

Using imatinib blood level testing to optimize therapy

A case-based review

EUTOS for CML



European Treatment and Outcome Study



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Editorial Reviewers

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INTRODUCTION

Background

Chronic myeloid leukemia (CML) is a proliferative disease characterized in 95% of patients by the presence of the Philadelphia chromosome, which is generated by a reciprocal t(9;22) chromosome translocation in a hematopoietic stem cell.^{1,2} This aberrant chromosome harbors a BCR-ABL fusion gene that encodes BCR-ABL, a fusion protein with deregulated (constitutive) tyrosine kinase activity that contributes to malignant transformation. BCR-ABL tyrosine kinase activity results in excessive proliferation and decreased apoptosis of CML cells, as well as decreased sensitivity to the regulatory influence of bone marrow stromal cells, leading to massive clonal expansion.^{3,4}

Identification of the underlying cause of CML led to the development of rationally designed drugs that target BCR-ABL tyrosine kinase activity as potential treatment for this disease. One of these drugs, imatinib mesylate (Glivec®/Gleevec®; STI571), is a 2-phenylaminopyrimidine that inhibits the tyrosine kinase activity of BCR-ABL, as well as certain other protein tyrosine kinases.⁵⁻⁸ More effective than previous therapies for CML, imatinib is now the standard of care for this disease.^{9,10}

Imatinib has activity in all phases of CML but produces its most extensive and durable responses in newly diagnosed patients with chronic-phase disease. Analysis of follow-up data for patients with newly diagnosed CML who received imatinib as initial therapy in the International Randomized Interferon Versus STI571 (IRIS) study^{11,12} showed that, at 60 months after initiation of therapy, 89% of the patients were still alive.¹³ This rate is higher than that reported in any previously published prospective study of CML treatment. Moreover, by 60 months, 87% of patients had achieved a complete cytogenetic response (CCyR). Imatinib also induces therapeutic responses in patients with advanced (accelerated phase or blast crisis) CML; however, response rates are lower, and relapse commonly occurs within 1 year.¹⁴⁻¹⁶

Relapse or suboptimal response in patients receiving Imatinib therapy can be caused by several factors, including emergence of point mutations within the gene encoding the kinase domain of the BCR-ABL protein that reduce the binding affinity of Imatinib, amplification of the *BCR-ABL* gene, and overexpression of the multidrug resistance (MDR) gene encoding P-glycoprotein.^{17,18} However, pharmacokinetic variability and nonadherence to the prescribed imatinib dosage regimen may also play a role in variable responses to imatinib.¹⁹⁻²¹

Pharmacokinetic Factors and Response to Imatinib

Many factors alter the disposition of imatinib: decreased absorption due to gastrointestinal anatomic abnormalities or disease states that interfere with this process; binding to plasma proteins, mainly alpha 1 acid-glycoprotein and albumin; interaction with drugs that increase or decrease the activity of major metabolic enzymes of imatinib such as CYP3A4; and extrusion by efflux transporters such as P-glycoprotein. These factors can affect the plasma concentration (level) of imatinib over time and subsequently alter its pharmacologic effect.^{20,22-27} Evidence suggests that plasma concentrations of imatinib correlate with clinical response,^{28,29} and thus too low a plasma concentration of this agent can result in decreased efficacy, seen as failure to achieve or maintain a CCyR or a major molecular response (MMR).

