

Imatinib blood level testing

A new initiative in the era of
targeted therapy for Ph+ CML

EUTOS for CML



European Treatment and Outcome Study

 **NOVARTIS**
ONCOLOGY

Imatinib (Gleevec®/Glivec®, formerly STI571) has sparked a revolution in cancer therapy by dramatically improving treatment for Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML). Imatinib has produced unprecedented response rates that are durable for years in patients with Ph+ CML. More than 8 years of experience with imatinib in clinical trials and 5 years in the post-approval setting have demonstrated that imatinib is not only active but also is easy to administer, safe, and tolerable. We have also learned that optimizing benefit with imatinib therapy involves ensuring that patients are taking the drug as prescribed by their healthcare provider.

This backgrounder provides information on the pharmacokinetics of imatinib and the potential utility of blood level testing to optimize therapy with imatinib in the treatment of Ph+ CML. There are 4 reasons why you may want to consider testing a patient's imatinib blood levels:

- You suspect that the patient may be nonadherent with imatinib.
- You suspect that 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 be.
- The patient is experiencing side effects that are unusually severe for the dose of imatinib he or she is taking.

CML is a clonal myeloproliferative disease characterized by the presence of the Philadelphia chromosome.¹ This karyotypic abnormality results from the reciprocal translocation of genetic material between chromosomes 9 and 22, t(9;22), and leads to a fusion gene, the product of which is the constitutively active protein-tyrosine kinase, BCR-ABL. Biochemical signal transduction pathways stimulated by BCR-ABL kinase activity are responsible for Ph+ CML oncogenesis.²

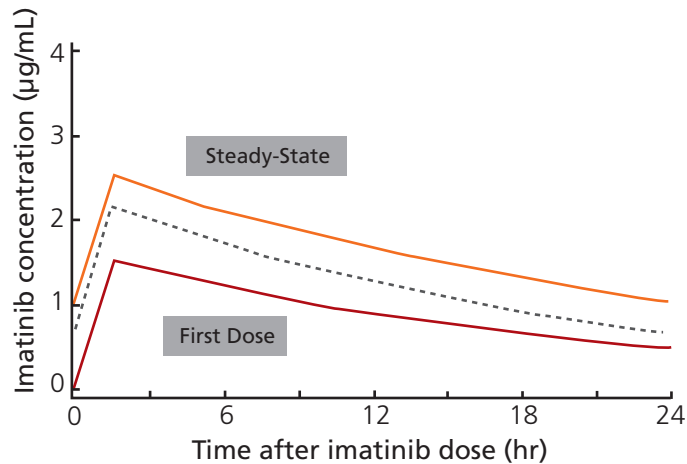
Imatinib is a small-molecule tyrosine kinase inhibitor that targets BCR-ABL.^{3,4} Inhibition of BCR-ABL kinase activity with imatinib underlies its clinical efficacy. Imatinib is currently the standard of care for all phases of Ph+ CML.⁵⁻¹⁰ In patients with Ph+ CML-chronic phase (CP), response rates to imatinib are high and durable, whereas patients in advanced phases of Ph+ CML may experience suboptimal responses and relapse more frequently.¹¹ Various factors have been shown to play a role in refractoriness to or relapse with imatinib therapy, including certain pharmacokinetic parameters of imatinib that can affect drug exposure.¹²

CLINICAL PHARMACOKINETICS OF IMATINIB

The pharmacokinetic parameters of imatinib have been determined in patients with Ph+ CML from the phase 1 dose-finding study.¹³⁻¹⁵ Imatinib doses ranging from 25 mg to 1000 mg daily were tested. Imatinib exposure, as defined by the area under the curve (AUC) of plasma concentration of drug versus time after drug administration, was found to be proportional to dose. A correlation was also observed with respect to imatinib dose and hematologic response in this trial.

Based on safety and efficacy results from the phase 3 International Randomized Study of Interferon and STI571 (IRIS) trial, imatinib 400 mg once daily is the recommended starting dose for patients with newly diagnosed Ph+ CML-CP.⁹ Imatinib dose escalation is recommended in cases of suboptimal response or loss of response.^{16,17}

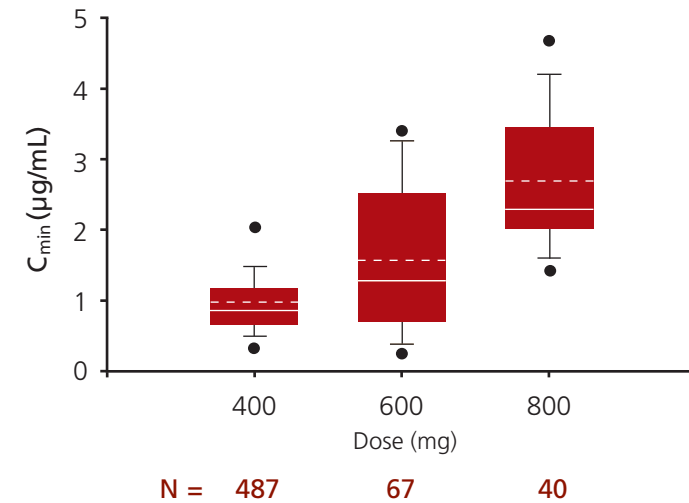
Figure 1. Plasma concentration versus time profiles of imatinib in patients treated with imatinib 400 mg once daily¹⁸



The lower and upper solid lines represent the pharmacokinetic profiles following the first dose on day 1 and at steady state.

