

# Managing Relapse of CML Using Therapeutic Imatinib Plasma Level

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## Case Report

A 52-year-old woman had been diagnosed 7 years earlier with de novo chronic-phase chronic myelogenous leukemia (CML) with an intermediate-risk Sokal score. A complete hematologic response and cytogenetic remission was achieved after 3 months of treatment with imatinib 400 mg daily. Molecular remission was achieved after 10 months.

Approximately 2 years after initial CML diagnosis, the patient developed intolerable gastrointestinal side effects and depression. She attributed these symptoms to imatinib (Gleevec, Novartis), and chose to discontinue her treatment. Five months later, she relapsed molecularly and resumed imatinib 400 mg daily. Ten months after re-initiating imatinib, she achieved a second molecular remission. The patient remained in remission for 30 months, then relapsed again molecularly with gradually worsening transcript levels. The patient remained compliant with her medication; however, molecular relapse was verified twice within the next 3 months and the patient was considered to have failed imatinib therapy.

BCR/ABL kinase domain mutational analysis was requested but there was insufficient BCR-ABL transcript for analysis. The trough plasma concentration of imatinib was assessed at 563 ng/mL (borderline low), and the imatinib dose escalated to 600 mg. One month after this imatinib dose adjustment the patient re-achieved molecular remission and has remained so for 15 months (Figure 1).

## Discussion

This case illustrates that in addition to medication adherence, achieving maximum benefit with imatinib

therapy may require optimal dosing as determined by therapeutic imatinib plasma levels. Pharmacokinetic factors such as individual patient variation in drug absorption and metabolism; interactions between prescribed medications; and other patient-related factors can affect drug exposure.<sup>1-4</sup>

This case also illustrates that relapse is not solely determined by resistance mechanism such as the BCR/ABL kinase domain mutation, which would require use of alternate treatment agents such as dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis).<sup>5</sup>

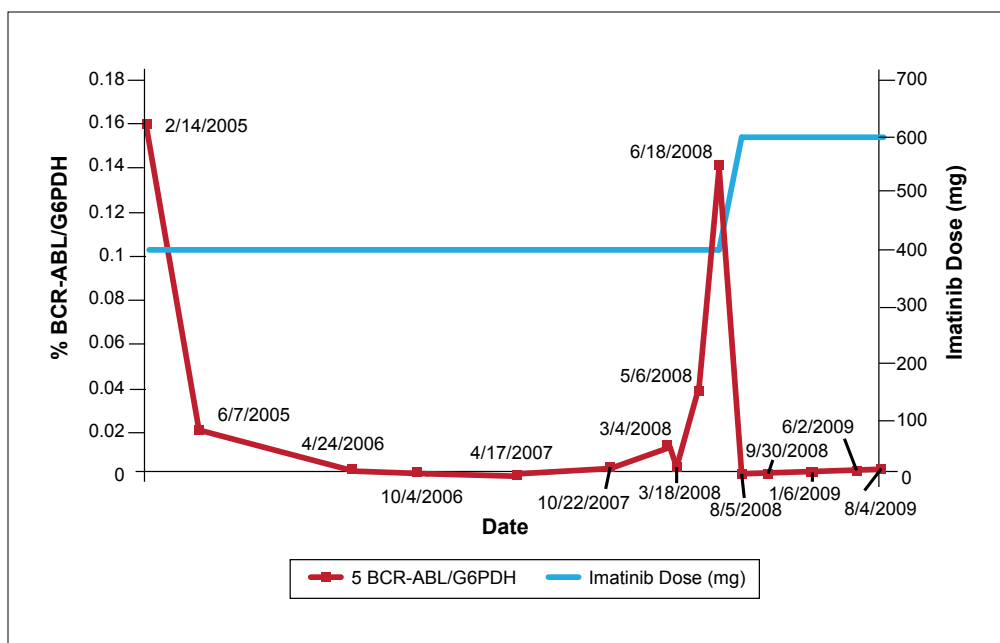
The overall goal of CML treatment should be to obtain earlier complete cytogenetic response (CCR) and major molecular response (MMR), and be able to maintain this response for a longer period of time. Those who have MMR early in the treatment course have a lower risk of relapse, and therefore have a better prognosis.<sup>6,7</sup> Overall response rates to imatinib are favorable, with the initial response rate over 80–90%.<sup>8,9</sup> Despite the initial high response rate to imatinib, some patients' response to treatment is inadequate; approximately 20–30% of patients with newly diagnosed chronic phase CML treated with imatinib will not achieve a CCR within 1 year of treatment.<sup>8</sup> Additionally, approximately 10% of patients will experience relapse within 5 years of follow-up, including approximately 10% who had achieved a CCR.<sup>10</sup> Higher rates of treatment failure occur in patients with accelerated- or blast-phase disease.<sup>11-13</sup>