A correlation was found in a phase 1 study between hematologic response and imatinib dose, area under the time/concentration curve (AUC), maximum plasma concentration (C_{max}), and trough plasma concentration (C_{min}).¹⁹ A correlation between imatinib C_{min} and achievement of a CCyR or MMR with standard-dose imatinib in patients with chronic-phase (CP) or accelerated-phase (AP) CML (CML-CP or CML-AP) was found in another study.²⁹ Samples for determination of imatinib trough plasma concentrations were obtained approximately 24 hours after the last dose in 68 patients. The analysis showed that, after 12 months of treatment, mean trough

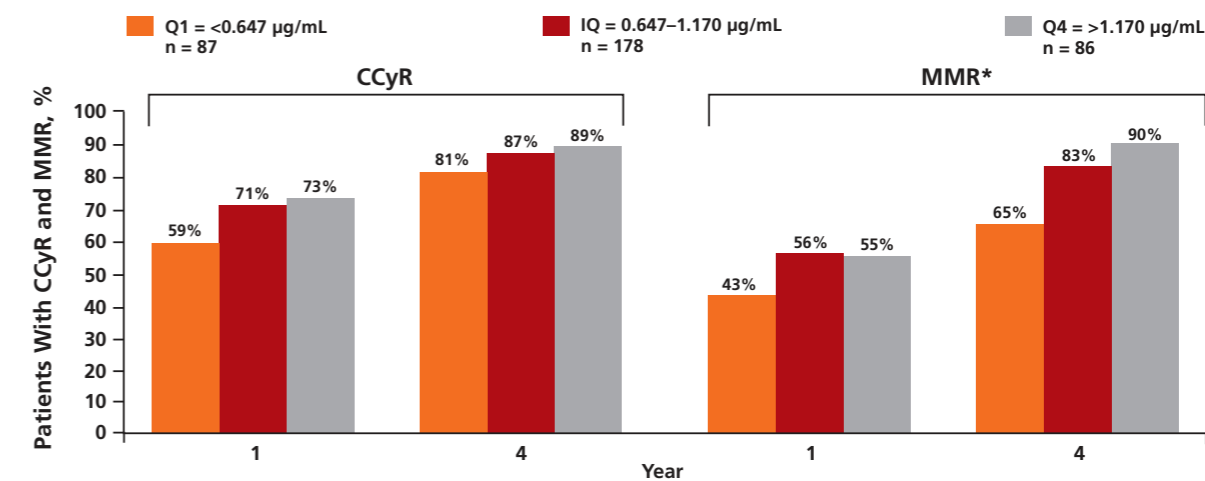
plasma concentrations of imatinib were significantly higher in patients who achieved CCyR or MMR compared with patients who did not reach these levels of response (CCyR: $1.123 \pm 0.617 \mu\text{g/mL}$ vs $0.694 \pm 0.556 \mu\text{g/mL}$, $P = 0.03$; MMR: $1.452 \pm 0.649 \mu\text{g/mL}$ vs $0.869 \pm 0.427 \mu\text{g/mL}$; $P < 0.0001$). In the IRIS study, the relationship between clinical response and steady-state trough plasma concentrations of imatinib after 400 mg dosing was examined in newly diagnosed patients with CML-CP.²⁸ Trough plasma concentrations were measured at day 1 and day 29 (steady state), and patients were then stratified according to drug trough concentration (lower quartile [Q1], values in the range of 0%–<25%; interquartiles [Q2 + Q3], values in the range of 25%–75%; upper quartile [Q4], values in the range of >75%–100%). Day 29 trough plasma concentrations of imatinib were predictive of CCyR or MMR at both 1 year and 4 years. The C_{min} of imatinib was significantly higher in patients who achieved CCyR compared with patients who did not ($1.01 \mu\text{g/mL}$ vs $0.812 \mu\text{g/mL}$ [$P = 0.0116$]). Rates of MMR at 1 year were lower in patients in the lowest imatinib plasma concentration quartile compared with all other patients (25% vs 40%) (Figure 1).²⁸ Trough plasma concentrations following the first dose of imatinib also correlated with CCyR and MMR rates, but were less predictive than the steady-

state trough level. Together, results of these studies suggest that monitoring to ensure adequate imatinib trough plasma concentrations could be useful in optimizing response in patients with CML.

