

Considerations in the Management of Patients With Philadelphia Chromosome–Positive Chronic Myeloid Leukemia Receiving Tyrosine Kinase Inhibitor Therapy

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The phenomenal success of therapy with tyrosine kinase inhibitors (TKIs) in Philadelphia chromosome (Ph) –positive chronic myeloid leukemia (CML) has drastically changed the prognosis of this disease. With imatinib mesylate, the estimated 7- to 10-year survival is 80% to 85%, 90% to 93% if only CML-related deaths are considered.¹⁻⁵ Nilotinib and dasatinib are more potent second generation TKIs with activity in CML after imatinib failure.⁶⁻⁸ In randomized trials of first-line CML therapy, nilotinib and dasatinib, compared with imatinib, demonstrated significantly higher rates of complete cytogenetic response (CCyR) and of major molecular response (MMR) at 12 to 18 months, reductions in the incidence of transformation to accelerated and blastic phases, and, on average, better tolerance.^{9,10} Both nilotinib (300-mg twice daily) and dasatinib (100-mg once daily) were recently approved for first-line CML therapy. In the accompanying article, Hehlmann et al¹¹ report the results of first-line CML therapy with standard dose imatinib with or without interferon alfa, and with high-dose imatinib. They analyze the incidence of MMR as the study primary end point.¹¹ This emphasis on MMR as a primary end point in CML therapy, and the availability of three TKIs for CML therapy, raise important questions related to the management of chronic phase CML in our daily practice. What are the important early end points of therapy with TKI in CML that predict long-term prognosis (eg, achievement of CCyR, MMR)? How should we monitor response to therapy (cytogenetic, fluorescent in situ hybridization [FISH], molecular studies, mutational analysis)? What are the long-term end points relevant to therapeutic decisions (survival, progression-free survival [PFS], event-free survival [EFS])? Imatinib will become available in generic formulations in the next few years, at a significantly lower cost than second generation TKIs. Oncologists are then faced with important therapeutic questions. Would it be better to use the less expensive TKI, imatinib, as first-line CML therapy and reserve the second generation TKIs for imatinib failure, or should second generation TKIs be used as first-line therapy? What is a clinically relevant definition of poor response to imatinib? If imatinib is selected for first-line therapy, is it better to change to second generation TKIs at the time of suboptimal response to imatinib, or at the time of cytogenetic or hematologic relapse? These questions raise

several important issues related to how best to integrate the new generation of TKIs into the management of patients with CML.

WHAT ARE THE IMPORTANT EARLY THERAPEUTIC END POINTS IN CHRONIC-PHASE CML THERAPY?

Historically, the achievement of CCyR has been associated with improved survival with older therapies as well as with imatinib.^{2,12} The achievement of MMR (BCR-ABL ratio by International Scale [IS] $\leq 0.1\%$) versus no MMR at 12 months was associated in an early analysis of the International Randomized Trials of Interferon- α + Low-Dose Cytarabine Versus STI571 (imatinib; IRIS) data with improved EFS, but not with improved survival.¹³ This was not confirmed in subsequent analyses, which showed that achieving MMR versus no MMR at 18 months (not at 12 months) was now associated with better EFS.^{2,3} Since then, several studies have analyzed the significance of achievement of MMR. There is no doubt that patients achieving MMR fare better than patients who do not achieve MMR, but the latter is a heterogeneous group of patients including patients in CCyR without MMR, and others (eg, complete hematologic response without CCyR). This heterogeneous mixture of patients is then compared to those who achieve MMR, with the suggestion that MMR results in improved long-term outcome. An important question is really whether, among patients achieving CCyR, the achievement of MMR is still important. The corollary to the question is whether one should consider a change of therapy in a patient in CCyR who does not achieve MMR, or who loses MMR, or who has rising levels of BCR-ABL ratio but remains in CCyR. CML experts have not advocated changes of therapy for such instances, and the European Leukemia Net (ELN) recommendations do not include lack or loss of MMR as a treatment failure, but rather as a suboptimal response. However, many CML experts express concerns regarding suboptimal response and advise closer monitoring (eg, every 3 months instead of 6 months) and performing mutational analysis among patients who lose MMR and/or show consistent BCR-ABL ratio increases of two-fold to one log (depending on the studies).¹⁴⁻¹⁷ Unfortunately, this may be understood in community practice as a suggestion that therapeutic change

