) after a 1-2 log reduction in CML burden. The detection limit of reverse-transcriptase PCR is approximately a 5- to 6-log reduction in disease burden. From Radich JP. *Blood.* 2009;114:3376-3381.[14]

Cytogenetic Analysis

Bone marrow examination at diagnosis provides information on morphology (important for diagnosis and blast count for phase determination), and cytogenetics (which identifies the Philadelphia chromosome and other clonal abnormalities indicative of advanced phase disease). The conventional metaphase cytogenetic examination is still the gold standard of early TKI response, and cytogenetic analysis has the strongest prognostic value. Cytogenetic analysis generally must be performed on bone marrow rather than peripheral blood, as it requires proliferating cells. Also, to gauge cytogenetic response (Table 2),[14] at least 20 metaphase preparations must be examined.

Fluorescence In Situ Hybridization

Molecular cytogenetic analysis can be performed using FISH probes for the fusion of BCR and ABL DNA. Metaphase (dividing) and interphase (nondividing) cells can be used, and thus FISH can be done on cells extracted from bone marrow or peripheral blood. FISH is more sensitive than cytogenetic analysis but less sensitive than PCR (see below). At diagnosis, FISH is not a substitute for cytogenetic analysis, because FISH can detect the Philadelphia chromosome but not other clonal chromosomal changes that suggest advanced-phase disease. Thus, most expert panels advocate using FISH as a diagnostic tool only when bone marrow cannot be obtained.

Polymerase Chain Reaction

The most sensitive approach to detect CML is quantitative PCR of chimeric *BCR-ABL* mRNA. Quantitative PCR can generally detect 1 CML cell in approximately 100,000 normal cells. A major benefit of quantitative PCR is that peripheral blood can be used rather than bone marrow, making monitoring relatively noninvasive. In general, the quantity of *BCR-ABL* mRNA is standardized against a reference "housekeeping gene" (eg, *BCR, ABL,* or *GUSB*). A common measure of relative CML response is the magnitude of reduction in *BCR-ABL* transcripts from a standardized baseline value,[5] and the major molecular response (MMR) is defined as a 3-log or greater reduction in the *BCR-ABL*/control gene ratio.

The major problem with quantitative PCR for *BCR-ABL* is a lack of standardization across reference laboratories. Different laboratories use different control reference genes, and thus the ratio of *BCR-ABL*/control gene differs. There is a movement to standardize *BCR-ABL* testing and reporting; a standardized international scale has been proposed by the National Institutes of Health Consensus Group, which uses the baseline values defined in the IRIS trial to represent 100% and fixes a 3-log reduction from the standardized baseline (MMR) at 0.10% and CCyR at approximately 1%.[12] There are a few limitations to the adoption of the international scale, however. First, because the calibration was performed by one central laboratory in Australia, it has been very difficult for many laboratories to quickly have their assay evaluated and given a laboratory-specific correction factor to convert local values to the international scale. Moreover, the international scale does not control for sensitivity of a local assay -- that is, each laboratory may have different levels of detection. This may affect the definition of complete molecular remission (CMR).

Response Criteria

Clinically useful levels of differential disease response are shown in Table 2.[14] The clinical utility of these landmarks has been demonstrated in several studies and forms the basis of the ELN and NCCN guidelines.[6,7] For example, Figure 1 shows the decrease in CML burden in a patient treated with a TKI.

Table 2. Response Criteria in Chronic Myeloid Leukemia Treatment

Level of Response	Definition
Complete hematologic response	Normal CBC and differential
Minor cytogenetic response[a]	35%-90% Ph-positive metaphases
Partial cytogenetic response	1%-34% Ph-positive metaphases
Complete cytogenetic response	0% Ph-positive metaphases
Major molecular response	≥3-log reduction of *BCR-ABL* mRNA
Complete molecular remission	Negativity by reverse-transcriptase PCR

CBC = complete blood count; mRNA = messenger RNA; PCR = polymerase chain reaction; Ph = Philadelphia chromosome

[a]All cytogenetic response categories should be based on analysis of at least 20 metaphases
From Radich JP. *Blood*. 2009;114:3376-3381.[14]

Hematologic Response

The first treatment goal is the normalization of peripheral blood counts, which occurs in almost all patients with chronic-phase CML within 1-3 months after treatment initiation. Failure to achieve a complete hematologic response by 3 months is associated with a low likelihood of successful therapy, and meets failure criteria in the ELN and NCCN guidelines.