Impact of Adherence on Response to Imatinib

Adherence to (compliance with) the prescribed regimen may also influence imatinib plasma concentration, with failure to follow the prescribed regimen potentially resulting in drug plasma concentration below the target concentration. This is a concern for physicians treating their oncology patients, as non-adherence to standard oral antineoplastic agent regimens has been associated with worsening of disease, increased physician visits and hospitalizations, unnecessary diagnostic testing, and changes in dose or regimen.³⁰ Adherence rates for oral antineoplastics range from 20% to 100%; patients may over-estimate their adherence by a factor of 2 in discussions with their physicians.³⁰ Typical reasons given by patients for not taking their medication as prescribed are that they forgot, had other priorities, or were experiencing unpleasant side effects. Often, patients are unaware of the critical importance of taking their medication as prescribed.

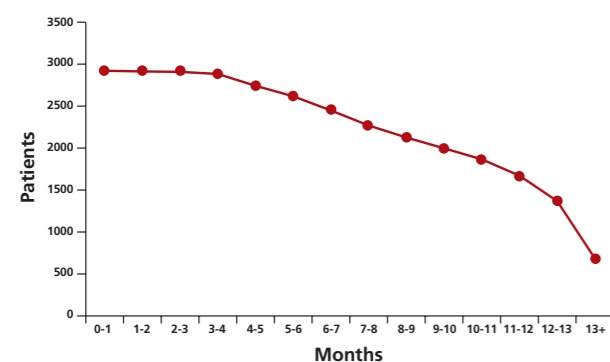
Figure 1. Correlation between response rates and imatinib trough levels after 1 year and 4 years of treatment²⁸



*In patients with CCyR. Ranges are in parentheses. CCyR, complete cytogenetic response; IQ, interquartiles; MMR, major molecular response.

Adherence to imatinib dosing was specifically investigated in a study that reviewed patient-level pharmacy claims data for 4043 patients with either CML or gastrointestinal stromal tumor.³¹ Analysis of these data revealed that, on average, CML patients took only 78% of their prescribed medication. Moreover, all patients were on therapy for only 62% of the study period (255 days out of 24 months), with adherence beginning to decline after 4 months of treatment (Figure 2). For patients with serious medical conditions, adherence rates of 95% or greater are considered the goal.³²

Figure 2. Adherence* to imatinib³¹



*Time on therapy without significant gaps in refills.

Factors driving suboptimal adherence and persistency can be summarized in 4 major points. The first is an inadequate response to initial doses. This can lead patients or physicians to stop or to switch treatment before considering a dose increase when indicated and giving the current medication time to reach peak plasma concentrations. Another factor is the patient misperception that a positive treatment response represents a 'cure'. Such misperception can also lead to treatment drop-off, as the patient erroneously believes that he or she no longer needs to take the medication. A third factor is patient- or physician-initiated treatment interruptions, for a variety of reasons. These can include inconvenient scheduling, forgetting to take a dose, or 'taking a break' from therapy. The fourth, and arguably the most important factor contributing to suboptimal compliance, is poor side-effect management. Unaddressed side effects may cause patients to stop or lower treatment

dosing on their own in an attempt to minimize the adverse reactions, or physicians will initiate the treatment interruption until side effects abate on their own.

Potential strategies to overcome problems with adherence to therapy include patient education, improved communication between physicians and patients regarding treatment expectations, improved dosing schedules for optimizing convenience, and the effective management of side effects. Therefore, clinical experts recommend routine patient support programs and improved communications to help optimize patient outcomes.

Monitoring Imatinib Levels in CML Patients

Clearly, monitoring imatinib plasma concentrations to ensure that the target concentration is being achieved can be a useful strategy for optimizing the benefits of imatinib therapy. There are several situations in which you may want to consider testing imatinib plasma levels in CML patients.

