Review Article

Issues in current management of chronic myeloid leukemia: Importance of molecular monitoring on long term outcome

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Abstract

Monitoring of CML patients while on therapy is vitally important and ENL has come up with specific guidelines for the same. Since we are currently talking about operational cure, this review shall focus on evaluating the emerging data to optimize response. This requires attention to all outstanding controversial issues. Only careful, accurate and regular monitoring with specific attention to grey areas will help us select first line therapy, decide when to discontinue TKIs and also move to second line TKIs in a timely manner.

Key words: Monitoring, polymerase chain reaction, remission, tyrosine kinase inhibitor, hematopoietic stem cell transplantation

Introduction

Chronic myeloid leukemia (CML), the commonest myeloproliferative disorder, is the result of a balanced, reciprocal translocation between chromosome 9 and 22 that results in a chimeric oncogene called *BCR-ABL* whose protein product has tyrosine kinase activity and causes uncontrolled proliferation of the myeloid cells.[1] Its cumulative rate (%) and lifetime risk up to the age of 74 years in greater Mumbai is 0.19% (1 in 526 among males) and 0.13% (1 in 768 among women).[2] The availability of oral imatinib revolutionized the way we think about CML and brought to the fore a disruptive concept of personalized therapy that has embedded itself into the modern management of cancer patients. For the first time, the oncologists and hematologists were able to provide the benefit of complete hematological remission, disappearance of the Philadelphia clone, and prolongation of life in chronic phase to a substantial number of patients without having to consider allogeneic hematopoietic stem cell transplantation (HSCT).[3]

Monitoring CML Patients – Response to Therapy

It is becoming increasingly clear that monitoring CML patients while on therapy cannot be stressed enough. ENL has come up with specific guidelines on how this should be done.[4]

Use of imatinib [and other tyrosine kinase inhibitors (TKIs)] has converted CML into a chronic illness. In fact, we are currently talking about operational cure, and in the foreseeable future, it might be the real possibility of cure in its truest form (no evidence of disease, no need for further treatment, and return to normal life expectancy) in a significant number of cases.[5] Such a bright outlook in CML is an example that other therapeutic areas are striving to emulate.[6-8]

So, is the management of CML streamlined enough for us to sit back and relax? Or are there still challenges faced by the clinicians?

Emerging data have shown that CML patients commenced on first-line treatment with TKIs can be divided into two broad groups. One group consists of those having an initial suboptimal response, and therefore the greater risk for ultimate failure of therapy. The other one will be the group having an "optimal" response whose chance of disease progression is small, has the potential to be cured, and may be potentially saved from lifelong therapy. Since currently we cannot put all patients into either of these two baskets, we still have a gray zone in between.

Consequently, discussing the disease, natural history, treatment options, as well as scheduling evaluation and consultations at progressive disease is now an entirely new ball game. In some ways, the task has become even more challenging. It has become very important to check disease status at specific time points to ensure timely monitoring of response efficacy as well as pick up early warning signs of drug resistance.[3,4] There is no role for complacency. Both drug compliance as well as the use of quantitative techniques such as real-time polymerase chain reaction (RT-PCR) to document the log change in *BCR-ABL* transcript levels needs to be stressed and reinforced to the patients at each visit.[1,9]

Issue 1: Is it time to bury the HSCT option for patients with CML?

At one time, human leukocyte antigen (HLA)-matched sibling HSCT was the only curative treatment available to patients with CML. The year 2010 saw the completion of 30 years of this therapeutic option. In spite of having a significant early mortality, in the 1990s, CML became the number one indication for HSCT worldwide.[10] With the introduction of imatinib, the use of HSCT has

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declined globally. In fact, several transplant centers have discontinued or are no longer receiving cases of CML. There is enough evidence against this modality as the first-line therapy easily accessible on the World Wide Web. As a result, most physicians as well as patients no longer consider this option as a routine. So, is it time to bury this option? The answer is clearly no. For patients who fail to respond and/or develop intolerance to TKIs, transplantation continues to have a place as a curative treatment option. In fact, combination of these two therapeutic options brings forth a novel strategy that continues to be explored.[1,3,10]

Issue 2: Choosing the right first-line TKI

Gleevec received Food and Drug Administration (FDA) approval in May 2001. With longer follow-up of the imatinib trials and consequently more reliable data, the overall survival of patients who present in chronic phase exceeds 95% at 2 years and 80%–90% at 5 years, and the 5-year probability of remaining in major cytogenetic response is approximately 60%–65%.[1,3,11,12] This remarkable effect, achieved with little toxicity, at that time was justification to recommend imatinib as the first-line treatment in most patients with newly diagnosed CML in chronic phase.

