

# Clinical Roundtable Monograph

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## Monitoring Blood Plasma Concentrations to Improve Outcomes in CML and GIST

### Moderator



Merrill J. Egorin, MD  
Professor of Medicine and Pharmacology  
University of Pittsburgh Cancer Institute  
Pittsburgh, PA

### Discussants



Richard A. Larson, MD  
Professor of Medicine  
University of Chicago  
Chicago, IL



George D. Demetri, MD  
Associate Professor of Medicine  
Harvard Medical School  
Dana-Farber Cancer Institute  
Boston, MA

### Abstract

Oral delivery of targeted therapy represents an emerging trend in the treatment of cancer patients. However, benefits do not come without challenges, many of which are different from those associated with the use of older therapies. For example, at-home patient self-administration of these drugs is impacted by patient adherence. This, coupled with drug-drug interactions and interpatient differences in drug absorption and metabolism can affect the amount of drug that actually reaches the tumor. To help clinicians address these challenges, recent research has investigated the potential role for monitoring drug plasma concentrations in order to improve clinical outcomes.

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# Therapeutic Monitoring of Drug Plasma Concentrations and Improved Outcomes in CML

Richard A. Larson, MD

The treatment of chronic myeloid leukemia (CML) was revolutionized in 2001 with the approval of imatinib, an oral small molecule inhibitor of tyrosine kinases. Specifically in CML, imatinib targets the BCR-ABL fusion protein, the constitutively activated enzyme that is a product of the Philadelphia chromosome (Ph).<sup>1</sup> The efficacy of imatinib as front-line therapy for CML was confirmed by the results of a long-term follow-up of the International Randomized Interferon versus STI571 (IRIS) study, an international open-label randomized phase III trial that included patients with newly diagnosed chronic phase CML.<sup>2</sup> After a median follow-up of 60 months, imatinib therapy (400 mg daily) resulted in an estimated 87% rate of complete cytogenetic response (CCyR; Ph-negative). Additionally, study patients who received imatinib had an estimated 5-year overall survival (OS) rate of 89%. A safety analysis showed that newly occurring or worsening grade 3 and 4 adverse events were uncommon and, in fact, diminished over time. The high, durable responses produced by imatinib, coupled with the favorable safety profile of the drug, have made imatinib the standard of care for Ph-positive CML.

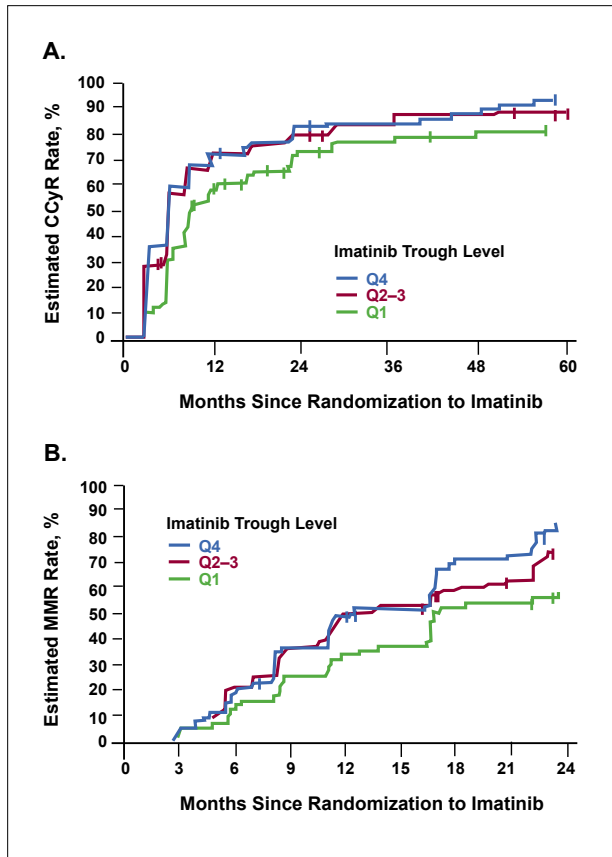
Studies in healthy volunteers as well as cancer patients reveal that imatinib absorption is rapid and complete, with an absolute bioavailability of approximately 98%.<sup>3-6</sup> Imatinib exposure is proportional to its dosage, and not significantly affected by age, race, sex, or body weight.<sup>4,6</sup> Imatinib is administered once daily, due to its relatively long half-life of approximately 18–20 hours, and achieves steady-state concentrations within a week of initiating treatment.<sup>4,6,7</sup>

