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Drug Plasma Monitoring in CML and GIST: A Case-based Discussion

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Abstract

Drug plasma monitoring has emerged as an important tool to obtain optimal levels of a particular drug among individual patients. Plasma monitoring of imatinib levels would appear to be practical in cases where there is lack of response, heightened toxicity, or evidence of poor adherence to therapy. However, the potential role of monitoring plasma drug concentrations in guiding treatment decisions and optimizing patient therapy has yet to be established. Currently, there are no clinical recommendations regarding how to incorporate imatinib drug plasma monitoring in patients with either chronic myeloid leukemia or gastrointestinal stromal tumors, indications for which imatinib is approved. Here, the latest research and evidence regarding imatinib drug plasma monitoring is discussed. Three cases are presented to illustrate the most common examples where monitoring imatinib plasma concentrations may help to guide treatment decisions. These cases include a suboptimal response to imatinib treatment, lack of patient adherence to imatinib, and imatinib-related toxicity. By understanding the potential role of monitoring plasma imatinib concentrations in patients with chronic myeloid leukemia or gastrointestinal stromal tumors, physicians can identify patients who may benefit from drug plasma monitoring and consider incorporating the data in order to improve patient outcomes.

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Drug Plasma Monitoring in CML and GIST: A Case-based Discussion

Merrill J. Egorin: An important question that is currently under debate in the field of targeted therapy is how often one should perform therapeutic drug plasma monitoring for patients receiving imatinib.

Imatinib is an oral small molecule tyrosine kinase inhibitor currently approved for patients with Philadelphia chromosome (Ph)-positive chronic myeloid leukemia (CML), c-Kit-positive gastrointestinal stromal tumor (GIST), and other diseases such as relapsed or refractory Ph-positive acute lymphoblastic leukemia, myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangements, aggressive systemic mastocytosis, hypereosinophilic syndrome, chronic eosinophilic, and unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans.[1]

In CML, imatinib targets the BCR-ABL fusion protein, the constitutively activated enzyme product of the Ph chromosome. In GIST, the main target of imatinib is the constitutively activated c-Kit tyrosine kinase receptor, although the activated platelet-derived growth factor receptor alpha (PDGFR□) is also inhibited in a small number of cases. Several clinical trials have evaluated the efficacy and safety of imatinib therapy in CML and GIST. Results from those trials, as well as other research, show that the plasma imatinib concentration may have a relationship with response. Therefore, the monitoring of plasma imatinib concentrations may provide a way for physicians to optimize patient outcomes. However, while the therapeutic drug plasma monitoring of imatinib concentrations seems to be an emerging and important tool, its optimal incorporation into the management of patients with CML or GIST remains unknown.

Currently, there are no published clinical recommendations that guide the use of therapeutic drug plasma monitoring for patients taking imatinib. One strategy would be to perform an initial measurement when the patient begins imatinib therapy in order to establish a baseline for future comparison. Later, at any point when there is a change in that patient's therapy or condition, the plasma imatinib concentration can be checked in order to find or to rule out alterations in imatinib concentration as a cause of the change in the patient's condition. For example, a progression of disease in a patient who initially had achieved a clinical response to imatinib treatment may be explained by a decrease in plasma imatinib concentrations. Physicians need to understand that progression of disease can reflect poor patient adherence to orally administered agents rather than resistant disease. Alternatively, the development of an imatinib-related toxicity may be a result of an increase in plasma imatinib concentration.

Michael J. Mauro: One setting in which drug plasma monitoring may be beneficial is when there is apparent clinical resistance to imatinib. Clinical resistance may be categorized as either primary or secondary, depending on the circumstances, and warrants investigation into cause and change in treatment to regain lost response or gain adequate response.