Cytogenetic Response

The next level of therapeutic response is measured by cytogenetic examination. The degree of cytogenetic response is based on the number of Philadelphia chromosome-positive metaphases. CCyR with no Philadelphia chromosome-positive metaphases is optimal, followed by partial cytogenetic response (PCyR) with 1%-34% Philadelphia chromosome-positive metaphases, then minor response (35%-90% Philadelphia chromosome-positive metaphases). Cytogenetic response is the strongest prognostic measure of treatment success: Cytogenetic response after 6 months of therapy is associated with the achievement of CCyR at 2 years**.** Patients with no response, minor response, or PCyR had a 15%, 50%, and 80% chance of achieving CCyR after 2 years of imatinib therapy, respectively.[2] At 12 months, patients with either no or minor cytogenetic response had a less than 20% chance of achieving CCyR, compared with 50% for those with PCyR.

Molecular Response

Once CCyR is achieved, more sensitive assays must be used to detect and quantify residual CML. In the IRIS trial, long-term response was measured by cytogenetic and molecular response at 12 months of therapy. At 24 months, overall PFS for patients without CCyR at 12 months was 85%. Among patients with CCyR, PFS was 95% for those who had a < 3-log reduction in BCR-ABL at 12 months and 100% for those who had a ≥ 3-log reduction in BCR-ABL.[5] Of the patients who achieved CCyR and MMR at 18 months, none progressed to accelerated or blast phase by 60 months of follow-up. Several subsequent studies have confirmed the IRIS PCR data and demonstrate that patients with a deeper molecular response (defined by the MMR) have very low odds of progression and superior PFS compared with patients with an inferior response.[15-18] Early monitoring after starting treatment with imatinib may also be useful in predicting response. The rate of decrease in BCR-ABL during the initial 2 or 3 months of imatinib therapy is a strong predictor of subsequent response, as patients with < 1-log reduction after 3 months had a 13% probability of achieving MMR after 2.5 years of follow-up, compared with >70% in patients with > 1-log response.[19] Cortes and colleagues found that patients who had a < 1-log reduction after 3 months of imatinib therapy had a 55% chance of ever achieving MMR at 2 years, compared with those who had a >1-log or > 2-log reduction, in whom MMR was achieved in 84% and 95%, respectively. [15]

Mutation Testing

Despite the success of imatinib in the treatment of chronic-phase CML, resistance to imatinib still occurs and provides the rationale for frequent molecular monitoring. A large proportion of resistance is caused by single point mutations in the *ABL* gene, which inhibits imatinib binding and thus allows resurgence of BCR-ABL kinase activity.[15-18] The prevalence of *ABL* mutations increases with "disease time"; that is, *ABL* mutations are rare in newly diagnosed chronic-phase disease and become far more prevalent in advanced-phase disease and chronic-phase disease that develops resistance.[20-22]

The screening of mutations is limited by the sensitivity of the available assays, because detection of a single point TKD mutation is a difficult task. The most common method of direct nucleotide sequencing can detect an *ABL* TKD mutation if it comprises 10%-20% of the total *BCR-ABL* sampled population. Other assays done in the research setting can improve the sensitivity by 10-fold or more.

The relatively poor sensitivity of these assays makes it difficult to identify point mutations early in the course of therapy. The routine screening of patients with chronic-phase disease and CCyR will detect a mutation in fewer than 5% of cases; the subsequent risk for relapse in these patients is approximately 4-fold higher than in those without a mutation, but such screening seems to be costly for the potential benefit. However, frequent monitoring by quantitative PCR can detect populations at a higher risk for relapse and mutation. Branford and co-workers [20] showed that 61% of patients with a > 2-fold increase in *BCR-ABL* had detectable mutations, compared with 0.6% of patients with stable or decreasing *BCR-ABL*.[20] Thus, screening for mutations would be reasonable in patients with advanced-phase disease; patients with chronic-phase disease who are not achieving cytogenetic milestones; and patients with increasing *BCR-ABL*, especially those with *BCR-ABL* values that are close to or higher than those that define MMR.

Common Questions From Community Physicians

Successful monitoring is time-dependent in that the specific response milestones rely on different tests at different times, owing to the increasing sensitivity of tests needed as response deepens.