In spite of the proven efficacy of imatinib, some patients have suboptimal responses or fail treatment after initially responding. Several factors have been investigated as possible reasons for suboptimal or failed therapy. Mutations within the *BCR-ABL* gene, either initially present or emergent, that render the protein uninhibited by imatinib have been identified.<sup>8</sup> Although much effort has focused on the importance of gene mutations in imatinib resistance, other factors may prove to be just as important. For example, several studies now show that poor patient adherence to imatinib and treatment interruption is common, occurring in approximately one third of CML patients.<sup>9-11</sup> This in part may be due to the high cost of imatinib therapy in the United States, estimated to be approximately \$43,000 per life-year saved.<sup>12</sup> Lack of

efficacy is also attributed to interpatient differences in drug-metabolizing enzymes, especially cytochrome (CYP) P450 3A4.<sup>13</sup> Interpatient variability may also affect drug uptake and efflux, thus affecting the amount of imatinib that enters the cell.<sup>14,15</sup> One recent study suggested that the organic cation transporter-1 (OCT-1) may be important for the cellular uptake of imatinib.<sup>16</sup> Importantly, OCT-1 has been shown to have considerable interpatient variability due to genetic polymorphisms.<sup>17</sup>

One important factor affecting imatinib response is the pharmacokinetic and pharmacodynamic profile of the drug. Increasingly, research indicates that the concentration of imatinib within the plasma is an important determinant of response. Therefore, monitoring plasma drug concentrations may allow therapy adjustment to increase the rate and durability of response.

The first evidence that the blood plasma concentration of imatinib impacts CML patient outcome came from a study led by Picard and colleagues.<sup>18</sup> This study included 68 CML patients who had received  $\geq 12$  months of imatinib therapy (400 mg daily to treat 50 patients with chronic-phase disease, 600 mg daily to treat 18 patients with accelerated-phase disease). Trough imatinib plasma concentrations were measured in patient blood samples taken 21–27 hours subsequent to the last drug administration. The investigators found that trough imatinib plasma concentrations varied greatly among patients (range, 181–2947 ng/mL). The mean trough plasma concentrations in patients receiving 400 mg and 600 mg imatinib daily were  $1058 \pm 557$  ng/mL and  $1444 \pm 710$  ng/mL, respectively. Significantly, the mean trough imatinib plasma concentration was higher in patients who had achieved a major molecular response (defined as  $\geq 3$  log reduction in *BCR-ABL* transcript levels) than in those who did not ( $1452.1 \pm 649.1$  ng/mL vs  $869.3 \pm 427.5$  ng/mL, respectively,  $P < .001$ ). Similarly, the mean trough imatinib plasma concentration was also higher in those patients achieving a CCyR than in those who did not ( $1123 \pm 617$  ng/mL vs  $694 \pm 556$  ng/mL, respectively,  $P = .03$ ). Picard and colleagues further used a receiver operating characteristic (ROC) curve analysis to show that a major molecular response was significantly associated with an imatinib plasma threshold concentration of 1002 ng/mL (odds ratio = 7.80, 95% confidence interval [CI], 2.64–23.03,  $P < .001$ ).