Drug exposure is usually described by plasma AUC. The trough plasma concentration at steady state (C_{min}) is another plasma drug measurement that is often used as the index for clinical monitoring of drug exposure because it is easy to obtain and varies less with time. At the recommended imatinib starting dose of 400 mg/day, the mean imatinib C_{min} is approximately 1.0 µg/mL (Figure 1).¹⁸ At imatinib doses of 600 mg/day and 800 mg/day (administered as 400 mg twice daily), the mean imatinib C_{mins} are approximately 1.4 and 2.9 µg/mL, respectively. Administration of the 800 mg dose as 400 mg twice daily resulted in a higher C_{min} compared with that expected from the 400 mg and 600 mg once daily doses (Figure 2). Recent PK/PD analysis results showed that imatinib trough level correlated with clinical response,^{19,20} and it is recommended that imatinib trough level should be maintained above 1.0 µg/mL for clinical efficacy for patients with CML-CP.

Figure 2. Pharmacokinetic trough levels of drug at indicated imatinib doses in patients with Ph+ CML^{14,18,21,22}



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

Table 1. Trough levels (C_{min}) of drug in patients with Ph+ CML treated with imatinib at 400, 600, and 800 mg doses (800 mg dosed as 400 mg twice daily)

	400 mg Once Daily (n = 487)	600 mg Once Daily (n = 67)	400 mg Twice Daily (n = 40)
Mean, µg/mL ± SD	0.98 ± 0.53	1.37 ± 0.82	2.88 ± 1.09
Median, µg/mL [range]	0.88 [0.18, 0.39]	1.17 [0.35, 3.82]	2.93 [1.02, 6.45]
CV, %	53.1	59.6	38.0

SD, standard deviation; CV, coefficient of variance.

SUMMARY OF IMATINIB PHARMACOKINETIC CHARACTERISTICS

Absorption

Imatinib is freely soluble in water and, after oral administration, is well absorbed from the gastrointestinal (GI) tract with a time to peak drug concentration of 1-3.3 hours. Imatinib is 98% bioavailable. Absorption is the same between the tablet and capsule formulations and is not affected by food.^{14,23,24} Imatinib is absorbed primarily from the small intestine, and the extent of absorption may be affected by the GI anatomic abnormalities or disease states.²⁵

Distribution

Circulating imatinib is approximately 95% bound to plasma proteins, mainly albumin and alpha 1-acid glycoprotein (AAG). Plasma AAG levels have been shown to influence imatinib pharmacokinetics in patients with CML.²⁶ However, AAG level may not affect the effective free-drug level because this is determined by intrinsic clearance in patients. Individual differences in AAG level and plasma protein binding may account for at least some of the interpatient variability in the observed total plasma exposure to imatinib. Imatinib is rapidly and extensively distributed into tissues, although with minimal penetration to the central nervous system.

Metabolism

Imatinib is metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5. Its major metabolite, *N*-desmethyl metabolite (CGR74588), has similar biologic activity to the parent drug compound.

Imatinib exposure has been shown to be influenced by drug-drug interactions with commonly prescribed drugs that are either CYP3A4 inhibitors or inducers.²⁷⁻²⁹ In addition, drugs that are substrates of CYP2D6 and 2C19 may be affected by imatinib. An updated list of drugs that are CYP3A4 inhibitors or inducers and CYP2D6 and 2C19 substrates can be found on the internet at: <http://medicine.iupui.edu/flockhart>.

Continued

Examples of CYP3A4 inhibitors include aprepitant, clarithromycin, cyclosporine, erythromycin, itraconazole, ketoconazole, pimozone, grapefruit juice, and others. Enzyme inducers include barbiturates, carbamazepine, dexamethasone, phenytoin, St. John's wort, and others.