Case #1 Chronic-phase CML Patient

A 60-year-old female patient presented with fatigue, weakness, loss of appetite, and night sweats. Her physician ordered several tests, including a complete blood count (CBC) and platelet count. Blood testing revealed an abnormally high white blood cell count and a "left shift" in the blood differential, with circulating immature forms. Results of a bone marrow aspirate and biopsy confirmed the initial diagnosis of chronic phase CML.

The patient began therapy with imatinib at a dose of 400 mg once daily. However, despite achieving a prompt hematologic response to therapy, she failed to achieve any cytogenetic response after 6 months of therapy. Blood samples failed to show the presence of any mutations in the BCR-ABL kinase domain. The oncologist decided to check the trough imatinib plasma level, which was 350 ng/mL. Based on these data, the oncologist escalated the dose to 600 mg daily. A follow-up drug plasma monitoring showed that her trough imatinib plasma level had improved to 710 ng/mL, but she had evidence of only a minor (50%)Ph-positive cytogenic response. The oncologist increased her imatinib dose to 800 mg daily. At her 12-month follow-up visit, the patient had a complete cytogenetic response (CCyR).

Approximately 15–25% of CML patients exhibit primary cytogenic resistance to imatinib, meaning that they

fail to achieve any level of cytogenic response at 6 months, a major cytogenetic response (MCyR) at 12 months, or a CCyR at 18 months.[2] Secondary resistance to imatinib also occurs in CML patients, evidenced by disease progression in a patient who had originally exhibited a response to imatinib treatment. While the major mechanism responsible for secondary resistance is the development of imatinib-resistant mutations within BCR-ABL, inadequate plasma imatinib concentrations may be one of the main causes of primary resistance. A study by Gambacorti-Passerini and colleagues showed that the binding of alpha-1-acid glycoprotein (AGP) to imatinib corresponded with significant effects on the pharmacokinetics, plasma concentrations, and distribution of imatinib in CML patients, as well as blocked imatinib activity.[3] Picard and colleagues conducted an evaluation of trough imatinib plasma concentrations in 68 CML patients, 34 of whom had a major molecular response (MMR) to imatinib therapy and 34 of whom did not.[4] Mean trough imatinib plasma concentrations were significantly higher in the group with an MMR compared with the group that did not have an MMR (1452 ± 649 ng/mL vs 869 ± 427 ng/mL, $P<.001$). Mean trough imatinib plasma concentrations were also significantly higher among the 56 patients with a CCyR compared with the 12 patients who did not have a CCyR ($P=.03$).

Perhaps the best data suggesting that an adequate plasma drug concentration of imatinib is important for clinical response come from the International Randomized Interferon versus STI571 (IRIS) trial.[5] This trial was an international, open-label, phase III study that randomized patients with newly diagnosed chronic phase CML to receive either imatinib or traditional treatment (interferon alfa plus low-dose cytarabine). A 5-year follow-up of the IRIS study reported an 87% rate of CCyR and an overall survival (OS) of 89% among patients receiving imatinib.[6] A recent subanalysis of the IRIS study correlated trough imatinib plasma concentrations with response and safety outcomes in these chronic-phase CML patients (Figure 1).[7] Steady-state trough imatinib concentrations were obtained from 351 patients on day 29 of treatment, with a mean of 979 ng/mL ± 530 ng/mL. Patients were then categorized into quartiles based on these steady-state concentrations. The lower quartile (Q1) included the 25% of patients with the lowest trough imatinib concentrations, while quartiles Q2 and Q3 included patients with trough imatinib concentrations ranging from 25% below to 25% above the median; the highest quartile (Q4) included the 25% of patients with the highest trough imatinib levels. The rates of CCyR and MMR were significantly different among these quartiles ($P=.01$ and $P=.02$, respectively), and patients with higher trough imatinib plasma concentrations had better rates of CCyR and MMR, as well as a trend for improved rates of event-free survival (EFS). Notably, the trough imatinib plasma concentrations were significantly higher in patients who achieved a CCyR compared with those who did not (1,009 ± 544 ng/mL vs 812 ± 409 ng/mL, $P=.01$). Further, an exploratory analysis indicated that trough imatinib plasma concentrations were predictive of a higher rate of CCyR. The odds ratio relative to achieving a CCyR with respect to a 250 ng/mL increase in trough imatinib plasma concentration was 1.77 (95% CI, 1.22-2.56; $P=.003$).