**Figure 1.** Estimated cumulative CCyR and MMR rates by PK category of steady-state imatinib trough levels. (A) The estimated cumulative CCyR rates in the 351 patients with available imatinib trough levels at steady state. CCyR rates were significantly lower during the 5-year period for patients in the lowest PK category (Q1 vs others,  $P=.005$ , and  $P=.01$  overall). (B) Estimated MMR rates in 265 patients who achieved a CCyR, and for whom PCR data as well as PK samples were available. Among patients with CCyR, lower MMR rates significantly correlated with the lowest imatinib trough levels (Q1 vs others,  $P=.008$ , and  $P=.02$  overall).

Data adapted from Larson RA, et al. *Blood*. 2008;111:4026.

This was followed by a subanalysis of the prospective IRIS study, described above.<sup>2</sup> This subanalysis included 351 of the 553 patients who had been randomized to receive imatinib.<sup>7</sup> In these patients, imatinib plasma concentrations were determined at steady-state (measured on day 29 of treatment). Again, plasma trough concentrations of imatinib were found to be significantly higher in patients who later achieved a CCyR compared with those who did not ( $1009 \pm 544$  ng/mL vs  $812 \pm 409$  ng/mL, respectively,  $P=.01$  by  $t$  test). Importantly, like the study by Picard and colleagues, these results indicated that a minimum imatinib plasma trough concentration of approximately 1000 ng/mL may be important for achieving a CCyR. To examine fur-

ther the effect of plasma trough concentrations of imatinib, the patient population was divided into quartiles (mean imatinib plasma trough concentrations  $490 \pm 120$  ng/mL,  $889 \pm 148$  ng/mL, and  $1661 \pm 602$  ng/mL for Q1, Q2/Q3, and Q4, respectively). Those patients in the higher quartiles (Q2–Q4) had a significantly higher rate of CCyR ( $P=.005$ ) compared with the lowest quartile (Q1; figure 1). Specifically, the rates of CCyR varied significantly according to the patient quartile (75.9%, 85.4%, and 91.9% rates of CCyR in Q1, Q2/Q3, and Q4, respectively,  $P=.01$ ). The durability of CCyR was also related to plasma trough concentrations of imatinib. More patients in Q1 lost CCyR compared with patients in Q2/Q3 and Q4 (24% vs 13% and 17%, respectively). Interestingly, the imatinib plasma trough concentration did not correlate markedly with rates of most adverse events. Slightly greater rates of fluid retention, nausea, musculoskeletal pain, rash, and anemia were noted among patients in Q4 relative to Q1. In contrast, a greater proportion of patients in the lowest quartile of imatinib plasma trough concentrations discontinued therapy due to an unsatisfactory therapeutic effect compared to patients in the higher quartiles (18.4% vs 15.2% and 8.1% in Q1 vs Q2/Q3 and Q4, respectively).

Most recently, the pharmacokinetics of imatinib were shown to be correlated with clinical outcome in the Tyrosine Kinase Dose Optimization Study (TOPS), an open-label, multicenter, phase III trial that investigated whether a higher dose of imatinib leads to improved efficacy. At the 2008 American Society of Hematology annual meeting, Guilhot and colleagues reported on the pharmacokinetic analysis of this study.<sup>19</sup> Patients with newly diagnosed chronic-phase CML were randomized to receive front-line therapy with either high-dose (800 mg; 400 mg twice daily) or standard dose (400 mg daily) imatinib. Plasma trough concentrations of imatinib were collected in each treatment arm at baseline (prior to therapy) and after 1, 6, 9, and 12 months of therapy. The median imatinib plasma trough concentration after 1 month of therapy was proportional to dosage (1190 ng/mL and 2720 ng/mL for patients in the 400 mg and 800 mg treatment arms, respectively). Importantly, plasma trough concentrations remained stable over time, and at month 12 were 1295 ng/mL and 2150 ng/mL in the 400 mg and 800 mg treatment arms. Guilhot and colleagues concluded from this study that, like the previous 2 trials, a threshold imatinib plasma trough concentration of approximately 1000 ng/mL is an important determinant of response. They also found that the higher dose may result in greater toxicity,<sup>19</sup> and only 61% of the patients who initiated 800 mg therapy remained on this dose at month 12; 17% reduced their dose to 600 mg, and the remaining 22% reduced their dose even further.<sup>20</sup> In contrast, 85% of the patients who initiated 400 mg therapy maintained this dose at month 12. Interestingly, although patients with a higher imatinib plasma trough concentration ( $>1165$  ng/mL) after