Unfortunately, not all patients continue to benefit from the "magic" of imatinib. And hence its recommendation needs to be revisited. Is there a case for using other TKIs as frontline treatment option in all or some newly diagnosed patients with CML? Data seem to suggest the value of deeper, faster, and more complete response with second-generation TKIs (vide infra).

Nilotinib was designed specifically to mimic compounds binding to *BCR-ABL* mutants, using the imatinib structure as a backbone. Saglio *et al*. in 2010 compared nilotinib with imatinib in a three-arm study with 300 mg nilotinib twice daily, 400 mg nilotinib twice daily, and 400 mg imatinib twice daily.[13] The percentage of patients with complete cytogenetic response was significantly greater in nilotinib arms as compared to imatinib arm at 12 months. Patients also achieved major molecular response (MMR) faster with nilotinib, translating into larger number of patients in MMR over 6–9 months as compared to imatinib arm. A 24-month follow-up study of ENESTnd by Larson *et al*.[14] showed that complete molecular response (CMR) achieved with nilotinib was far greater than that with imatinib at 18 months, with fewer deaths related to CML. Progression rates at the end of 24 months to accelerated phase or blast crisis in patients was significantly lower in both the nilotinib arms as compared to imatinib arm. GIMEMA and MDACC studies also confirmed that patients on nilotinib had higher and faster achievement of MMR and complete cytogenetic response (CCyR).[12,15,16]

A study in 2011 indirectly compared the efficacy of nilotinib versus dasatinib in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) patients (a matching adjusted comparison).[17] It reported a significantly higher rate of MMR with nilotinib (56.8%) as compared to dasatinib (45.9%). This translated into a higher overall survival rate with nilotinib (99.5%) as compared to dasatinib (97.3%) at 12 months.

Was this advantage at the cost of higher toxicity? Fortunately it is not. Patients discontinuing therapy due to adverse events were also higher with imatinib as compared to nilotinib.[3] Thus, nilotinib is a faster and deeper acting drug as compared to imatinib, with lower risk of disease progression (to AP or BC) without increasing toxicity, even as the first-line therapy for CML.[1,3] Table 1 compares the toxicity profile of dasatinib as compared to nilotinib.[18,19] It confirms that nilotinib is safer of the two.

Issue 3: Importance of age

CML occurs at all ages. Patient age and overall condition may influence the outcome goals of TKI therapy. For example, when treating younger patients compared to the elderly, the longer time at risk for progression might favor a second-generation TKI. Thus, in the younger patient, the achievement of published "optimal" responses is even more important.[1,3]

Issue 4: Monitoring response

Patients of CML require timely, regular, and appropriate monitoring to optimize management.

Complete hematological response (CHR) is defined as white blood cell count $<10 \times 10^9$ cells/L, basophils <5%, absence of myelocytes, promyelocytes, and myeloblasts in the peripheral blood, a platelet count $<450 \times 10^9$ cells/L, and spleen that is not palpable.[1,3]

To document cytogenetic response, a bone marrow sample is required. A minimum of 20 metaphases should be examined.[1,3] Response is of two levels, either <35% or <65% Philadelphia chromosome-positive metaphases.[11,13]

Achieving an MMR is an important predictor of progression-free survival in CML.[1,3,9] The importance of documenting molecular response became even more evident after demonstrating the value of deeper, faster, and more complete response. This is done by real-time quantitative reverse-transcription polymerase chain reaction

Table 1: Comparison of toxicity profile of 2nd generation TKIs

	Hematological (Gr. 3 or 4)	Non hematological
Dasatanib	Anemia (10)	Fluid retention / Oedema (19)
	Neutropenia (21)	Diarrhoea (17)
	Thrombocytopenia (19)	Rash (11)
Nilotinib	Anemia (3)	Rash (31–36)
Neutropenia (10–12)	Nausea (11–19)	
Thrombocytopenia (10–12)	Fluid retention/ Oedema (7–8)	

QTc > 500 msec, Nilotinib trial: 1 patient on imatinib, no patients on nilotinib, Dasatinib trial: 1 patient on imatinib, 1 patient on dasatinib