Resistance to imatinib can be BCR-ABL dependent or independent<sup>11</sup>; it can also be primary or acquired based on whether resistance is present at diagnosis or developed later during imatinib therapy. Such mechanisms of resistance include:

- Increased plasma protein binding to imatinib
- Increased imatinib efflux via the p-glycoprotein pump
- BCR-ABL mutation
- Philadelphia chromosome amplification
- BCR-ABL independent transforming pathways such as an overexpression of Src-related kinases

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**Figure 1.** Imatinib dose and percent BCR-ABL/G6PDH level.

Pharmacokinetic monitoring of trough plasma levels of imatinib may be helpful to predict, detect, and prevent relapse when used in conjunction with standard monitoring of CML by quantitative polymerase chain reaction. In a recent study, Picard and colleagues reported higher average trough levels of imatinib in patients who respond better with a level of 1,452 ng/mL found in patients who achieved a MMR compared to those who did not achieve a MMR ( $P < .001$ ).<sup>4</sup> Another study<sup>14</sup> reported higher trough imatinib levels of 1,009 ng/mL in patients who obtained a CCR compared to an average level of 812 ng/mL in those who did not respond as well ( $P = .0116$ ). When the investigators used a cutoff level of 647 ng/mL, they found that the group with higher trough imatinib levels had MMR of 40% at 1 year and 80% at 4 years, compared to 25% at 1 year and 53% at 4 years in the lower trough level group.

Determination of plasma trough levels of imatinib at certain key points during the treatment course could be helpful not only by providing prognostic data, but by providing useful information toward ensuring and reinforcing compliance. Routine monitoring would allow for individual dose adjustments to maintain higher imatinib levels. Based on the half-life of 20 hours, a steady state should have been achieved within 1 week of imatinib therapy.<sup>14</sup> If a patient has a sub-optimal response or progression of CML, checking

the trough imatinib level could determine if there is a need to increase the imatinib dose or if imatinib is not likely to be effective any longer. Checking levels when a patient is experiencing excessive side effects could indicate need for a dose decrease to minimize side effects, while still maintaining therapeutic drug levels. Also, checking imatinib blood levels when compliance is in question may help determine if the patient is not taking the medication at all, or not taking the full amount as prescribed. Patients may intentionally underdose or not take the medication due to side effects<sup>14-16</sup> and cost issues.<sup>17-20</sup>

This case illustrates the importance of determining the plasma trough level of imatinib and also the effectiveness of increasing the dose of imatinib. Rather than conclude imatinib to be ineffective altogether, this dose escalating approach has allowed the patient to continue on a well-tolerated regimen and thus far has been a successful and appropriate option. Although there are alternative treatment options for CML, the options are somewhat limited. Adjustments to dose should be made first before exhausting the utility of imatinib. Starting at higher doses of 800 mg daily has been studied<sup>15,16,21</sup>; however, this may be a higher dose than necessary for most, as they are likely to respond to the standard dose of 400 mg daily. Also, higher risk of side effects<sup>14,22</sup> (mainly gastrointestinal toxicities, arthralgia/myalgia, rash, fatigue, and myelosuppression) and greater cost accompany higher doses.<sup>17-20</sup>