1 month of treatment were more likely overall to achieve a major molecular response than patients with a lower concentration ( $<1165$  ng/mL;  $P=.0149$ ), there appeared to be no significant difference in the rate after 12 months of therapy.<sup>20</sup> The cause of this lack of difference remains unclear, and may have been due to the need for dose reduction in many of the patients receiving 800 mg imatinib.

A prospective randomized trial conducted by the GIMEMA Working Group in Italy also compared 400 mg daily and 800 mg daily imatinib in 217 patients with newly diagnosed, chronic phase CML.<sup>21</sup> However, this study differed in that only high-risk patients (identified using the Sokal prognostic scoring system) were included.<sup>22</sup> Similar to the results of the TOPS trial, no significant difference in the rates of either CCyR or major molecular response was observed between the 2 treatment arms. Additionally, a dose reduction was required in approximately half of the patients who initiated 800 mg imatinib. Importantly, a CCyR rate of 91% was achieved among these high-risk patients who remained on the 800 mg dosage, while only 69% of patients who required a dose reduction achieved a CCyR.

Is assessment of the plasma trough concentrations of imatinib an important tool for the optimization of therapy for CML patients?<sup>23</sup> Certainly a lack of response due to nonadherence can be identified and addressed in patients by measuring a drug level. Perhaps more importantly, measurement of plasma trough concentrations can be used to ascertain if a patient has achieved a steady-state imatinib concentration of  $\geq 1000$  ng/mL, which seems to be an important threshold concentration identified in the above studies. In fact, even patients exhibiting a response to therapy may benefit from verification of steady-state imatinib concentration, as plasma trough concentrations  $\geq 1000$  ng/mL are also associated with more durable responses. Adjusting patient dosage by monitoring imatinib plasma trough concentrations may be an effective strategy to improve outcome. In a recently presented French study involving over 1000 CML patients, Molimard and colleagues reported that 57% had plasma concentrations  $<1000$  ng/mL at the first determination. On the second determination, 62 of these patients subsequently had a concentration  $>1000$  ng/mL, and 63% had undergone an imatinib dose increase.<sup>24</sup>

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# Therapeutic Monitoring of Drug Plasma Concentrations and Improved Outcomes in GIST

George D. Demetri, MD

Although imatinib was originally developed as an inhibitor of the BCR-ABL fusion tyrosine kinase, subsequent research has found it is able to block the action of other kinases as well.<sup>1</sup> Mutations in one of these, the KIT protein, leads to its constitutive activity and downstream activation of pathways important for proliferation and anti-apoptosis. *KIT* mutations occur in a majority (up to 86%) of gastrointestinal stromal tumors (GIST) and, in fact, have been shown to be a critical determinant in the molecular basis of these malignancies.<sup>2-4</sup> A smaller subset of GIST that does not express *KIT* mutations is instead linked to activating mutations in the gene coding for platelet-derived growth factor receptor- $\alpha$  (PDGFR- $\alpha$ ).<sup>5</sup> Constitutive activation of PDGFR- $\alpha$  also leads to overactivation of the same downstream targets as the KIT protein, and like KIT, PDGFR- $\alpha$  is also inhibited by imatinib.<sup>1</sup> Therefore, imatinib is currently the front-line standard therapy for treatment of metastatic or unresectable GIST, as well as recurrent disease.<sup>6,7</sup>