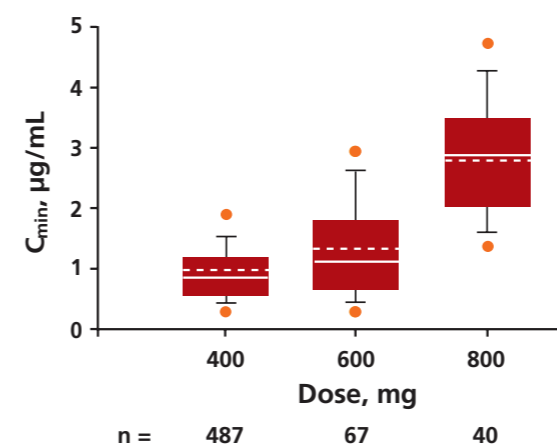
- You suspect the patient may be nonadherent to imatinib therapy.
- You suspect the patient may be experiencing a drug-drug interaction.
- The patient is not responding to imatinib as well as you believe he or she should.
- The patient is experiencing side effects that are unusually severe for the dose of imatinib being taken.

Trough plasma concentrations of imatinib are especially suitable for monitoring as they are easy to obtain and vary less over time than the plasma AUC. Titier et al³³ recently described a high-performance liquid-chromatography method coupled to electrospray-ionization tandem mass spectrometry for the quantitation of imatinib in human plasma. The method is rapid, simple, sensitive, and suitable for routine application.³³ Other high-performance liquid-chromatography assays have also been used to determine imatinib plasma concentrations, including those described by Bakhtiar et al³⁴ and Parise et al.³⁵ At the recommended starting dose of 400 mg/d, the

mean trough plasma concentration (SD) of imatinib at steady state is approximately 0.98 (0.53) µg/mL. At doses of 600 mg/d administered once daily and 800 mg/d administered daily as 2 divided doses (400 mg x 2), the steady-state mean trough plasma concentrations are approximately 1.37 (0.82) and 2.88 (1.09) µg/mL, respectively (Figure 3).^{19,36,37}

The minimum effective plasma concentration of imatinib has not been fully defined, and the

Figure 3. Pharmacokinetic trough concentrations of imatinib in patients with Ph+ CML^{19,36,37}



Top and bottom walls of each box represent the 75th and 25th percentiles. Whiskers (error bars) above and below each box indicate the 90th and 10th percentiles, and the dots represent the 95th and 5th percentiles.

relationship between imatinib blood concentrations and outcomes remains under investigation. Nevertheless, maintaining trough concentrations at or above the average concentration at the intended dose (1 µg/mL for 400 mg/d) is recommended when tolerable. Blood concentrations below this should be avoided, and the physician should make every effort to determine the underlying cause.

Summary

- Inadequate imatinib exposure due to pharmacokinetic factors or nonadherence may compromise clinical outcomes in CML patients.
- Monitoring imatinib trough plasma concentrations could help avoid low exposure in certain clinical situations.

- Monitoring imatinib trough plasma concentrations may ensure that the target concentration is achieved and may initiate discussion of the importance of adherence and guide clinical decision making.

The following are selected case studies describing how monitoring of trough plasma concentrations of imatinib helped physicians to identify nonadherence or suboptimal dosing and institute measures to optimize therapy. The cases reflect treating physicians' clinical judgment, and the steps taken may not conform to current treatment algorithms.

Case 1:

Nonadherence

Synopsis

The patient is a 50-year-old woman with de novo CML-CP and a high-risk Sokal score. She is currently receiving imatinib 400 mg/d. At 3 months, she had not achieved a complete hematologic response (CHR) (Table 1). The lack of a CHR was confirmed at 6 months, and the patient was considered in failure.