Table 1. Monitoring Recommendations for Chronic Myeloid Leukemia

Parameter		ELN 2006	Our Approach
Objective	Frequency		Frequency
Hematologic	Every 2 weeks until CHR, then every 3 months or as required		Same as ELN
Cytogenetic	At diagnosis, at 3 months and at 6 months, then every 6 months until CCyR, then at least every 12 months if molecular monitoring cannot be assured; always at time of treatment failure and for unexplained cytopenias		Every 6 months until CCyR; then marrow for CG every 2-3 years in stable CCyR (in the future this may not be necessary with longer follow-ups); marrow for CG every 6 months only if CG abnormality in Ph-negative cells; monitoring in stable CCyR as in Table 2 by FISH and QPCR every 6 months; at time of treatment failure and for unexplained cytopenias
Molecular	Molecular every 3 months until MMR confirmed, then every 6 months		Every 6 months (Table 2)
FISH	If insufficient metaphases or if bone marrow cannot be sampled		Every 6 months (Table 2)
Mutations	If failure or suboptimal response; always required before changing therapy		If failure (decision to change therapy)

Abbreviations: ELN, European Leukemia Net; CHR, complete hematologic response; CCyR, complete cytogenetic response; CG, cytogenetic; Ph-negative, Philadelphia chromosome-negative; FISH, fluorescent in situ hybridization; QPCR, quantitative polymerase chain reaction; MMR, major molecular response.

in such patients may be beneficial. Despite occasional claims from descriptive analyses,¹⁸ no studies, to our knowledge, randomized or otherwise, have shown that a change of therapy for suboptimal response (eg, CCyR but no MMR) would improve survival, PFS, or EFS. Changing therapy to second generation TKIs in patients on imatinib at the time of cytogenetic relapse has been associated with improved outcomes (eg, CCyR, EFS) compared to changing therapy at the time of hematologic relapse, but this earlier intervention was in the context of true imatinib failure (loss of CCyR or loss of hematologic response) not in the context of imatinib suboptimal response as defined by failure to achieve MMR.¹⁹

Four large scale studies (including the present report by Hehlmann et al¹¹) have evaluated the significance of achieving CCyR versus CCyR plus MMR in CML.^{11,14,20,21} In the IRIS trial evaluating 476 patients,²⁰ the authors highlight significant differences in EFS and survival rates by molecular response, but most of the differences are between patients achieving BCR-ABL ratios (IS) ≤ 1% versus higher than 1%, that is patients who achieved CCyR versus no CCyR. Within patients achieving BCR-ABL ratio ≤ 1%, the authors note some differences in EFS rates and of time without accelerated-blastic phase rates, but no differences in survival rates. The survival rates in patients in CCyR, as a function of whether they achieved MMR or not at 12 months, were 92.5% versus 96.7%, respectively. Similarly, the survival rates in patients in CCyR at 18 months by MMR or not were 94.9% versus 95.7%, respectively. This emphasizes two points: therapeutic interventions on the basis of molecular levels (MMR v no MMR) in patients in CCyR may not be justifiable, and it is possible that therapeutic intervention at cytogenetic relapse offers the same benefit as earlier interventions in CCyR for increasing molecular levels, since the former is how most patients included in the analysis were managed after an event. In the second study, de Lavallade et al²¹ analyzed the outcome of 204 patients with newly diagnosed CML treated with imatinib. Patients achieving CCyR at 12 months had significantly better rates of PFS and survival. However, achieving MMR did not confer further advantage. In the third study from MD Anderson Cancer Center,¹⁴ we analyzed the outcome of 276 patients with newly diagnosed CML treated with imatinib. We observed a strong association between achievement of a major cytogenetic response (Ph-positive metaphases < 35%) at 6 to 12 months and survival as well as PFS. Achievement of MMR in patients in CCyR showed some associ-

ation with PFS but not overall survival.¹⁴ Similar findings were reported in the fourth study by Hehlmann et al¹¹: achieving MMR in CCyR did not confer a further therapeutic benefit over achieving CCyR without MMR.