The efficacy of imatinib against GIST was first shown in several phase I and II clinical trials, which further investigated the optimal dosage of the drug for these malignancies. In one study, 147 GIST patients were randomized to receive either 400 mg or 600 mg of imatinib daily.<sup>8</sup> Although no complete responses (CR) were observed after a median follow-up of 24 weeks, approximately half (53.7%) of the patients had a partial response (PR). Similarly, a phase I study conducted by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group found that 51% of GIST patients receiving imatinib achieved and maintained a PR after a 10-month follow-up.<sup>9</sup> This study also determined that 800 mg imatinib (400 mg twice daily) was the maximum tolerated dose in these patients. A subsequent phase II study from the EORTC Soft Tissue and Bone Sarcoma Group evaluated this dosage in 27 GIST patients.<sup>10</sup> At a 1-year follow-up, a majority of patients achieved a response (4% CR, 67% PR), and most adverse events were mild or moderate and did not require study discontinuation. A retrospective population pharmacokinetic analysis of

the phase I and II EORTC studies was performed by Judson and colleagues to examine imatinib disposition in GIST patients.<sup>11</sup> Low imatinib clearance was correlated with low body weight and high granulocyte count. The investigators also noted that imatinib clearance seemed to increase over time, especially after chronic, long-term (12 month) exposure.

Two phase III clinical trials evaluated imatinib in GIST, the EORTC/Italian Sarcoma Group/Australasian Gastrointestinal Trials Group Study 62005 and the North American Intergroup Study S0033.<sup>12,13</sup> The designs of these trials were similar: in each, patients with unresectable or metastatic GIST were randomized to receive either standard-dose (400 mg daily) or high-dose (800 mg daily) imatinib. Treatment was continued until disease progression, at which point patients in the 400-mg arm were allowed to cross over to high-dose imatinib. Between and within each study, response rates did not differ significantly among treatment groups. In the 62005 study, patients in the 400-mg daily and 800-mg daily arms achieved 5% and 6% rates of CR and 45% and 48% rates of PR, respectively. Similarly, in the S0033 study, the CR rate was 3% and the PR rate was 45% for both the groups receiving 400 mg daily and 800 mg daily imatinib. Importantly, these 2 studies identified 2 patient categories that benefit from treatment with high-dose (800 mg daily) versus standard-dose (400 mg daily) imatinib.<sup>14</sup> The first group of patients includes those who experienced tumor progression following initial therapy with 400 mg imatinib, of whom approximately one third benefited from a dosage increase. The second group of patients identified was those with mutations within exon 9 of the *KIT* gene. Among patients with exon 9 mutations, a 61% reduced risk of disease progression was observed in those receiving 800-mg daily imatinib compared with those receiving 400-mg daily.

The phase II registration study B2222 was a randomized study that compared imatinib 400 mg and 600 mg daily in 147 patients with unresectable or metastatic GIST. Recently, the long-term results (median follow-up of 63 months) of this study were reported.<sup>15</sup> Among all treated patients, the median OS was 57 months. The overall response rates were similar between the 2 arms, including a 1.4% rate of CR