(RQ-PCR) method that provides a reliable, high-throughput method to accurately assess the level of treatment response and provides an early indication of emerging drug resistance.[9,20,21] Using the ABI Prism 7700 Sequence Detection System and TaqMan fluorogenic probes, it was possible to estimate copy number compared to a control gene which takes into consideration variations in the efficiency of the PCR cycles as well as the degree of RNA degradation. This requires careful selection of the appropriate control gene, and assay design to avoid polymorphism areas as well as to exclude the amplification of contaminating DNA. The quality assurance, therefore, requires regular monitoring of the performance of the RQ-PCR by the use of quality control samples. In order to ensure reproducibility as well as comparison across laboratories in different parts of the world, an international scale (IS) has been developed. *BCR-ABL1*/control gene ratio of 0.10% represents MMR in this IS.[21] The international reference laboratory is in Adelaide, S.A., Australia.[21] Recently, a regional reference laboratory for India has also been established at CMC, Vellore.[21] This is the first step in ensuring that South Asia will be able to standardize reports from labs doing RQ-PCR in this region.

Using these techniques and quality assurance, the definition of molecular response is shown in Table 2.

Table 2: Understanding Molecular Response in CML(log reduction is reduction from IRIS baseline and NOT individual pre-treatment levels)

	International scale (IS)	
	100%	IRIS baseline
	10%	
	1%	
	0.1%	IRIS MMR
MR4.0 (≥ 4 log reduction; ≤ 0.01%)	0.01	
MR4.5 (≥ 4.5 log reduction; ≤ 0.0032%)		
MR5.0 (≥ 5 log reduction; ≤ 0.001%)	0.001%	
	Bcr-abl undetectable	

CML = Chronic myeloid leukemia, MMR = Major molecular response, MR = Molecular response, IRIS =

This is especially important since we are discussing the use of the second-generation TKIs (dasatinib and nilotinib) as frontline therapy for chronic phase CML, where higher response rates are achieved at earlier time points when compared with standard-dose imatinib therapy.[1,3]

To summarize the monitoring of patient, it should be done to document therapeutic response at 3, 12, and 18 months [Table 3]. At these time intervals, response is considered as optimal, suboptimal, or therapeutic failure as per ENL guidelines [Table 4].

Issue 5: What are the alternatives to predict long-term outcome?

A selected subset of patients with CML achieving MMR while on imatinib can stop therapy and remain in CMR, at least for several years. In such patients, either the disease has been eliminated or residual leukemic cells persist but fail to proliferate. To base clinical management decision on this molecular testing is a big responsibility. Hence, it is important to understand the limitations and advantages of such testing by RQ-PCR [Table 5]. The Australian group used a highly sensitive DNA-based patient-specific nested quantitative PCR to look for evidence of genomic *BCR-ABL1* in such patients.[22] Interestingly, in seven of eight such patients, there was at least one DNA-based PCR test that showed persistent malignant cells. Further, the *BCR-ABL1* DNA levels increased in all patients who lost CMR after imatinib cessation.[23] No doubt there is clear evidence that the *BCR-ABL1* DNA PCR is the more sensitive assay. The next question is whether this test will help us pick up patients who should be moved to second-line TKIs – while on imatinib (suboptimal response) or when imatinib is discontinued.

Issue 6: Stopping imatinib

The stopping imatinib (STIM) trial has raised the possibility that selected patients who achieve a stable molecular response may be able to discontinue treatment with imatinib and remain free of molecular relapse.[24] We should be considering such a strategy because of the potential for organ toxicity with long-term TKI therapy, its impact on quality of life (QoL), its questionable safety

Table 3: ELN guidelines (2009) for follow-up testing and time schedule to assess response to TKIs in CML

	Optimal response	Suboptimal response	Failure
Baseline	NA	NA	NA
3 months	CHR, and At least minor CyR (Ph+ ≤ 65%)	No CyR (Ph+ > 95%)	Less than CHR
6 months	At least PCyR (Ph+ < 35%)	Less than PCyR (Ph+ > 35%)	No CyR (Ph+ > 95%)
12 months	CCyR	PCyR (Ph+ ≤ 35%)	Less than PCyR (Ph+ > 35%)
18 months	MMR	Less than MMR	Less than CCyR
Any Time	Stable or improving MMR	Loss of MMR Mutations(1)	Loss of CHR Loss of CCyR Mutations(2) CCA/Ph+