Thus, while all four studies reported different degrees of associations between MMR/CCyR and PFS/EFS, none reported significant differences in survival in patients in CCyR by whether they did or did not achieve MMR. The reason CCyR became the gold standard for a favorable response to therapy in CML is because it is associated with a survival advantage.^{2,12} This is not the case for achievement of MMR. At present, achievement of CCyR remains the goal of TKI therapy in CML, although the additional achievement of MMR may protect against a higher probability of events and, to lesser extent, of transformation to the accelerated or blastic phases.

HOW DO WE MONITOR TREATMENT RESPONSE WITH TKIs?

Various monitoring approaches have been proposed by the ELN²² (Table 1) and by CML experts.¹⁵⁻²⁰ Oncology community practice appears to be shifting gradually toward monitoring with the single tool of molecular analysis, although this is not necessarily the recommendation of CML experts or of recent publications. In a recent report, Hughes et al recommend “using molecular monitoring to determine patient response...after the achievement of MMR” in patients who are already in CCyR, and resume regular cytogenetic analysis if MMR is lost.²⁰ We agree with this recommendation under the ideal conditions of precise, well-standardized, molecular studies for community practice. Endeavors are ongoing to improve the standardization of molecular procedures,^{16,23} but this is unfortunately not the norm. In our experience, there is significant discordance in the molecular results (usually performed within a time range of 1 to 2 months) between well-respected commercial laboratories and our institutional molecular laboratory. Thus, therapeutic reactions to modest changes in transcript levels should be discouraged, particularly when the variability of the assay in the laboratory involved is not known. A proposed monitoring approach for patients in durable CCyR (eg, after 12 to 18 months of therapy, when concordance between CCyR and BCR-ABL ratio [IS] improves) is shown in (Table 2).²⁰ This approach proposes to supplement the molecular analysis with FISH testing (peripheral

Table 2. Proposed Monitoring by FISH and Molecular Studies in Patients in Durable Complete Cytogenetic Response

FISH	BCR-ABL Ratio International Standard (%)	Interpretation
Negative	≤ 0.1	Excellent response; 6-month follow-up
Negative	0.1-1	Follow-up every 6 months, follow-up in 3 months if one log ↑ of BCR-ABL ratio; assess compliance
Positive	≤ 0.1	FISH or molecular tests are false positive or false negative; repeat in 3 months
Negative	> 1	FISH or molecular tests are false positive or false negative; repeat in 3 months
Positive	> 1	Check marrow and cytogenetics; possible relapse; assess compliance

Abbreviation: FISH, fluorescent in situ hybridization.

blood; avoids painful marrow procedure), and to check for concordance, particularly in patients who do not achieve MMR. Negative FISH studies with BCR-ABL ratio (IS) ≤ 0.1% confirms a sustained MMR. Patients in CCyR but without MMR (FISH negative, BCR-ABL ratio 0.1% to 1%) continue to be monitored every 6 months, unless there is a significant increase in BCR-ABL ratio (eg, 0.5 to 1 log), at which time more frequent monitoring (every 3 months) would be indicated. Discordant values (eg, positive FISH with BCR-ABL ratio ≤ 1%, or negative FISH with BCR-ABL ratio > 1%) require follow-up in 3 months. Positive FISH and BCR-ABL ratio (IS) higher than 1% requires checking marrow (and mutational analysis) to investigate cytogenetic relapse.