Pharmacokinetic factors such as individual patient characteristics including age, sex, race, and weight; variation in drug absorption and metabolism; and interactions between prescribed medications may affect drug exposure. Achieving maximum benefit with imatinib therapy may require optimal dosing as well as adherence to therapy.<sup>14</sup> In addition to affecting response and adverse effect, maintaining optimal trough level may have influence on the emergence of resistance clone. One hypothesis for the absence of a certain BCR/ABL mutation in the Asian population is that at the same doses of imatinib, plasma imatinib levels in Asian patients are higher than those in Caucasian patients, resulting in the suppression of low-level imatinib-insensitive mutation. Conversely, the frequencies of high-level imatinib-insensitive mutations are similar in both the Asian and Caucasian populations.<sup>23</sup>

## Conclusion

Achieving maximum benefit with imatinib therapy may require optimal dosing as well as adherence to therapy. Maintaining patients at optimal therapeutic trough level is beneficial for response and the adverse effect profile. This balanced strategy may have influence on delaying or preventing the emergence of resistance clone.

Most patients with CML will respond to the conventional starting dose of 400 mg per day. In CML patients with suboptimal response to imatinib at 400 mg per day, monitoring blood levels of imatinib would be most helpful to physicians in determining if the dose should be increased, or whether, in the case of imatinib failure, alternative therapies such as dasatinib, nilotinib, and allogeneic stem cell transplant (in eligible patients) should be considered.

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# Review

## Imatinib Plasma Trough Levels in the Management of CML: Ready for Prime Time?

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### Introduction

The advent and no-cost access of imatinib (Gleevec, Novartis) trough level testing has brought much interest and potential for use as optimization of chronic myelogenous leukemia (CML) therapy continues. Onitilo and colleagues<sup>1</sup> describe a case of typical chronic phase CML, determined as intermediate risk by the long-established Sokal score, prognostic in the imatinib era, where plasma trough level testing at the time of molecular relapse after prior prolonged treatment interruption was utilized to guide clinical decision-making. What do we know about this “tool” for the CML clinician and patient, and what are its limitations?

### The Case

After very prompt remission (ahead of schedule relative to National Comprehensive Cancer Network<sup>2</sup> and European LeukemiaNet<sup>3</sup> guidelines “optimal” time landmarks) the patient experienced limiting nonhematologic toxicity later in the treatment course. Typically, imatinib toxicity is evident early on (prior to 18 months) and thus attribution to imatinib may be subjective. Relapse occurred within several months of imatinib discontinuation, consistent with recent reports of the time course and frequency of relapse after imatinib discontinuation.<sup>4</sup> Molecular remission was then regained and sustained over a period of years.

Onitilo and colleagues describe late molecular relapse despite ongoing treatment and confirmed adherence to prescribed dose. This raises the question of the quality of

a remission regained after imatinib discontinuation and re-treatment at the time of relapse, and the potential for emergence of disease with novel biologic or molecular features less likely to remain in stable remission. Not unusual with low-level molecular positivity only, transcripts were insufficient for analysis.

### The Role of Trough Level Testing

We now turn to the question at hand: what is the role of imatinib trough level testing in this case, and in general at this point in the management of patients on imatinib therapy for CML? We see in the presented case a trough level of 563 ng/mL at the time of relapse, described as “borderline low”. How do we define imatinib trough levels? The primary data regarding imatinib trough levels are derived from the IRIS trial, where patients with newly diagnosed CML were treated with standard imatinib, and at day 29 of therapy, samples were taken measuring plasma trough concentrations of imatinib and its main metabolite, CGP74588.<sup>5</sup> Not surprisingly, a Gaussian-like (“bell-shaped”) distribution was demonstrated, and patients were thus divided into 4 quartiles. The conclusions from this study were that steady state imatinib trough levels correlated significantly with response (lower quartile faring worse than upper 3 quartiles), higher levels showed a trend towards event-free survival, and levels inconsistently predicted toxicity. Also in conjunction with Sokal risk score, trough level was a strong predictor of likelihood of cytogenetic response. Other reports have confirmed this conclusion,<sup>6</sup> and a single report has refuted the association.<sup>7</sup>