and a 66.7% rate of PR. OS was substantially longer in patients who either responded or experienced stable disease following imatinib treatment compared with patients who initially progressed on the drug (estimated 5-year OS: 55% vs 9%, respectively). An analysis of imatinib plasma trough concentrations in a subset of patients (n=73) from the B2222 study, reported at the 2008 American Society of Clinical Oncology annual meeting, found that clinical response was correlated with drug exposure.<sup>16</sup> In this substudy, patients were divided into quartiles based on their imatinib plasma trough concentrations (Q1: <1110 ng/mL; Q2/Q3: 1110–2040 ng/mL; Q4: ≥2040 ng/mL). Significantly more patients in the higher quartiles achieved a response compared with those in the lowest quartile (67% and 74% in Q2/Q3 and Q4 vs 44% in Q1,  $P=.06$ ). Additionally, time to disease progression was significantly longer for patients in the higher quartiles compared with those in the lowest quartile (30 months vs 11.3 months in Q2/Q3/Q4 vs Q1, respectively,  $P=.0029$ ). However, no significant difference in OS was observed among the quartiles.<sup>17</sup> Interestingly, this subanalysis revealed that, as in CML, a threshold imatinib plasma trough concentration of approximately 1110 ng/mL seems to be an important determinant of response in GIST patients. Another important aspect of this substudy was its confirmation of the high variability in imatinib pharmacokinetics among patients, with an approximately 40% coefficient of variation.<sup>17</sup> Although patient demographics such as age, sex, and body weight did not influence the pharmacokinetics, baseline plasma albumin concentrations and white blood cell counts may have contributed to the interpatient variability. Together, these results suggest that it may be beneficial to monitor imatinib plasma trough concentrations in GIST patients at the time of disease progression to ensure the drug has not reached a subtherapeutic concentration. Additionally, because imatinib plasma trough concentrations seem to be an important determinant of clinical outcome, dose escalations up to the maximally tolerated dose of 800 mg daily may be justified in patients who progress on lower doses.

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# Promises and Pitfalls of Oral Cancer Chemotherapy

Merrill J. Egorin, MD

The past several years have seen a fundamental shift in cancer therapy paradigms from a focus on intravenous to oral chemotherapies. In fact, the growing body of evidence promoting the benefits of orally administered drugs for cancer treatment suggests this change will become even more prevalent in the future. Importantly, this effect is not limited to CML or GIST—for example, systemic chemotherapy of breast cancer was revolutionized with the introduction of orally administered aromatase inhibitors. However, important implications in the shifting of focus from intravenous chemotherapy to oral agents are often lost among the medical community.

Although many benefits are associated with oral cancer chemotherapy, drawbacks do exist. For example, while intravenous drugs are prepared by a pharmacist and therefore adjustable on an individual patient basis, the clinician has less flexibility in prescribing preformulated oral agents. This prompts the question of whether a recommended dosage should be rounded up or down, either of which may impact the final plasma trough concentration of the drug. Another drawback is that even when patients adhere to the correct number of tablets per day, they may be inconsistent in when they take them, which can affect plasma peak and trough concentrations. For example, if a patient is prescribed an 800 mg daily dosage of imatinib to be taken as 400 mg twice daily, variability in the times of day the patient administers their dose will affect imatinib plasma trough concentrations.

One of the major benefits of oral cancer chemotherapy is that it allows for chronic suppression of its target. This is not practical with traditional intravenous chemotherapy, which would require the patient to visit the clinical setting on a daily basis. Although subcutaneous administration is a viable approach for at-home daily therapy, it is not an option for imatinib, due to its associated irritation. However, unlike intravenous therapy, which results in 100% systemic bioavailability of the drug, a number of factors can potentially affect the bioavailability of an oral agent.

In the case of imatinib for GIST patients, the absorption and subsequent bioavailability of the drug can be significantly affected by prior surgical resection and removal of a portion of the gastrointestinal (GI) tract. Drug-drug

interactions may alter the bioavailability of oral chemotherapy. For example, it has been well established that substances that induce or inhibit the drug metabolizing enzyme CYP450 3A4 can alter the rate of drug metabolism, thereby reducing or increasing, respectively, the concentrations of the active drug. Additionally, drug absorption from the GI tract may be limited by the intake of other drugs, including antacids, proton pump inhibitors, and fiber supplements. One common adverse event associated with imatinib is GI upset, and therefore antacids are frequently used by patients in conjunction with therapy.<sup>1</sup> Although a recent study revealed that antacid use does not significantly alter imatinib absorption, it does lead to a nearly 2-fold reduction in absorption of the second generation tyrosine kinase inhibitor dasatinib.<sup>2,3</sup> Food may also have an important effect on the bioavailability of an oral drug. In the case of nilotinib, a second-generation tyrosine kinase inhibitor for Ph-positive CML, the drug bioavailability is increased by 82% when administered within 30 minutes of a high-fat meal.<sup>4</sup> This is especially significant because of the association between nilotinib and prolonged QT intervals.<sup>5</sup> The impact of food is also well-known for the tyrosine kinase inhibitor lapatinib, a newly approved breast cancer drug. When taken with a high-fat meal, much of this fat-soluble drug bypasses the liver, thus partially avoiding first-pass metabolism.<sup>6</sup> This leads to higher-than-expected systemic concentrations of lapatinib, impacting drug bioavailability.