Elimination

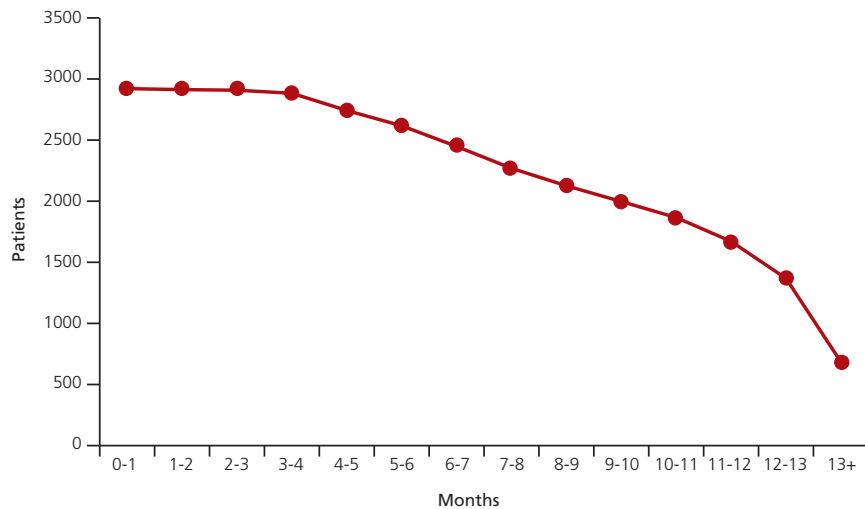
The elimination half-life of imatinib is approximately 18 hours, and thus it can be dosed once daily. The dose can be administered twice daily to minimize GI side effects or to maintain a low peak-to-trough concentration ratio for the high imatinib doses. Steady state (no change with time) is reached within a week.

ADHERENCE WITH IMATINIB

With the advent of oral, targeted agents for cancer that are prescribed for use as chronic therapy,^{30,31} the issue of adherence (compliance) to the prescribed regimen is emerging as a reason for concern by oncologists. One study showed that patients may overestimate their adherence to oral cancer therapies by a factor of 2 in discussions with their physicians.³¹ Reasons for patients not taking their pills as prescribed include not fully understanding the importance of taking the medication as prescribed, experiencing unpleasant side effects, or simply forgetting to take the pills.³⁰ For patients with life-threatening diseases, 95% adherence or greater is generally considered the goal.³⁰

Recent studies have revealed that adherence for some patients with Ph+ CML is suboptimal.³² A pharmacy record analysis of 4043 patients prescribed imatinib indicated an average adherence rate of 78% over the 24-month study period for patients with Ph+ CML. Patients were on therapy an average of 255 days over 24 months. Adherence to therapy began to decline after the first 4 months of treatment (Figure 3).

Figure 3. Imatinib adherence



MONITORING OF PLASMA IMATINIB CONCENTRATIONS IN MANAGEMENT OF CML

Imatinib is the standard of care in CML. In the largest study ever performed in patients with newly diagnosed Ph+ CML-CP, 89% of patients randomized to imatinib are still alive with 5 years of trial follow-up.¹⁰ Achieving maximum benefit with imatinib therapy may require optimal dosing as well as adherence to therapy. Pharmacokinetic factors such as individual patient variation in drug absorption and metabolism, interactions between prescribed medications, or other patient-related factors such as patients' GI abnormalities or disease conditions can also affect drug exposure and place maximum benefit of therapy at risk.

The minimum effective concentration of imatinib has not been fully defined, and the relationship between imatinib blood levels and outcome remains a subject of investigation. Further studies are also needed to characterize the safety/tolerability profiles of imatinib. Nevertheless, monitoring the drug levels in certain clinical situations as a first step to avoid low exposure would likely benefit patients. Maintaining trough levels above the average concentration at the intended clinical dose (1 µg/mL for 400 mg once daily dose), if tolerable, is recommended. Imatinib blood levels below this average concentration should be avoided and trigger further inquiry.

While pharmacokinetic monitoring is widely used in many other branches of medicine, such as neurology, cardiology, and psychiatry, it has not been widely applied, to date, in clinical oncology practice. However, monitoring of imatinib would most likely be beneficial to physicians managing patients with Ph+ CML who demonstrate:

- Adherence concerns
- Suspicion of a drug-drug interaction
- A less-than-expected response to imatinib
- Side effects that are unusually severe for the dose of imatinib taken

Although imatinib is an easy drug to dose and administer, inadequate drug exposure due to pharmacokinetic factors or lack of adherence to therapy may compromise clinical outcomes. Blood level testing may offer a positive way for healthcare providers to initiate an 'evidence-based' discussion of the importance of adherence with patients who are suspected of being non-adherent. Information regarding imatinib blood exposure during therapy has the potential to serve as a valuable tool to guide clinical decision making in the era of targeted therapy for cancer.

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Merrill J. Egorin, MD University of Pittsburgh Cancer Institute Pittsburgh, Pennsylvania, USA	Mathieu Molimard, MD, PhD Université Victor Ségalen CHU de Bordeaux Bordeaux, France	François-Xavier Mahon, MD, PhD Université Victor Ségalen CHU de Bordeaux Bordeaux, France
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CLEAR ADHESIVE CD POCKET