Questions Related to the Initial Months of Therapy

Question 1: What is the most important measure of initial treatment success? Cytogenetic response is the first, and most proven, measure of treatment success. Achievement of any cytogenetic response after 6 months of imatinib therapy is associated with the likelihood of achieving CCyR at 2 years.

Question 2: When should I switch to another TKI? Guidelines from the ELN and NCCN suggest that patients have at least a major cytogenetic response by 12 months and CCyR at 18 months; patients who do not achieve this level of response should be given second-generation TKI therapy.[6,7] Response is considered suboptimal in patients who do not achieve CCyR by 12 months, and these patients can be considered for treatment with a second-generation TKI.

Question 3: What drug should I start with? As noted above, the second-generation TKIs nilotinib and dasatinib are effective in patients with imatinib resistance. Both drugs have been evaluated as first-line therapy in newly diagnosed chronic-phase CML. Two single-center trials of dasatinib and nilotinib have been performed at the University of Texas MD Anderson Cancer Center.[23,24] At 18-24 months, both agents showed a similarly small but consistent benefit in CCyR over historical controls treated in imatinib trials. A phase 2 study from Italy of nilotinib in patients with newly diagnosed chronic-phase disease showed a similarly high rate of CCyR of greater than 90% after 12 months of therapy.[25] Recently, the results of 2 randomized trials of nilotinib and dasatinib were published.[26,27] On the basis of these results, nilotinib has been approved by the US Food and Drug Administration for newly diagnosed patients, and dasatinib is now under consideration. The results of the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) trial showed an improvement in 12-month CCyR rates in the nilotinib arms compared with imatinib (80% with nilotinib 600 mg/day, 78% with nilotinib 800 mg/day, and 65% with imatinib 400 mg/day).[27] Moreover, the MMR rates were significantly higher in the nilotinib arms than the imatinib arm (44%, 43%, and 22%, respectively) (Table 3). Finally, fewer patients in the nilotinib arms progressed to advanced-phase disease (<1% in each nilotinib arm vs 4% in the imatinib arm). Similar results were reported in the dasatinib trial: 77% of patients receiving dasatinib achieved CCyR and 46% MMR, compared with 66% and 28%, respectively, of imatinib recipients.[26] However, both trials report only 12-month endpoints, and at this time, there were no differences in survival outcomes for any of the arms. Thus, it is unclear whether using second-generation TKIs up front rather than imatinib will have long-term advantages.

Table 3. Phase 3 Trial Results for Nilotinib and Dasatinib

Response at 12 Months	Imatinib 400 mg/day	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Dasatinib 100 mg/day
CCyR	65%[a]/66%[b]	80	78	77
MMR	22%[a]/28%[b]	44	43	46

CCyR = complete cytogenetic response; MMR = major molecular response

[a]Value from nilotinib trial
[b]Value from dasatinib trial
Data from Kantarjian H, et al.[26] and Saglio G, et al.[27]

Questions Related to Molecular Response

Question 1: What is the significance of MMR? In patients who have achieved CCyR, obtaining MMR is associated with a benefit in PFS and a low level of progression.[20-24] Long-term follow-up of patients in the IRIS trial demonstrates the outstanding prognosis of those who achieved MMR at 18 months. These patients have an event-free survival rate at 7 years of 95%; only 3% lost CCyR, and no patient had progression to the accelerated or blast phase.[4]

Question 2: Should increasing values of *BCR-ABL* on quantitative PCR be a reason for major concern? Increasing *BCR-ABL* values on quantitative PCR often cause great concern, if not (usually unnecessary) panic. These values may increase in a patient for several reasons, including adherence to therapy, assay variability, sampling variation (which is more of a problem at lower levels of disease burden), and relapse.