Recent clinical data suggest that a target plasma threshold for trough imatinib concentrations, at least in

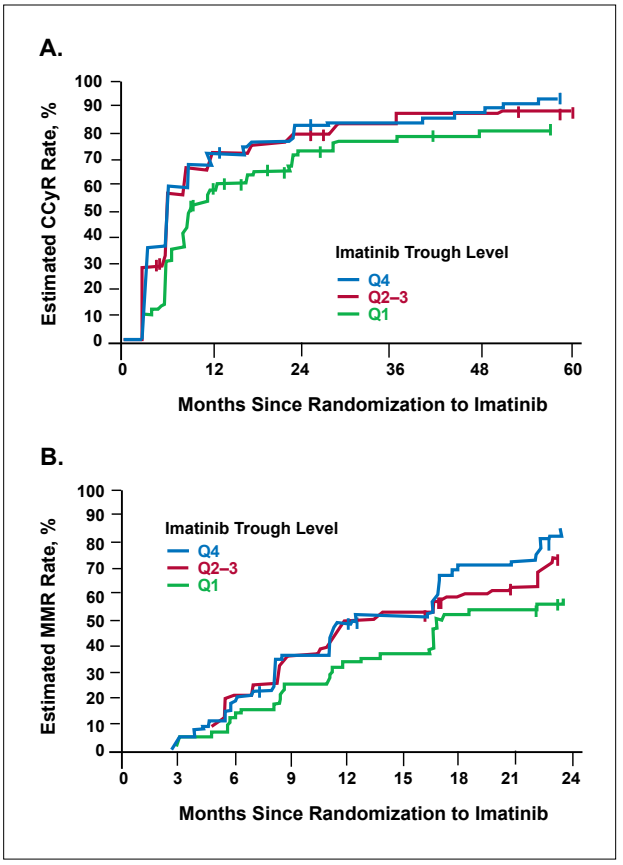

Figure 1. Estimated cumulative CCyR and MMR rates by PK category of steady-state imatinib trough levels. (A) The estimated cumulative CCyR rates in the 351 patients with available imatinib trough levels at steady state. CCyR rates were significantly lower during the 5-year period for patients in the 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;111:4022-4028.

CCyR=complete cytogenic response; MMR=major molecular response; PK=pharmacokinetic; PCR= polymerase chain reaction

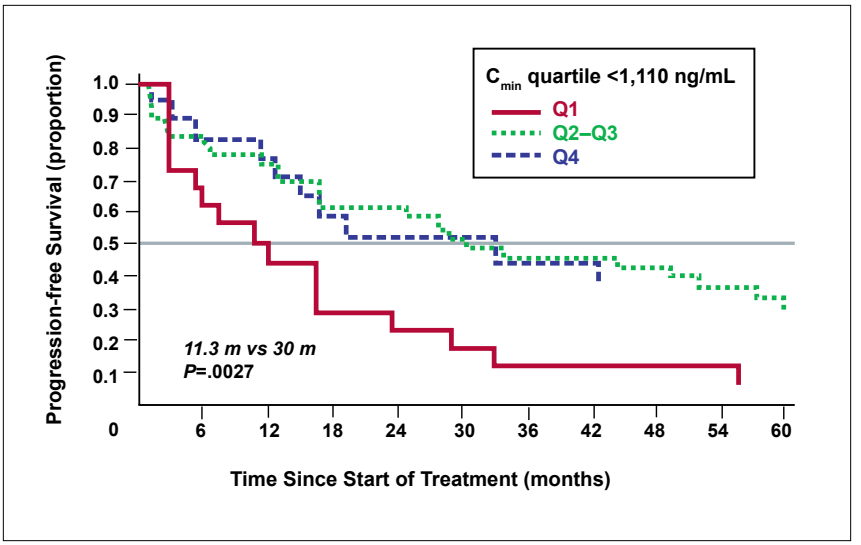

Figure 2. GIST patients whose imatinib exposure was in the lowest quartile had a shorter progression-free survival. Time to progression by imatinib day 29 through level (C_{min}) quartile (Q).