Clinical Discussion

The National Comprehensive Cancer Network (NCCN) guidelines and a recent European LeukemiaNet consensus paper cite achievement of a CHR by month 3 of therapy as a minimum initial response and lack of complete hematologic response by month 6 as failure (Table 1).^{9,10} Based on these guidelines, this patient was considered a treatment failure. Under the guidelines, 'failure' indicates that continuing imatinib therapy at the present dose is no longer appropriate for the individual patient and that an alternative treatment strategy should be considered. In such cases, there are several therapeutic options, including increasing the dose of imatinib or switching to another tyrosine kinase inhibitor or to combination therapy. Kantarjian and his colleagues, for example, escalated the dose of imatinib to either 600 mg daily or 400 mg twice a day in

Table 1. Criteria of response to imatinib⁹

	3 Months	6 Months	12 Months	18 Months
Failure	No hematologic response	>95% Ph+	>35% Ph+	>0% Ph+
Suboptimal Response	No complete hematologic response	35%-95% Ph+	1%-35% Ph+	0% Ph+; <3-log decrease in BCR-ABL transcripts
Optimal Response	1- to 2-log decrease in BCR-ABL transcripts	<35% Ph+	0% Ph+; ≥3-log decrease in BCR-ABL transcripts	0% Ph+; ≥3-log decrease in BCR-ABL transcripts

54 patients with CML-CP who showed resistance to, or had relapsed on, imatinib 400 mg/d.³⁸ Of 20 patients with hematologic resistance or relapse, 13 (65%) achieved a complete (n = 9) or partial (n = 4) hematologic response (HR), and of 34 patients with cytogenetic resistance or relapse, 19 (56%) achieved a complete (n = 6) or partial (n = 7) cytogenetic response (CyR).

Because this patient was treated in an investigational setting, mutation analysis was performed before making any decisions regarding modification of the patient's imatinib therapy. However, no mutation in the kinase domain was detected. The trough plasma concentration of imatinib was then determined and was found to be <0.01 µg/mL at 3, 6, and 9 months despite imatinib dose escalation to 600 mg/d between 3 and 6 months and to 800 mg/d between 6 and 9 months. This was far below the anticipated trough concentrations of ~1.0 µg/mL with imatinib 400mg/d and 1.4 and 2.9 µg/mL with imatinib 600 mg/d and 800 mg/d, respectively.

Follow-up

Upon further questioning, the patient acknowledged that she was forcing herself to vomit after taking her prescribed medication. This case of nonadherence illustrates that failure to medicate correctly can result in a low plasma trough concentration and a poor outcome in patients receiving oral targeted agents, including

imatinib, as chronic therapy for cancer. This case also illustrates potentially unexpected behavior in a patient who may be assumed to correctly take her medication, highlighting the need for physicians to thoroughly explore any instances of, and reasons for, patient nonadherence, as well as to reinforce with their patients the importance of following the prescribed medication regimen.

Case 2:

Discontinuation of Imatinib Without Recommendation

Synopsis

A second case of nonadherence was that of a 55-year-old man with newly diagnosed CML-CP who had been started on imatinib 400 mg/d. Over the next 6 months, he achieved a CHR, but by month 9 of therapy, he lost his hematologic response. The patient initially stated he was following his prescribed regimen. However, subsequent testing at that time showed that the patient's imatinib plasma concentration was zero. On further questioning, the patient admitted to discontinuing imatinib therapy without discussing this with his physician.

Clinical Discussion

This case, like the preceding one, illustrates the crucial issue of adherence to chronic oral therapy in patients with malignancies. Chronic administration by the oral route raises a number of concerns not encountered with intermittent parenteral therapy. These concerns include the potential for less than 100% absorption of the administered dose; the fact that the patient may not receive all of the intended dose because he or she does not adhere to the chronic oral ingestion required; and the fact that the drug effect, be it toxic or therapeutic, need not be related to a single administration of the drug. Patients fail to adhere to chronic oral therapy for many reasons, including simply forgetting to take their medication, poor side-effect management, psychological reasons for discontinuing therapy,

and the belief that once they have achieved a response and are not experiencing disease symptoms or side effects there is no need to continue therapy. It is important to recognize that disease progression is not necessarily the same as resistance, and that, in some patients, progression or reappearance of disease may reflect patient-initiated discontinuation of therapy rather than disease mutation to a resistant state. These concepts are well recognized in psychiatry, infectious disease, cardiology, hypertension, and other areas of medicine. Recent studies have described patient characteristics associated with decreased adherence; have demonstrated that approximately 30% of patients may discontinue imatinib for at least 30 days during their first year of therapy; and have calculated the high costs associated with nonadherence to imatinib therapy.³¹