An increasing number of *BCR-ABL* transcripts that is validated by a repeat assay (usually around 1 month later) deserves attention. Studies suggest that increasing *BCR-ABL* transcript numbers are associated with increased risk for an *ABL* point mutation and resistance.[20-22] In addition, loss of MMR is associated with high risk for relapse and a reduction in PFS.[28] However, not all patients with increasing *BCR-ABL* transcript numbers (with or without a mutation) have relapse.[29-31]

Poor adherence to therapy can affect imatinib levels and therefore have a deleterious effect on treatment endpoints. The Adagio study[32] compared self-reported adherence to actual pill consumption. Sixty-four percent of patients self-reported perfect adherence, but the reality was much worse: Only 14% had perfect adherence, and 71% of patients were taking less than the prescribed dosage. Patients with perfect adherence had a CCyR rate of 91%, compared with 76% in patients with suboptimal adherence. A similar study showed that patients with > 90% adherence had an MMR rate of 94.5%, compared with only 28.4% in patients with 90% or less adherence to the prescribed drug schedule.[33] Thus, a poor treatment response or increasing BCR-ABL level may be due to poor adherence. Measurement of

plasma imatinib levels may be of some help, but this too can be misleading because it only reflects recent drug exposure.

Question 3: What is a reasonable approach to the patient with increasing *BCR-ABL* transcript numbers on quantitative PCR? The first response should be to repeat the test. If values are still increased, then testing for *ABL* mutations should be pursued. The next step depends on how much the *BCR-ABL* level has increased. For example, an increase from the lowest levels of detection (0.0001%) to a value even 10 times higher would still be well within the range of MMR (0.1%). However, a patient with values that begin at the MMR and increase above that level is heading toward cytogenetic relapse; in that situation, obtaining bone marrow aspirate to look for cytogenetic reoccurrence would be warranted.

Several studies have demonstrated that these mutations are associated with both an increase in loss of cytogenetic response and progression to advanced-phase disease.[25-27] However, in some cases, particularly in patients with a low disease burden, mutations are detected yet remain at a low level and do not cause problems.

Figure 2 shows several examples of an increasing *BCR-ABL* value. In case A, the level is increasing before MMR has been reached. Several studies have shown that this pattern is associated with a high risk for progression, and it therefore demands close attention.[14] Case B shows an increase in a patient with MMR; although these patients have a higher risk for relapse, the greatest risk is in those whose *BCR-ABL* levels exceed the MMR threshold.[14]

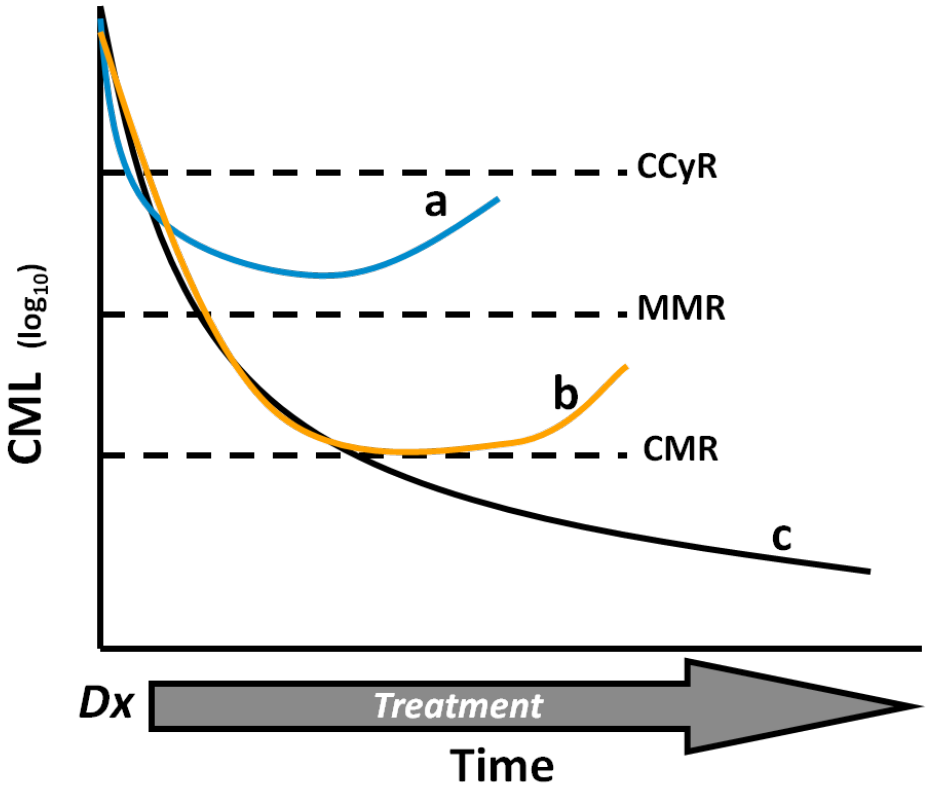

Figure 2. Monitoring scenarios. Curve "a" shows a patient with CCyR but not MMR who has increasing *BCR-ABL* values. This is a worrisome case that demands close follow-up (Table 3). Curve "b" shows a patient with CCyR and MMR and an increasing *BCR-ABL* value. This case requires follow-up but is not necessarily cause for major concern unless the increase continues, Curve "c" shows a patient with the best of circumstances: CCyR, MMR, and a stable or decreasing *BCR-ABL* value. From Radich JP. *Blood.* 2009;114:3376-3381.[14]