Data adapted from Demetri GD, et al. *J Clin Oncol.* 2009;27:3141-3147.

the case of CML, is up to 1,000 ng/mL.[4] Drug plasma monitoring can help to monitor the patients' trough imatinib concentrations and guide the oncologist in adjusting imatinib dosages. In cases where imatinib levels are less than 1,000 ng/mL, dose escalation may be attempted to increase levels to above the proposed threshold concentrations. Conversely, the imatinib dosage could be reduced in cases where a patient has achieved a response but the imatinib concentrations are far in excess of 1,000 ng/mL and the patient is experiencing unacceptable toxicity.

Both primary and secondary imatinib resistance has also been documented among patients with GIST. In both cases, mutations have been attributed as the major mechanism of resistance.[8] Primary resistance is associated with mutations in exon 9 of c-Kit or exon 18 of PDGFR□, while secondary resistance is associated with c-Kit exon 11 mutations.[9] Relatively few studies have explored the effects of imatinib plasma drug concentrations on clinical response in GIST. Demetri and colleagues recently reported an analysis correlating imatinib pharmacokinetics with response of GIST patients treated in a phase II trial.[10] In this study, patients were randomized to receive imatinib at a dose of either 400 mg or 600 mg daily; baseline (day 1), and steady-state (day 29) pharmacokinetic data were obtained in a subset of these patients (n=73). Based on trough imatinib plasma concentrations, patients were categorized into quartiles. Compared with patients in the lowest quartile (Q1), all other patients (Q2-Q4) achieved a higher median time-to-progression (TTP) (11.3 vs >30 months, *P*=.0029). Similarly, the overall objective benefit rate was lowest among patients in the lowest quartile (Figure 2).

Michael J. Mauro: Another case in which plasma drug monitoring may be beneficial is for monitoring patient compliance and adherence to the prescribed dose of imatinib.

Jonathan C. Trent: It is very difficult to figure out if somebody is truly being adherent to their therapy. I check plasma concentrations in patients, once a month at most, usually every 2–3 months. However, if I am checking every 2 months, the patient could potentially not take imatinib 7 weeks and then take it for the last week, and I probably would not have a clue. Therefore, monitoring is not an absolute way to figure out whether or not somebody is being adherent. However, I do think that the fact that I am monitoring may encourage some patients to be more adherent.

Case #2 Nonadherent GIST Patient

A 43-year-old woman, diagnosed with GIST, was started on adjuvant imatinib therapy (400 mg daily) following surgery. A computerized tomography (CT) scan at 3 months revealed evidence of disease progression, and her oncologist increased the dose to 800 mg daily. At a later follow-up appointment, she still had evidence of disease progression. Upon questioning by the oncologist, the patient assured him that she took her medication on a regular basis, as prescribed. The nurse then came in to take a full patient history, and during this session, the patient confessed to her that she only took approximately half of her prescribed dose of imatinib. When asked why, the patient listed financial reasons as her primary reason for nonadherence.

Several studies now show that poor patient adherence is an important factor to consider when evaluating a suboptimal response to imatinib. Darkow and colleagues performed a retrospective analysis of 267 imatinib-treated CML patients listed in an electronic healthcare claims database from a managed care provider in the United States.[11] In this study, reduced patient adherence to imatinib appeared to be a prevalent condition. Patient adherence was measured by the medication possession ratio (MPR), which was calculated as the total days' supply of imatinib divided by 365. The mean MPR was 77.7%, which decreased as the number of concomitant medications increased (P=.002). Mean MPR was lowest among women (P=.003), patients with high cancer complexity (P=.003), and patients with a higher imatinib starting dose (P=.04).