Using frequent molecular monitoring alone may result in misinterpretation of results in the oncology community. Under optimal conditions, the variation of BCR-ABL ratio (IS) can be up to 0.5 log, even in the best academic and commercial laboratories. Therapeutic overreactions may follow such variations, particularly since frequently performed tests may provide more opportunity to observe false elevations in the BCR-ABL ratio (IS). An increase in the BCR-ABL ratio (IS) may result in therapeutic interventions that could increase cost (increasing the dose of imatinib; changing to new TKIs), increase toxicity (increasing the dose of imatinib), or discard a treatment that may still be effective (changing from imatinib to new TKIs). Therapeutic interventions for variations in molecular results in patients in CCyR have not yet been proven to improve patient outcome. Occasionally, these interventions have been reported to improve the transcript levels, but whether this favorably affects long-term outcome remains to be proven. Randomized studies of therapeutic intervention (increasing imatinib dose or changing to new TKIs) versus continuation of same therapy have been designed for patients with suboptimal response, but never accrued enough patients, and therefore have not shown that changing therapy improved outcome. In our opinion, therapeutic interventions in patients in CCyR based on increases of BCR-ABL ratio or loss of MMR are not justified at present, and maybe harmful (increasing costs, increasing toxicity, abandoning effective TKI therapy).

Bone marrow studies for response monitoring have been mostly replaced with peripheral blood analyses. The pretreatment marrow sample is indispensable for proper staging (ie, to assess the percents of blasts and basophils), as well as to detect clonal evolution. A pretreatment marrow may also help avoid diagnostic errors related to false-positive or false-negative FISH and BCR-ABL studies on peripheral blood. A marrow cytogenetic analysis may still be required on clinical trials at 6 and 12 months into therapy for landmark response evaluations, although it could be argued that negative FISH studies at 6 or 12 months would obviate the need for a painful marrow analysis. A high

concordance rate has been reported between CCyR by cytogenetic analysis and a negative FISH test. Thus, FISH analysis can be used to monitor CCyR.²⁴ In patients in stable CCyR (eg, beyond 2 years of therapy), the course of CML is quite predictable.^{3,20} Sudden blastic transformations are rare, mostly occurring in the first 2 years, usually in younger patients who develop sudden lymphoid blastic transformations. Beyond the second year, CML transformation on first-line TKI therapy is infrequent (< 1% annually). This is the basis for recommending monitoring every 6 months rather than every 3 months by FISH/PCR in stable CCyR. Marrow studies are unnecessary in stable CCyR, unless chromosomal abnormalities are noted in the Ph-negative cells, a warning signal that requires marrow follow-up studies every 6 to 12 months.²⁵

Mutational studies are not helpful pre-TKI therapy in newly diagnosed CML, and are of limited value in patients responding to TKI therapy. The occasional exception is a patient with rising BCR-ABL ratios in whom mutational studies detect an unfavorable mutation. It could be argued that a change of therapy before cytogenetic relapse may help in such patients. Mutational analyses are useful in patients with resistance to a TKI, in order to guide the next step in management. Detection of a T315I mutation predicts failure of second generation TKIs (dasatinib, nilotinib, bosutinib)²⁶ and dictates

Table 3. Summary of Suggested Practical Guidelines During Chronic Phase Chronic Myeloid Leukemia Therapy

Achievement of CCyR remains the most important goal of therapy; achievement of MMR may be additionally beneficial but should not guide therapy decisions
Molecular monitoring as a single tool after achieving MMR in CCyR is reasonable but over-reaction to modest changes should be avoided; in CCyR (with or without MMR), monitoring with peripheral molecular and FISH studies ensures robust interpretation of response results (Table 2)
In stable CCyR (usually after 2 years of therapy) sudden blastic transformations are rare; consequently, monitoring response every 6 months is reasonable; routine blood tests and physician visits every 3 months help emphasize/monitor patient compliance
In stable CCyR, routine marrow studies are not necessary (replaced by peripheral molecular and FISH studies); bone marrow cytogenetics indicated if there is evidence of chromosomal abnormalities in Ph-negative cells (then perform marrow cytogenetics every 6 months until disappearance of abnormalities), at the time new therapies are started, and in case of unexplained cytopenias or significant changes in peripheral blood differential (eg, increase in blasts or basophils)
Imatinib blood levels is not a useful monitoring procedure
Mutational studies at the time of cytogenetic or hematologic relapse are useful in guiding the choice of the next therapy
Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; FISH, fluorescent in situ hybridization studies; Ph-negative, Philadelphia chromosome-negative.

the need to consider allogeneic stem-cell transplant as soon as possible, or use of selective T315I inhibitors when transplant is not an option.²⁷ There are also particular mutations with high IC50 (a high inhibitory concentration that suppresses CML colony growth by 50%) to either nilotinib (mutation IC50 > 150 nmol/L) or dasatinib (mutation IC50 > 3 nmol/L), thus guiding choice of alternate TKIs.