Mutations still sensitive to imatinib; (2) Mutations poorly sensitive to imatinib, ELN, Baccarani *et al.*[1], CCA, clonal chromosomal abnormalities

Table 4: Interpretation of response. Adopted from Baccarani *et al*[1]

Failure	A favourable outcome is unlikely. Change Patient's Rx
Suboptimal	The Patient may still have substantial long term benefit from ongoing Rx. But reduced chance of optimal outcome. Patient eligible for alternative Rx
Optimal	Projected survival is close to 100% at 6-7 yrs. Dont change Rx

Based on ELN Guidelines published by Baccarani *et al*.[1]

Table 5: Benefits and limitations of RQ-PCR

Strengths
- Only technique that can clearly assess molecular therapeutic milestones:
  Major molecular response (MMR) and Complete molecular response (CMR)
- Can be routinely performed on peripheral blood

Weaknesses
- Technically challenging
- Issues in comparing results between centers/laboratories/countries
- Several variables/methods/units of measurement used

during pregnancies, and the significant financial cost of lifetime TKI therapy. Hence, studies on TKI discontinuation are ongoing.[5,25,26] Data indicate that there is some emerging evidence of potential cure.[24]

In the prospective, multicenter, non-randomized STIM study, further imatinib was discontinued in patients with CML who were more than 18 years of age, had already been on imatinib for more than 2 years, and had >5-log reduction in *BCR-ABL* or undetectable transcripts on quantitative RT-PCR.[25] In this interim analysis of 69 (out of total of 100) patients with at least 12 months of follow-up, 42 (61%) had relapsed (40 before 6 months, 1 patient at month 7, and 1 at month 19).[5] Fortunately, all patients who relapsed responded to reintroduction of imatinib. Multivariate analysis indicates that lower baseline Sokal score ($P = 0.008$) and the duration of imatinib therapy of >60 months ($P = 0.047$) are the most important predictors of freedom from relapse after imatinib discontinuation.[25] The same group also looked at 33 CML patients with stable undetectable molecular residual disease (UMRD) who discontinued treatment with either nilotinib or dasatinib.[26] This group had a 24% rate of relapse, which looks to be significantly lower than that with imatinib. Even at a median follow-up of 11 months, 25 out of 33 patients who had been on first-line second-generation TKIs (76%) maintained UMRD, which was substantially more than the 40% reported in the STIM trial.

However, it is still premature to recommend this as standard of care. It is not a realistic goal for vast majority of patients. It is estimated that only 5% patients will be eligible for discontinuation at the end of 3 years of imatinib using the STIM criteria. And at 8 years, an estimated 50 of the 415 (12%) patients would maintain response if imatinib was discontinued after stable CMR (Personal Communication, Tim Hughes). Also, we do not know the long-term risk of progression and drug resistance. Hence, several questions remain unanswered and we should not fall into the danger of sending a wrong message to patients and community oncologists. Hence, discontinuing TKI treatment is not currently recommended outside of a clinical trial. If, for any specific patient, it is vital to consider stopping TKIs in CML outside of a clinical trial, this can be an option only if he/she fulfills all of the following criteria: Patient in first chronic phase, there is no history of resistance or TKI failure, the TKI therapy is ongoing for at least 5 years, sensitive PCR test is negative on every test for at least 2 years, and the patient is willing for and has access to sensitive monthly PCR testing in the first year of cessation.

Issue 7: Drug compliance

When considering a change in therapy, one is labeling the patient as having suboptimal response or intolerance to existing treatment. This is a significant decision point. It is therefore important to check for treatment interruptions and nonadherence to therapy.[27,28] Studies have shown that approximately 25%–45% of patients have adherence levels <85%.[27] Moreover, patients with suboptimal responses to first-line TKI therapy have significantly higher mean percentages of TKI not taken.[28]

One study included 103 patients who had been on imatinib for more than 12 months.[29] The differences in the mean trough imatinib serum levels were interesting. In the group with CMR it was 2891 ± 856 ng/ml, for the group with MMR it was 2337 ± 434 ng/ml, whereas in the group with CCyR it was 1817 ± 563 ng/ml, and finally for the group without CCyR it was 1723 ± 673 ng/ml.

In another study of 68 patients, the mean trough levels were higher in the group with MMR [34 patients (1452 + 649 ng/ml)] than in the group without MMR [34 patients (869 + 427 ng/ml); $P < 0.001$].[30]

The importance of perfect adherence to TKI therapy should be reinforced to all patients with CML at initiation of therapy and rechecked before the patient is labeled as having "suboptimal response" or treatment failure.[31] Also, it would be preferable to back this up by checking serum levels of imatinib in such cases.