Two studies investigating imatinib patient adherence were reported at the 2006 American Society of Clinical Oncology (ASCO) Annual Meeting. In the first, Feng and colleagues assessed claims data from a United States health plan, identifying 413 imatinib-treated CML or GIST patients with 15 months or more continuous eligibility.[12] The mean MPR among these patients was 76%. In the second study, Tsang and colleagues determined patient compliance and persistency by assessing prescription-filling activity compared with the prescribing activity of their physicians.[13] Overall compliance, or MPR, was calculated as the apparent mg taken divided by the mg prescribed. The overall mean MPR was 75% and was slightly higher among CML patients (78%) compared with GIST patients (73%). Half of the patients were determined to be 100% compliant, and compliance was highest among patients with an initial dose of 300 mg or 400 mg daily. Persistency, the time on therapy without significant gaps in prescription refills, averaged 255 days, with the most persistent patients being those with an initial imatinib dose of 300 mg or 400 mg daily (13.0 and 12.9 months, respectively).

Results of the Adherence Assessment with Gleevec: Indicators and Outcomes (ADAGIO) study were recently published.[14] This prospective study aimed to determine the prevalence of nonadherence to imatinib, assess various determinants of patient nonadherence, and evaluate an association between patient adherence and treatment response. A total of 169 CML patients were included. A total of 14.2% of patients were found to be 100% adherent, while approximately one-third (32.7%) were nonadherent according to the Basal Assessment of Adherence Scale (BAAS). The BAAS determines nonadherence if any one question of a four-question clinical interview is answered positively.[15] The most frequently reported nonadherent behaviors included occasionally not taking a dose (13.3%) and taking a dose with a delay of more than 2 hours (25.3%).[14] Importantly, the nonadherence measure of pill count (determined by percent not taken of percent prescribed) was associated with the level of treatment response that was recorded at study entry. Patients who had an optimal response to imatinib therapy had a significant lower percentage of pills not taken than those who had a suboptimal response to imatinib therapy (7.3% vs 23.2%, P=.005). Among patients who were treated with imatinib for 12 months or longer, those who achieved a CCyR had a significantly lower mean percentage of imatinib not taken compared with patients who did not achieve a CCyR (9.1% vs 23.9%, P=.004). No statistically significant correlations were found between imatinib adherence, the occurrence of general or imatinib-specific adverse events, number of patient-reported symptoms, or discomfort from these symptoms.

In a multivariate analysis, patient-related determinants of nonadherence to imatinib included (in decreasing order of correlation) older age, longer duration of CML illness, living alone, male sex, longer duration on imatinib, imatinib dose 600 mg daily or greater, higher degrees of chronic care received, and higher self-reported functional status and quality of life.

Assessing imatinib plasma drug concentrations may help to monitor adherence, especially when poor adherence is suspected.[16] However, it is important to note that drug plasma monitoring is not a simple, straightforward approach to determining patient adherence. White-coat compliance is an important consideration when performing drug plasma monitoring for the patient with suspected poor adherence or nonadherence.[17] When aware of an appointment for assessing a trough imatinib plasma concentration, patients may intentionally correct their medication compliance, thereby altering their usual imatinib pharmacokinetic concentrations. The obvious goal would be to not warn the patient ahead of an appointment for drug plasma monitoring in order to avoid this white-coat compliance. However, this may not always be feasible. Incorporation of "real-time" trough concentration sampling, not requiring the blood draw to be at the time of plasma trough measurement (0–2 hours prior to planned daily dose time), and using extrapolation of random levels to calculate trough levels, is forthcoming and will improve the ability of plasma trough sampling in the assessment of compliance/adherence.