In cases A and B, there is no clear evidence that changing therapy in a patient with an increasing *BCR-ABL* level will change the natural history of disease. Ongoing clinical trials are addressing this issue.

Question 4: What do I do when I receive results of mutation testing? In patients with imatinib resistance, sequencing of the *ABL* kinase domain will detect a mutation in approximately half of cases. How does one use these data to change therapy?

There are limitations to the performance and interpretation of mutation testing. Most notably, these include how the assay is performed (and thus the sensitivity of detecting the mutated clone) and how the in vitro sensitivity of mutations are performed and calculated, However, along with clinical judgment, knowledge of the mutation type can help guide therapy.[34] For example, in studies of imatinib resistance,[35] the CCyR for patients with an *ABL* mutation switched to nilotinib was 32%, compared with 40% in those without a mutation. However, when evaluated by those mutations with good vs poor sensitivity to nilotinib, the CCyR for patients with sensitive mutations was 40%, compared with 0% for patients with poor sensitivity mutations, such as *E255K/V*, *F359C/V*, and *Y253H*. The same was found in dasatinib trials of imatinib resistance, in which patients with dasatinib-sensitive mutations had a CCyR of 53% vs 32% in those with poor-sensitivity mutations.[36] The nilotinib-insensitive mutations *E255K/V*, *F359C/V*, and *Y253H* are generally sensitive to dasatinib, whereas the poor-risk dasatinib mutation *F317L* and the infrequent *V299L* seem to be sensitive to nilotinib. Overall, about 40% of imatinib-resistant patients who harbor mutations will have a mutation that may influence decision-making (*T315I*, *E255K/V*, *F359C/V*, *Y253H*, or *F317L*). Because roughly one half of imatinib-resistant patients will have a mutation when resistance develops, about one fourth of imatinib-resistant patients will

have mutations that are differentially sensitive to nilotinib or dasatinib, or resistant to both (*T315I*).

Questions About the Significance of a "Negative" BCR-ABL Result

A minority of cases will have undetectable BCR-ABL. What does this mean, and how should it influence clinical decision-making?

Question 1: How reliable is a negative PCR result? One has to approach "PCR-negative" disease or CMR cautiously, because a negative test result can be reproducibly produced under the conditions of a poor sample (quality or quantity) or a poor assay.

Question 2: For patients with CMR, do we still need to adhere to a compulsive set of monitoring guidelines? ELN and NCCN guidelines suggest peripheral blood testing by quantitative PCR every 3 months.[6,7] However, if a patient has been in MMR or CMR for months, the frequency of testing can be reduced to every 6 months. If *BCR-ABL* levels increase, moving back to testing every 3 months is reasonable.

Question 3: Can patients in CMR be taken off drug treatment? Several studies have addressed this question in patients with sustained (usually 2 consecutive years) CMR. In general, approximately one half of patients in whom TKI therapy is stopped remain in CMR over follow-up of 1-2 years. Patients with relapse have again responded to TKI when therapy is reintroduced. However, the consequences of unopposed *BCR-ABL* activity for months before restarting TKI therapy are not known. Have the CML "stem cells" had the chance to obtain new molecular lesions that will eventually launch them into the pathway of progression? The answer to this question may not be known for years. For this and other reasons, patients in CMR should continue to receive TKIs unless they are enrolled in a trial that is specifically addressing the issue of discontinuation.