Follow-up

The importance of continuing imatinib therapy was discussed with the patient, and imatinib was reinitiated at a dose of 400 mg/d. The patient once again achieved a CHR and went on to achieve a CCyR. Repeat assessment of plasma imatinib trough concentrations documented them to be consistent and within the range associated with clinical activity.

Case 3:

CCyR Without MMR

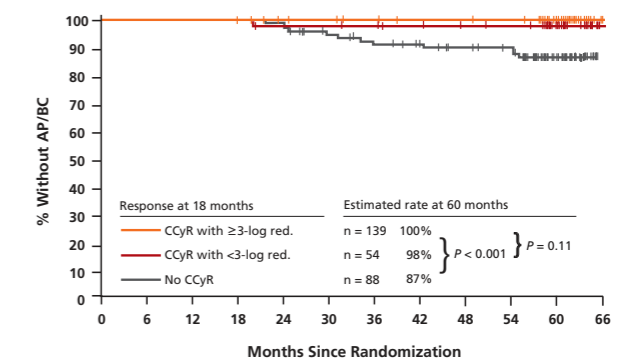
Synopsis

A 51-year-old man was diagnosed in 1998 with Philadelphia-chromosome-positive (Ph+) CML-CP (Sokal score, 0.63; Hasford score, 1036). He underwent leukapheresis and was treated with interferon alfa until 2000. Because no CHR was achieved, treatment with imatinib 400 mg/d was initiated in March 2001. With imatinib therapy, the patient achieved a major cytogenetic response (MCyR) after 3 months and a CCyR after 6 months. Molecular monitoring with real-time quantitative polymerase chain reaction (RQ-PCR) methodology, performed 6 months after

initiation of imatinib treatment, revealed that, despite having a sustained CCyR, the patient did not achieve an MMR, ie, a ≥3-log reduction in BCR-ABL transcripts compared with baseline value.

In 2005, at which time the patient had been receiving imatinib for 4 years, his imatinib trough plasma concentration at steady state was tested on 2 occasions. Levels were 0.61 µg/mL and 0.58 µg/mL, respectively, which is about half the expected concentration. His imatinib dose was therefore escalated to 600 mg/d. Clinical Discussion Testing for achievement of an MMR is a new approach to monitoring response to imatinib but is currently not an established criterion of response. However, achievement of an MMR has been associated with a good long-term outcome in CML patients. Follow-up data for the IRIS study have shown that, at 60 months, rates of freedom from progression to AP/BC disease were 100% in patients with newly diagnosed CML and both a CCyR and ≥3-log reduction in BCR-ABL transcripts after 18 months of imatinib therapy, 98% in patients with a CCyR and <3-log reduction in BCR-ABL transcripts, and 87% in patients without CCyR (**Figure 4**).¹³

Figure 4. Survival without AP/BC by molecular response at 18 months on first-line imatinib



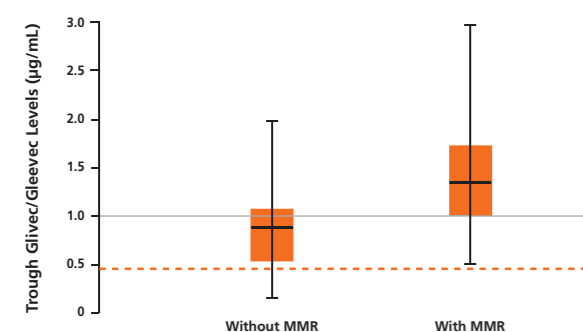
Rate of progression to CML-AP or CML-BC based on molecular response after 18 months of imatinib therapy. At 60 months, 100% of 139 patients with a CCyR and at least a 3-log reduction in levels of BCR-ABL transcripts at 18 months were free from progression to accelerated phase or blast crisis. Corresponding rates for 54 patients with a CCyR and <3-log reduction in transcripts and 88 without a CCyR were 98% and 87%, respectively.