Jonathan C. Trent: A patient presenting with a high level of toxicity while on imatinib treatment represents a third case in which imatinib drug plasma monitoring may be beneficial.

Case #3 Patient and Imatinib-related Toxicity

A 58-year-old woman presented with widespread metastatic GIST. She was quite small in stature (4'9" in height) and weighed 105 lbs. She initiated therapy at a dose of 400 mg daily. Fairly quickly, the patient developed sig-

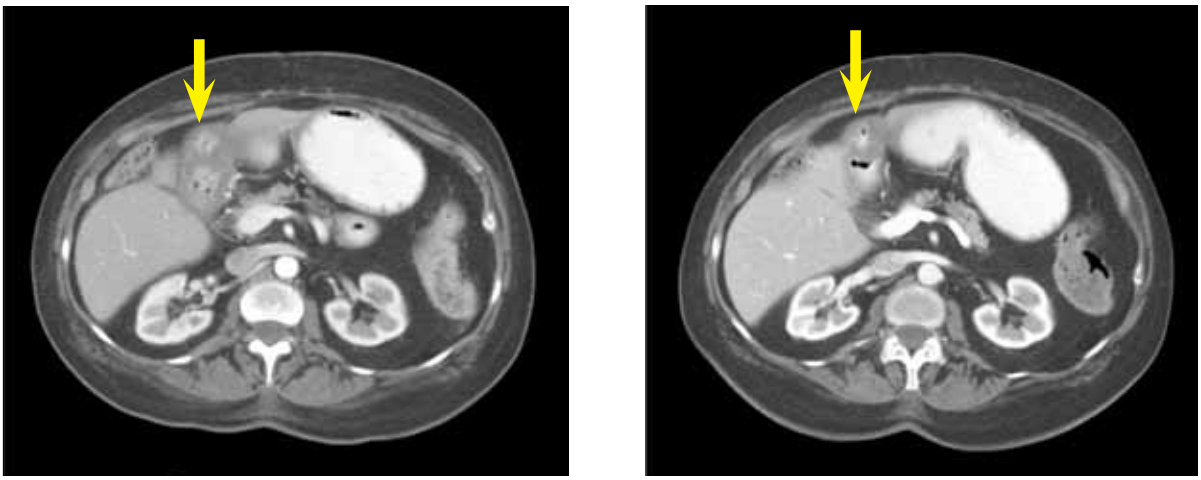

Figure 3. Computerized tomography image showing long-term response to imatinib.

nificant symptoms of abdominal cramping and diarrhea, experiencing up to 5–6 loose stools per day. The patient's quality of life deteriorated to the point where she was wearing adult diapers upon leaving her house. CT imaging showed an impressive long-term response to imatinib that continued over several years (Figure 3). After the first CT imaging showed evidence of response, the oncologist discussed lowering her imatinib dosage to 300 mg in order to try to reduce her symptoms of diarrhea. The patient refused this, citing her response and lack of disease progression. Approximately 1 year later, the oncologist ordered imatinib plasma monitoring, and the patient's plasma imatinib concentration was 4,300 ng/mL. The oncologist discussed with the patient recent clinical evidence that suggested that the plasma imatinib concentration may only need to be between 1,000–1,100 ng/mL. The patient agreed to a strategy of decreasing her imatinib dosage to 300 mg daily. This decrease in dosage quickly reduced her diarrhea symptoms to only 1 loose stool per day and dramatically improved her quality of life. Monitoring 3 months later showed that her plasma imatinib concentration was 3,210 ng/mL. A CT scan continued to show no evidence of disease progression.