Another major issue to consider regarding at-home administration of oral cancer chemotherapy is the level of health literacy of the patients and their ability to accurately interpret the label of their prescription drug.<sup>7</sup> One study showed that nearly half (46%) of patients misunderstood one or more set of dosage instructions on a sample prescription drug container label.<sup>8</sup> An example of a common misunderstanding was the misinterpretation of the dosage instruction “take 2 tablets by mouth twice daily” to mean “take it every 8 hours”. In another example from a different study, a number of patients mistook the dosage instruction “take 1 pill twice a day” to mean cut 1 pill in half and take one half in the morning and the other half in the evening.<sup>9</sup> The issue of health literacy is further confounded because drug labels are regulated at the state, not federal level.

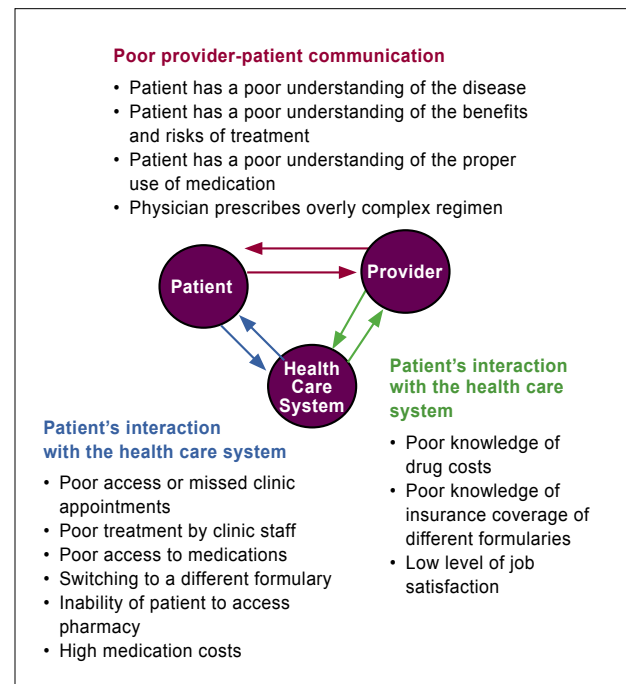
**Table 1.** Major Predictors of Poor Adherence to Medication

- Presence of psychological problems (eg, depression)
- Presence of cognitive impairment
- Treatment of asymptomatic disease
- Inadequate follow-up or discharge planning
- Side effects of medication
- Patient's lack of belief in benefit of treatment
- Patient's lack of insight into the illness
- Poor provider-patient relationship
- Presence of barriers to care or medications
- Missed appointments
- Complexity of treatment
- Cost of medication, copayment, or both

Data adapted from Osterberg L, et al. *N Engl J Med.* 2005; 353:487-497.