Conclusion

The advent of TKIs and use of molecular monitoring to guide therapy and predict treatment outcome have revolutionized the management of patients with CML. Currently, clinicians may select from a substantial therapeutic arsenal that includes imatinib mesylate, the second-generation TKIs nilotinib and dasatinib, and allogeneic transplantation. The clinical challenge is understanding how to use cytogenetic and molecular monitoring to guide patients through therapy. Guidelines exist to help the clinician navigate outcome milestones and treatment options, but these are adjusted frequently on the basis of emerging data. Research in CML has led the way in many facets of leukemia translational medicine, and the development of molecular monitoring is the latest in that trend. As molecular testing becomes both more available and standardized, cytogenetic testing may soon be performed routinely at diagnosis, with all further monitoring done by peripheral blood quantitative PCR until monitoring suggests an unusual event (an increasing BCR-ABL value that suggests relapse, or decreasing transcript numbers that suggest a myelodysplastic clone). This evolution of monitoring in CML may eventually lead the way for monitoring in all types of leukemia.

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Clinical Resource

How to Monitor Patients Who Have CML

Clinical Resource – How to Monitor Patients Who Have CML

The challenge for clinicians who treat patients with CML lies in understanding how to use cytogenetic and molecular monitoring to inform and modify therapy. Guidelines assist clinicians in the navigation of outcome milestones and treatment options.

Response Criteria and Treatment Recommendations The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) recommend that patients with chronic phase CML start with an imatinib dose of 400 mg/day.[1,2] Patients who do not attain a complete hematologic response by 3 months, any cytogenetic response by 6 months, a major cytogenetic response by 12 months, or a complete cytogenetic response within 18 months of the start of therapy are considered to have failed imatinib and should go on to receive second-line treatment with one of the second-generation tyrosine kinase inhibitors. The clinically useful levels of differential disease response are shown in the Table.[3]

Table. Response Criteria in CML Treatment

Level of Response	Definition
Complete hematologic response	Normal CBC and differential counts
Minor cytogenetic response[a]	35%–90% Ph-positive metaphases
Partial cytogenetic response	1%–34% Ph-positive metaphases
Complete cytogenetic response	0% Ph-positive metaphases
Major molecular response	≥3-log reduction of *BCR-ABL* mRNA
Complete molecular remission	Negativity by RT-PCR

[a]All cytogenetic response categories should be based on the analysis of at least 20 metaphases
From Radich JP.*Blood*. 2009;114:3376-3381.[3]

Patients With Increasing Quantitative Polymerase Chain Reaction – What to do?
The first step should be to repeat the test. If the *BCR-ABL* level is still increased, then testing for ABL mutations should be pursued. The next step depends on how high the *BCR-ABL* level has risen.

Value of Mutation Testing in Guiding Therapy Choices
Roughly one fourth of imatinib-resistant cases will have mutations that will be differentially sensitive to nilotinib, dasatinib, or resistant to both (T315I). Thus, knowing the mutational status may inform the therapy.

Patients in Complete Molecular Remission – Monitoring Guidelines and Treatment Recommendations
The NCCN and ELN recommend peripheral blood testing for Q-PCR every 3 months.[1,2] If a patient has been in a major molecular response or a complete molecular remission for months, however, one can extend testing frequency to every 6 months. Patients in complete molecular remission should stay on tyrosine kinase inhibitors unless they are enrolled in a specific trial addressing the issue of discontinuation.

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Support documents

Focus on Molecular Monitoring in CML: What You Need to Know for Clinical Practice

Focus on Molecular Monitoring in CML: What You Need to Know for Clinical Practice

Jerald Radich, MD
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Fred Hutchinson Cancer Research Center; Professor of Medicine
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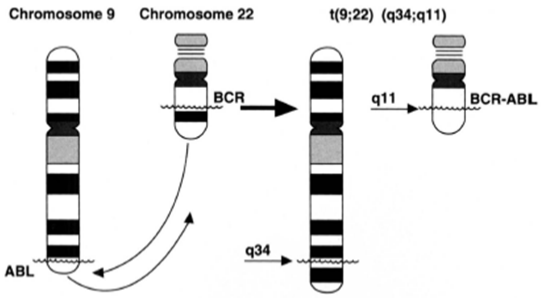
MedscapeCME

CML
Pathophysiology

- Arises from a translocation t(9;22)(q34;q11), known as the Philadelphia chromosome[a]
- Resulting *BCR-ABL1* fusion gene codes for a constitutively active tyrosine kinase[a,b]