Currently, there are conflicting data regarding the implications of trough imatinib plasma concentrations and imatinib-related toxicity. In the subanalysis of the IRIS study, discussed earlier, the correlation of trough imatinib plasma concentrations with patient disposition and rates of adverse events was also examined.[7] A total of 29.9% of the evaluated patients discontinued imatinib during the study. Of these, nearly half (41.4%) were in the lowest quartile classification of trough plasma imatinib concentrations (Q1), while the remainder were in the middle (Q2-Q3; 27.5%) or highest (Q4; 23%) quartile classification of trough plasma imatinib concentrations. During the first 3 months of imatinib therapy, the types and grades of many reported adverse events, except for fluid retention, nausea, musculoskeletal pain, rash, myalgia, and anemia, were similar among all 3 trough plasma imatinib concentration categories. These adverse events were reported more frequently by patients in the upper quartile of trough imatinib plasma concentrations (Q4) compared with the lowest quartile (Q1).

Several factors may affect imatinib plasma levels and thus imatinib-related toxicity (Table 1). The disposition of imatinib in GIST patients was examined in a retrospective population pharmacokinetic analysis of 2 studies from the European Organization for Research and Treatment of

Table 1. Factors That May Influence Plasma Imatinib Levels

- GIST patients who undergo a partial or complete gastrectomy may have poor imatinib absorption.
- Dosing of imatinib is 400 mg daily for all patients with kit exon 11 mutation and not adjusted for weight or BSA.
- Metabolism of some TKIs is reduced in Asians, women.
- Metabolism is inhibited by hepatic dysfunction.
- Imatinib levels may decrease over time, by as much as 30–40% in some patients over one year.
- Concomitant medications.

Data adapted from Judson I, et al *Cancer Chemother Pharmacol.* 2005;55:379-386.
Blanke CD, et al *J Clin Oncol.* 2008;26:620-625.

BSA=body surface area; GIST=gastrointestinal stromal tumors; TKI=tyrosine kinase inhibitor

Cancer (EORTC).[18] This analysis utilized detailed imatinib pharmacokinetic data taken from days 1 and 29 from both a phase I and a phase II study. Imatinib clearance was shown to be affected by low body weight and high granulocyte count, decreasing in both cases. Additionally, chronic long-term imatinib exposure (over 12 months) was correlated with an increase in imatinib clearance.

Imatinib is metabolized primarily by the metabolic enzyme CYP3A4, although CYP3A5 is also thought to be important.[19] The predominant imatinib metabolite is CGP 74588, which is also known as desmethyl imatinib and is as potent as imatinib in inhibiting BCR-ABL and PDGF-□.[20] Many agents can affect the metabolism of imatinib by inhibiting or inducing CYP3A4 and can therefore dramatically alter plasma imatinib concentrations. Strong inhibitors of CYP3A4 can result in an increase in imatinib concentrations. Some examples of drugs that strongly inhibit CYP3A4 include ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole. In a 2-period crossover-design trial, 14 healthy subjects were administered a single, oral, 200-mg dose of imatinib followed by a 7-day wash-out period by a single, oral, 200-mg dose of imatinib plus a single, oral, 400-mg dose of ketoconazole.[21] The mean maximum concentration (Cmax) of imatinib was increased significantly by ketoconazole (26%, $P<.005$), as was the 24-hour area under the plasma concentration versus time curve ([AUC] 40%; $P<.0005$), reflecting a decrease in imatinib clearance ($P<.0005$). Additionally, grapefruit and grapefruit-containing products should also be avoided because they contain substances that inhibit CYP3A4.[1]

Conversely, strong inducers of CYP3A4 can decrease imatinib concentrations. Some examples of drugs that strongly induce CYP3A4 include dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, and phenobarbital. In addition, the herbal agent St. John's Wort has been shown to induce CYP3A4, so it also should be avoided. In a 2-period, open-label, fixed-sequence study, 12 healthy volunteers were administered 400 mg imatinib on day 1, 300 mg of St. John's Wort 3 times daily on days 4 to 17, and 400 mg imatinib again on day 15.[22] St. John's Wort increased imatinib clearance by 43%, from 12.5 ± 3.6 L/h to 17.9 ± 5.6 L/h ($P<.001$) so that the imatinib AUC was decreased by 30% ($P<.001$). Other pharmacokinetic parameters, including imatinib half-life (12.8 vs 9.0 hours, $P<.005$) and Cmax (2.2 □g/mL vs 1.8 □g/mL, $P<.005$) were also significantly decreased.