Therefore, there are no unifying rules regarding how a drug dosage is written. In one study, the same prescription submitted to 6 different pharmacies resulted in 6 different dosage labels.<sup>9</sup>

Patient adherence is an important factor for the administration of oral drugs. Some are of the opinion that drug adherence in cancer patients is not a significant problem, as most patients will properly take their medication due to the potential seriousness of the disease.<sup>10</sup> However, a study of breast cancer patients who were prescribed an oral cyclophosphamide regimen to be taken at home reported a 43% rate of patient non adherence to therapy.<sup>11</sup> There are many reasons why patients do not properly adhere to their therapy (Table 1). One of these is drug cost, which is high in the case of imatinib, despite the fact that it is less expensive than other targeted treatment options indicated for CML and GIST.<sup>12</sup> Another reason for lack of adherence is a high pill burden, which was shown in a retrospective analysis by Darkow and colleagues to significantly negatively impact adherence to imatinib ( $P=.002$ ).<sup>13</sup> This same study identified other factors that resulted in imatinib treatment interruption, including high cancer complexity ( $P=.003$ ) and a higher starting imatinib dose ( $P=.04$ ). Adherence improved with increasing patient age until age 51, at which point it began to worsen ( $P<.001$ ).<sup>14</sup> Importantly, patient adherence to imatinib therapy has a significant impact on health care-related costs.<sup>13,15</sup> In fact, a 10% increase in adherence was found to be associated with a 5% reduction in total health care costs ( $P=.021$ ). CML- or GIST-related health care costs during the first year of therapy were also markedly affected by patient adherence (\$34,086 vs \$103,118 for patients with an adherence rate of 90–100% vs <50%, respectively). It is important to note that the association of poor patient

**Figure 2.** Barriers to adherence.

Data adapted from Osterberg L, et al. *N Engl J Med.* 2005; 353:487-497.

adherence with increased health care costs observed in this study was not necessarily a cause-effect relationship.

One of the reasons patient adherence is such an important consideration is that poor adherence leads to low or uneven drug concentrations. Chronic exposure of cancer cells within a tumor to noncytotoxic drug concentrations may allow for the selection of cells that are resistant to the drug.<sup>16</sup> In fact, this phenomenon has implications beyond merely poor adherence. For example, if a patient exhibiting a favorable response to imatinib therapy was found to have a subthreshold imatinib plasma trough concentration of 600 ng/mL, would administration of a higher dose to increase the plasma trough concentration to closer to 1000 ng/mL delay the development of imatinib-resistant cancer cell clones? This is a difficult question to test. Additionally, one cannot assume imatinib conforms to linear dosing and bioavailability.<sup>10</sup> This is to say that doubling a patient's dose from 400 mg daily to 800 mg daily does not necessarily translate into a doubling of the plasma trough concentrations, because many other factors may affect the bioavailability of the drug. Previously, testing of imatinib plasma trough concentrations was only available through a laboratory at the University of Pittsburgh Cancer Institute. However, free testing of imatinib plasma trough concentrations is now being offered as a service of the CML and GIST Alliance through Avantix Laboratories

(www.bloodleveltesting.com), an independent, full service GLP and GCP compliant, CLIA certified laboratory.<sup>17</sup>

Both poor patient adherence as well as dosage misinterpretation could be improved by changes to drug packaging. Calendar packs or blister packs are examples of drug packaging systems designed to facilitate daily oral drug administration.<sup>18-21</sup> These packaging systems are used on a routine basis for drugs such as hormonal and birth control therapy, with a high rate of success. The use of calendar packs has been implemented in the second-generation tyrosine kinase inhibitor nilotinib, for which twice-daily dosing is necessary.<sup>22</sup> However, their use for imatinib has not occurred, and this represents an important intervention that may be implemented in the future.

In many ways, imatinib represents a pioneer drug. The nature of its development paved the way for rationally designed oral, targeted therapies against a myriad of diseases for which the molecular basis is known. However, it is imperative that as clinicians increasingly prescribe these therapies, basic principles such as drug pharmacology and disposition not be ignored. The example presented here, which implicates the threshold imatinib plasma trough concentration as an important determinant of therapeutic effect, demonstrates the need to understand the pharmacology of novel, orally available targeted agents.<sup>23</sup>

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# Notes

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