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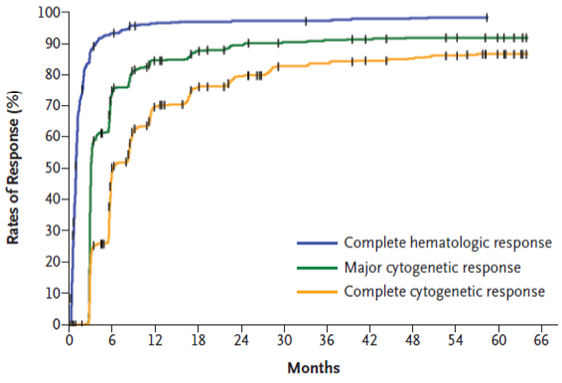
CML Therapy
Response Criteria

Level of Response	Definition
Complete hematologic response	Normal CBC and differential
Minor cytogenetic response	35%–90% Ph-positive metaphases
Partial cytogenetic response	1%–34% Ph-positive metaphases
Complete cytogenetic response	0% Ph-positive metaphases
Major molecular response	≥3-log reduction of BCR-ABL mRNA
Complete molecular remission	Negativity by RT-PCR

Radich JP. *Blood*. 2009;114:3376-81.

MedscapeCME

TKI Therapy: Remarkably Effective
IRIS Trial



- At 8 years, estimated overall survival was 85%; when only CML-related deaths were considered, estimated overall survival was 93%

Druker BJ, et al. *N Engl J Med*. 2006;355:2408-2417.
Deininger M, et al. ASH 2009. Abstract 1126.

MedscapeCME

Imatinib Failure
NCCN and ELN Operational Criteria

Evaluation Time (mo)	Failure
Baseline	NA
3	Less than CHR
6	No CyR (Ph + > 95%)
12	Less than PCyR (Ph + > 35%)
18	Less than CCyR
Any time during treatment	Loss of CHR; loss of CCyR; mutations; CCA/Ph+

O'Brien S, et al. *J Natl Compr Canc Netw*. 2009;7:984-1023.
Baccarani M, et al. *J Clin Oncol*. 2009;27:6041-6051.

MedscapeCME

Bone Marrow Analysis

Important in Patients With Suspected CML at Diagnosis

May Provide Information About Additional Chromosomal Abnormalities and Number of Blasts

MedscapeCME

When to Switch to Another TKI?

Patients who do not achieve a CCyR by 12 months should be considered for a second-generation TKI

MedscapeCME

Patients With Newly Diagnosed CML-CP

Nilotinib vs Imatinib: Phase 3 ENESTnd Trial

Response (%)	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
MMR			
• At 12 mo (ITT)	44*	43*	22
• At 18 mo (n = 525)	69	63	36
• At 24 mo (n = 145)	86	88	48
CCyR			
• At 12 mo (ITT)	80*	78†	65
• At 18 mo (n = 442)	99	99	89

Rate of progression to AP/BC CML

- Nilotinib 300 mg BID: 0.7% (*P* = .006 vs imatinib)
- Nilotinib 400 mg BID: 0.4% (*P* = .003 vs imatinib)
- Imatinib 400 mg QD: 4.2%

******P* **< .0001 vs imatinib.**
†*P* **< .001 vs imatinib.**

Larson RA, et al. ASCO 2010. Abstract 6501.

MedscapeCME

Patients With Newly Diagnosed CML-CP

Dasatinib vs Imatinib: Phase 3 DASISION Trial

	Dasatinib	Imatinib	
	n (%)		*P*
CCyR (≥ 20 metaphases)			
3 mo	140 (54)	80 (31)	
6 mo	189 (73)	154 (59)	
12 mo	216 (83)	186 (72)	.0011
MMR			
3 mo	21 (8)	1 (<1)	
6 mo	70 (27)	21 (8)	
12 mo	119 (46)	73 (28)	< .0001

Kantarjian H, et al. ASCO 2010. LBA6500.