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Therefore, directing therapy to achievement of an MMR in patients being treated for CML appears clinically sound. The European LeukemiaNet⁹ recommendations suggest that molecular response be checked every 3 months to assess continued reduction of transcripts and to detect signs of loss of response. The NCCN¹⁰ guidelines note that molecular monitoring by RQ-PCR analysis of patients who have achieved a CCyR can be extremely useful in determining whether transcript levels are going up or down.¹⁰

The case described here illustrates a situation in which monitoring of imatinib plasma trough concentrations was useful for the management of CML patients and should be undertaken in cases of treatment failure or suboptimal response. Our group recently demonstrated that the plasma trough concentration of imatinib is correlated with clinical response.²⁹ In addition, using a receiver operating characteristic (ROC) curve analysis, a trough plasma concentration of 1.002 µg/mL was identified as the efficient plasma threshold for imatinib levels in vivo (Figure 5). In the study, 26 (76%) of 34 patients with an MMR had imatinib trough plasma concentrations exceeding the 1.002 µg/mL threshold, whereas 24 (71%) of the 34 patients

Figure 5. Box-plots of imatinib trough plasma levels



The graph shows the dispersion around the median for patients with MMR (n = 34; median = 1.350 µg/mL) and those without (n = 34; median = 0.885 µg/mL). The line across each box is the median, the bottom edge is the first quartile, and the top edge is the third quartile; the error bars represent minimal and maximal values; the orange line shows the 0.4936 µg/mL target concentration required to result in BCR-ABL-positive cell death in vitro; the gray line shows the 1.002 µg/mL efficient plasma threshold for trough imatinib levels in vivo. Of note, 27 patients without an MMR (79%) had imatinib trough plasma levels exceeding the initially described target concentration (0.4936 µg/mL) required to result in BCR-ABL-positive cell death in vitro,²⁹ suggesting that this target is not always sufficient to achieve MMR in vivo.

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without an MMR had imatinib trough plasma levels below this level. These findings suggest that the imatinib plasma trough concentration should be maintained above 1.0 µg/mL for clinical efficacy for patients with CML-CP to achieve MMR.

Follow-up

After 3 months on an increased dose of 600 mg, the patient's imatinib plasma trough concentration had risen to 1.15 µg/mL, and the patient achieved an MMR that has been sustained for more than 6 months. Although achieving a CCyR remains the accepted marker of successful treatment, the favorable results reported for patients achieving an MMR helped justify our decision to increase the imatinib dose to a level that resulted in an MMR.

Case 4:

Drug-Drug Interaction Synopsis

A 64-year-old man presented with CML-CP and a history of seizure disorder. The patient's only medication at presentation was phenytoin 300 mg/d. The patient was started on imatinib 400 mg/d and tolerated therapy well; however, he failed to achieve an HR. His imatinib trough plasma concentration was found to be much lower than the concentrations found in other CML patients taking imatinib 400 mg/d. The patient stated that he was adherent to his daily imatinib therapy. A drug-drug interaction between imatinib and phenytoin was therefore suspected. A similar low trough plasma concentration was obtained 1 week after the first trough plasma level was determined.