With regard to the case described by Onitilo and colleagues, it is important to note that resistance may not be related to imatinib exposure per se; imatinib-resistant BCR-ABL kinase domain mutations have been demonstrated in advanced Philadelphia chromosome positive leukemias prior to imatinib exposure,<sup>8</sup> suggesting that clonal instability and genesis of resistant subpopulations may be more part of the natural history of the disease. A prolonged period of treatment interruption could either allow for de novo resistance to develop, or permit proliferation of previously quiescent elements, either case resulting in more challenging disease at treatment re-challenge. In describing what appears to be dose-escalation-related regaining of molecular response—presumably by increasing the “borderline” trough level to or over the proposed 1,000 ng/mL “threshold”—the case raises the important question of the impact of attempts to optimize the trough level. We do not have information about a new “corrected” trough level in this case to associate with restoration of response, and data in this area are limited to date. Based on the “target”

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threshold trough of 1,000 ng/mL, correction of patients' trough up to this level has been associated in 1 study<sup>9</sup> with an improvement in molecular response; however, it may be premature to state that this is a proven strategy to subvert resistance or improve outcome.

A recent review outlined the potential variables affecting imatinib trough levels and clinical scenarios where knowledge of the level may be useful and relevant.<sup>10</sup> Variables may include incomplete adherence, intrinsic variations in the metabolism of imatinib, and drug-drug interactions. Clinical scenarios where testing is likely being done or where it has been proposed include inadequate response (treatment failure) and suboptimal response (first and foremost), when poor adherence is suspected, when adverse reactions are unusually severe, or when there are possible drug-drug interactions. Other work aimed at understanding underlying mechanisms of imatinib resistance has described additional potential assessable factors, such as variable transport of imatinib via the cation transporter OCT-1<sup>11</sup> and differential binding of imatinib to the plasma protein alpha-1 acid glycoprotein.<sup>12</sup>

### Limitations of Imatinib Trough Testing

Currently the use of imatinib trough level testing as a tool to investigate adherence/compliance is limited by the "staged" nature of the test. The clinician must give advanced notice to the patient and query about dosing regularity and timing, this certainly raises the possibility that the patient may change their behavior and thus affect the reading. Of course, for all instances it remains vitally important for the trough level to be timed appropriately pre-dose and that a detailed history is known about antecedent patient dosing to confirm steady-state status, especially if clinical action (eg, dose escalation or reduction) is taken on trough levels. Repeating the trough level may be reasonable to confirm unusual findings where intervention is planned, and follow-up trough levels after intervention are certainly logical.

### Conclusions

Much more research is needed to allow full understanding of imatinib trough levels and their implications; however, there is a sufficient body of evidence to support incorporation of such testing in the appropriate clinical situations in a routine fashion. Clinical trials are ongoing in order to better understand the role of widespread use ("screening") with imatinib therapy for CML. As we incorporate this

assay further we must differentiate what we know—that early levels are likely predictive of subsequent response and risk—from what remains to be proven conclusively, such as the implications of trough levels in the case of toxicity, the role of "correcting" the trough level in the case of inadequate imatinib response, and the ability to monitor compliance and adherence with trough level testing. Forthcoming development in this field will include the ability to assay the plasma level at variable time points and extrapolate the trough level,<sup>13</sup> making the use for the purpose of compliance/adherence as well as for other clinical scenarios much more practical and attainable to the clinician. As has been stated widely, imatinib trough level testing is one of several tools the clinicians should utilize to optimize therapy for the CML patient on imatinib.

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