Issue 8: Mutation analysis

When considering a change in therapy, it is important to consider a *BCR-ABL* kinase domain mutational analysis.[32,33] *BCR-ABL* mutation T315I is resistant to all of the currently approved TKIs. Some mutations (Y253H, E255K/V, and F359V/C) are less sensitive to nilotinib, and others (F317L and V299L) are less sensitive to dasatinib. Clinical data suggest that one of the second-generation TKIs will be preferred in the second line based on a mutation analysis after imatinib failure.[18] If failure occurs

with one of the second-generation TKIs, the other second-generation TKI should be prescribed as second-line therapy except in cases where the T315I mutation is detected or in patients unable to tolerate therapy.[32,33]

Issue 9: Switching to second TKI

Raja has elegantly outlined the criteria for switching to a second TKI as well as what is the choice of the drug in such an eventuality.[3] Important considerations are how long has the patient been on first-line therapy, when was the molecular remission testing done, and what is the *BCR-ABL*/*ABL* IS ratio using QT-PCR on peripheral blood?

In one study of 282 patients, a single molecular measurement of *BCR* transcripts at 3 months was identified as the best way to pick up patients who do not develop optimal response, thereby allowing early switch to a second-generation TKI.[34]

Blood α-defensin 1–3 and α-defensin 4 expression could also be of prognostic and predictive importance. At initial presentation, α-defensin 1-3 and α-defensin 4 expression was significantly lower in the group that ultimately showed resistance to imatinib (as compared to the responders).[35] Curiously in the same publication, for patients already on imatinib, a dramatic increase of α-defensin 1-3 and α-defensin 4 expression predicted imminent relapse and preceded increase in *BCR-ABL* transcript levels.

Another retrospective study included 488 CML patients in chronic phase who were treated with imatinib as first-line TKI.[36] Of these, 96 (19%) had suboptimal response after 18 months of treatment. Of these, 65 patients (67%; Group 1) continued with imatinib (either initial dose or higher dose), whereas the remaining 31 (33%; Group 2) were switched to either dasatinib or nilotinib. Group 2 (given second-generation TKIs) showed better CMR (27% vs. 3.8%) and MMR (69% vs. 41.5%; $P = 0.006$). Time to achieving best molecular responses was also significantly lower in Group 2 (4.1 vs. 20.2 months; $P = 0.004$).

Thus, it is possible to identify patients who are unlikely to have optimal response to imatinib as well as those who are in imminent danger of losing their response. Also, early switching to second-generation TKIs gives them the potential benefit of deeper and faster response – features that are surrogate markers for better long-term outcome.

Issue 10: Treatment beyond current TKIs

Ponatinib is a promising novel TKI active against the T315I *BCR-ABL* mutation, which confers resistance to currently available TKIs. In the phase II PACE study, ponatinib produced major cytogenetic and hematologic responses in more than half of patients.[37] Targeting stem cells is an important future therapeutic direction in CML.[38]

Immunotherapy with K562/GM-CSF vaccine produced a decline in disease burden in early phase clinical testing, including MMR and CMR.[39] The Hedgehog inhibitors targeting an important pathway for stem cell proliferation and maintenance of integrity in CML and other leukemias are in clinical testing.[40] Strong responses in clinical trials are leading to development of new strategies to improve long-term outcomes.

Summary and Conclusions

We have come a long way in the management of CML.[41] Timely and accurate monitoring is the key to optimizing patient management. If the patient secures an optimal therapeutic response as per ENL guidelines, then there is no need to change therapy. If the patient has suboptimal response, he/she is eligible for alternative drugs (second-generation TKIs) that may give better response. However, this shift becomes mandatory if the patient has therapeutic failure on first-line drugs. Nilotinib has the edge over dasatinib as the first choice of a second-generation TKI (vide supra) in many ways. Other options include bumping up the dose of imatinib, hematopoietic stem cell transplantation, or the use of an agent undergoing clinical trials. The choice of the second-line therapy is also dictated by whether the patient has a T315I mutation or not – ponatinib being the most promising agent in such a case. In spite of the rapid advances in this field, several issues remain open, including but not limited to choice of first therapy for CML in CP, appropriate monitoring of patients, whether imatinib can be discontinued, selecting the right second line therapy and what to expect in the near future.

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