MedscapeCME

Patients With Rising Q-PCR

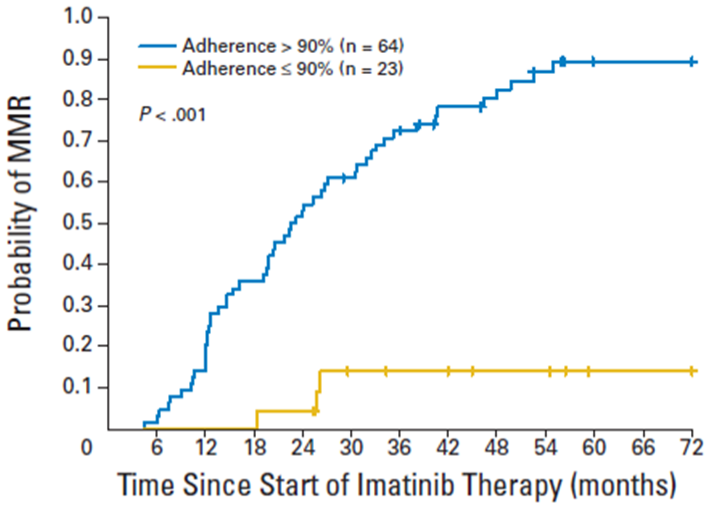
What to do?

- The first step should be to repeat the test
- If it is still increased, then testing for ABL mutations should be pursued
- The next step depends on how high the BCR-ABL level has risen

MedscapeCME

Adherence

Major Effect on Response



Marin D, et al. *J Clin Oncol*. 2010;28:2381-2388.

MedscapeCME

Summary

- The treatment of patients with CML has been revolutionized by the advent of tyrosine kinase inhibitor therapy and the use of molecular monitoring
- Today, clinicians have a substantial therapeutic arsenal available, including imatinib mesylate, second-generation TKIs nilotinib and dasatinib, and allogeneic transplantation
- The challenge for clinicians who treat patients with CML lies in understanding how to use cytogenetic and molecular monitoring to inform and modify therapy

MedscapeCME

CME Posttest

PLEASE NOTE: Typically Medscape's enduring materials include a statement such as the following before the posttest:

To obtain credit, you should first read the entire article, "Reassessing the Standard of Care in Indolent Lymphoma: A Clinical Update to Improve Clinical Practice." After reading the article, you should be able to answer the following, related, multiple-choice questions.

Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. To complete the questions and earn continuing medical education (CME) credit, please go to medscapecme.com/clinicalupdate/indolentnhl. Thank you for your participation.

1. Which tests would you use to adequately stage suspected early chronic-phase chronic myeloid leukemia (CML) in a 58-year-old woman before initiating therapy?

- ❏ Fluorescence in situ hybridization only
- ❏ Bone marrow analysis
- ❏ Quantitative polymerase chain reaction (PCR) only
- ❏ Mutational analysis only

A bone marrow examination at diagnosis provides information on morphology (important for diagnosis and blast count for phase determination), and cytogenetics (which identifies the Philadelphia chromosome and other clonal abnormalities indicative of advanced disease).

2. According to the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) recommendations for the treatment of patients with CML, your patient with early chronic-phase CML would be considered to have failed imatinib therapy if he did not achieve:

- ❏ Major cytogenetic response at 3 months
- ❏ Complete cytogenetic response (CCyR) at 6 months
- ❏ CCyR at 9 months
- ❏ CCyR at 18 months

According to the NCCN and ELN recommendations, imatinib is considered to have failed in patients who do not have a complete hematologic response by 3 months, any cytogenetic response by 6 months, a major cytogenetic response by 12 months, or CCyR within 18 months of the start of therapy. These patients should go on to receive second-line treatment with a second-generation tyrosine kinase inhibitor (TKI).

3. What would you consider first for a patient with early chronic-phase CML who is still in CCyR, but whose BCR-ABL transcript numbers have increased on 1 quantitative PCR?

- ❏ Allogeneic transplantation
- ❏ If currently receiving imatinib, switch to a second-generation TKI
- ❏ Repeat the test
- ❏ A novel agent, such as omacetaxine

The first response should be to repeat the test. If the BCR-ABL transcript numbers are still increased, then testing for ABL mutations should be pursued.

4. Your patient with chronic-phase CML, who has been receiving imatinib 400 mg/d, achieved complete molecular remission (CMR). How would you monitor him from that point on?

- ❏ Quantitative PCR on peripheral blood every 3 months
- ❏ Quantitative PCR on peripheral blood every 2 months
- ❏ Mutational analysis only
- ❏ FISH only

ELN and NCCN guidelines suggest peripheral blood testing by quantitative PCR every 3 months. However, if the patient has been in major molecular response or a CMR for months, testing can be extended to every 6 months.