Clinical Discussion

The patient's failure to achieve a response to imatinib appropriately raised suspicion of inadequate imatinib concentrations produced by his 400 mg/d dose. This hypothesis was confirmed by assessment of imatinib trough plasma concentrations. Low plasma concentrations of imatinib can result from a

variety of causes, including nonadherence and high imatinib clearance. The fact that the repeat imatinib value was similar to the initial low value confirmed the drug level test and argued for a phenytoin-induced increase in imatinib clearance as the cause for the low, and probably subtherapeutic, imatinib concentrations in this patient. Phenytoin, a known inducer of the major imatinib-metabolizing enzyme CYP3A4, has been documented as increasing imatinib clearance approximately 4-fold.⁴¹ Given the apparent involvement of phenytoin in the patient's failure to respond to imatinib, change of the antiseizure medication to a nonenzyme-inducing antiseizure medication was indicated. An alternative strategy, if the patient's seizures were not well-controlled with a nonenzyme-inducing antiseizure medication, would have been to continue his phenytoin, increase the imatinib dose, and monitor the imatinib trough plasma concentration to see if it increased to a therapeutic range.

Follow-up

The patient's antiseizure medication was changed from phenytoin to valproic acid without adverse neurologic consequences. The patient rapidly achieved a CHR, and thereafter, a sustained CCyR and complete molecular response (CMR). One month after the change in antiseizure medication, the patient's imatinib trough plasma level was in the range observed in other CML patients taking imatinib 400 mg/d. These responses following the change in antiseizure medication confirmed our suspicion of a drug – drug interaction as causing increased imatinib clearance and low imatinib levels. It should be remembered that drug-drug interactions can occur with over-the-counter and herbal medications that patients may neglect or be unwilling to divulge to physicians taking a history. An example of such an interaction is that of imatinib with St John's wort: St John's wort-associated induction of imatinib clearance results in subtherapeutic imatinib concentrations.^{42,43}

Case 5:

Low Imatinib Clearance

Case Synopsis

A 45-year-old woman with newly diagnosed CML-CP was started on imatinib 300 mg twice a day. On this regimen, she developed grade 3/4 musculoskeletal pain, as well as bone marrow hypoplasia associated with transfusion-dependent anemia. Administering erythropoietin and reducing the imatinib dose to 200 mg twice a day failed to reverse the anemia. The patient's imatinib trough plasma concentration was 3.1 µg/mL, which was much higher than expected with a 400 mg/d dose. The patient achieved a CMR but remained transfusion dependent. Repeat testing revealed imatinib trough plasma concentrations above 3.0 µg/mL.

Clinical Discussion

This patient had lower imatinib clearance than most patients and therefore maintained higher-than-expected imatinib trough plasma concentrations while on standard doses of therapy. Although the patient achieved a response with standard-dose therapy, she experienced unacceptable toxicity. Documentation of the higher trough plasma concentrations led physicians to explore whether decreasing the patient's dose of imatinib would allow maintenance of therapeutic levels of drug while producing concentrations lower than those responsible for the hematologic toxicity she was experiencing.

Follow-up

The patient's imatinib dosage was reduced to 300 mg/d, after which she became transfusion independent. Over the next 12 months, repeat testing revealed imatinib trough plasma concentrations of approximately 2.0 µg/mL, and the patient went on to achieve a CMR. Thus, the strategy of close plasma concentration monitoring and dose reduction (although to a level below that currently recommended) resulted in clinical benefits for the patient.

CONCLUSION

Although imatinib is highly effective in treating patients with CML, inadequate drug exposure due to pharmacokinetic factors or patient nonadherence to therapy may compromise clinical outcomes. Testing of imatinib trough plasma levels may provide a simple and rapid means for determining whether target levels of imatinib are being achieved and for alerting physicians to institute appropriate corrective measures when inadequate levels are detected, eg, in cases of nonadherence, drug-drug interactions, and patient pharmacokinetic variability. Moreover, given the relative ease and rapidity of imatinib trough plasma level testing, it is conceivable that such testing should be performed prior to mutational analysis in patients displaying suboptimal responses. Results from plasma drug level testing may aid in distinguishing nonadherence or the presence of drug disposition-altering pharmacokinetic factors from a lack of responsiveness to imatinib.

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