Monitoring imatinib blood levels has been advocated to optimize the imatinib dose. This was based on an evaluation in population pharmacokinetic studies of the 4-week trough blood level of imatinib and its correlation with cytogenetic and molecular response,²⁸ as well as anecdotal evidence of correlation of high blood levels with some imatinib-related toxicities. This was erroneously interpreted to mean that individual blood levels at any time may help in adjusting the imatinib dose (ie, low imatinib levels with suboptimal response prompting an increase in the imatinib dose, and high imatinib levels with clinical toxicity prompting a decrease the imatinib dose). Nevertheless, it is clear that clinical decisions can be implemented without the use of imatinib blood levels. In studies by Marin et al,²⁹ the most significant independent prognostic factor for long-term outcome was achievement of CCyR, with imatinib blood levels not being independently prognostic. Randomized studies of changing imatinib dose versus continuing on the same dose among patients with low imatinib blood levels, and correlation of the treatment modification with improved outcome, have not been conducted. At present, imatinib blood levels, in our opinion, are not useful in monitoring or adjusting treatment.

RELEVANT LONG-TERM END POINTS DURING TKI THERAPY IN CHRONIC-PHASE CML

In the future, our choice of first-line TKI therapy may depend on the maturing data concerning long-term end points. With imatinib therapy, the estimated 7- to 10-year survival may exceed 85%.^{3,5} To demonstrate a significant survival benefit for second-generation TKIs may require very large numbers of patients in randomized trials observed for long periods. Even then, the statistical difference may be weighed against its clinical relevance versus cost of therapy. Other long-term end points chosen in different studies like PFS and EFS may become more relevant. Regrettably, different studies have used different definitions of PFS and of EFS. In some studies, patients taken off therapy for reasons other than event or progression (as variably defined in different studies) are censored for other reasons, many of which can be reasonably considered to constitute an event. This is true for 20% of patients on the IRIS and other recent studies removed from TKI therapy for various reasons, particularly toxicity. This reflects the limited abilities of large multi-institutional studies to observe patients who were removed from therapy beyond 30 to 60 days, and also because it is presupposed that events/progression that occur while off the TKI treatment cannot be attributed to the treatment which had already been discontinued. This also assumes that toxicity and event/progression are completely independent of each other, which may not be true. For example, myelosuppression or severe bone pain as toxicities, may be a prelude to CML transformation. More concerning, some studies may not code deaths occurring beyond 30 to 60 days after treatment discontinuation if the reason for coming off study is not an event/progression (eg, toxicity). This accounts for the extensive censoring observed in some PFS and EFS curves, even with the long-term

median follow-up of patients. In a recent analysis of 435 newly diagnosed patients on TKI therapies (Kantarjian, manuscript submitted for publication) long-term outcomes by different definitions of EFS, PFS, or time without progression used in the IRIS,³ Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd),¹⁰ Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients (DASISION),⁹ and MD Anderson trials,¹⁴ showed corresponding EFS/PFS rates at 5 years of 96%, 90%, 89%, and 81%, respectively, for the different definitions applied to the same patients. This highlights the importance of developing uniform outcome criteria if PFS and EFS become important in guiding the choice of first-line TKI therapy. In addition, censoring should be clearly marked and explained in any report of EFS/PFS.

In summary, ours are exciting times in the management of CML. The favorable treatment results, and the availability of several TKIs and different monitoring procedures to evaluate early and late surrogate end points of therapeutic benefit and prognosis, mandate familiarization with the treatment end points and monitoring procedures and their benefits and pitfalls. General suggestions are summarized in Table 3. As discussed, achievement of CCyR remains the primary goal of therapy, although achievement of MMR may further protect against increased risk of progression. Different monitoring procedures are available but may, under certain circumstances, be misleading. Finally, long-term end points need to be better defined in order to more effectively guide the choice of TKI therapy.

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