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Notes

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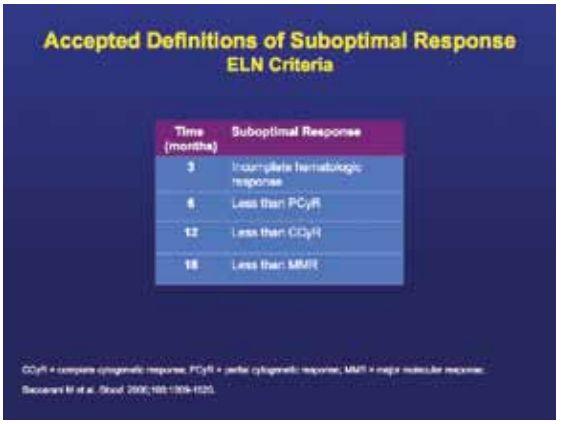

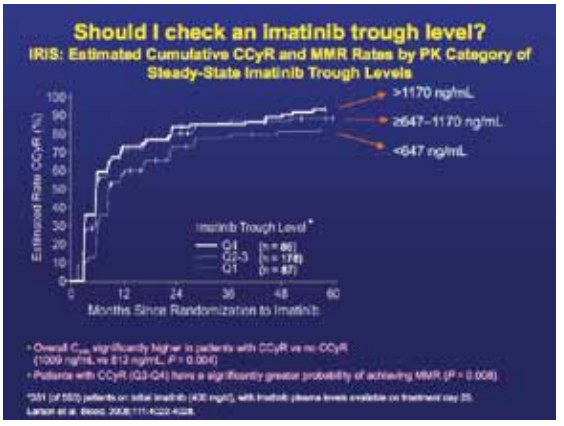

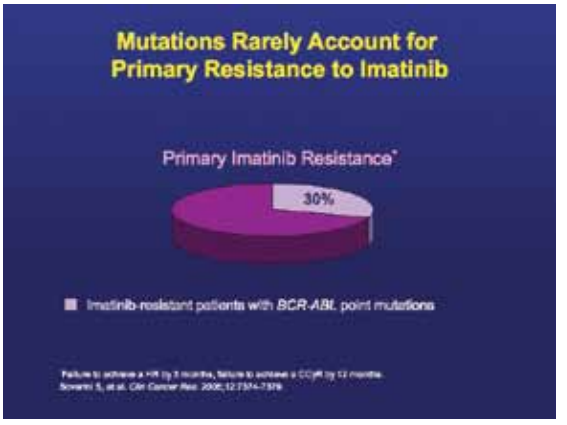

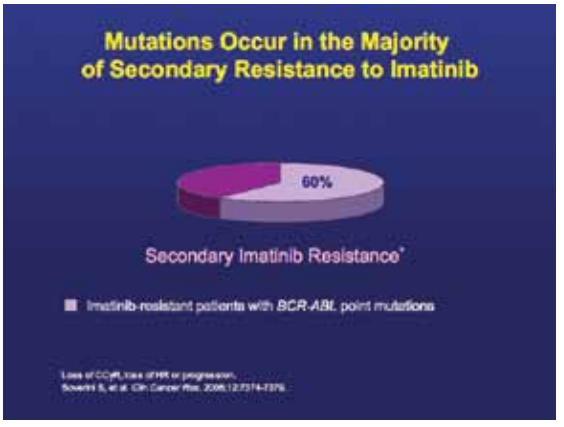

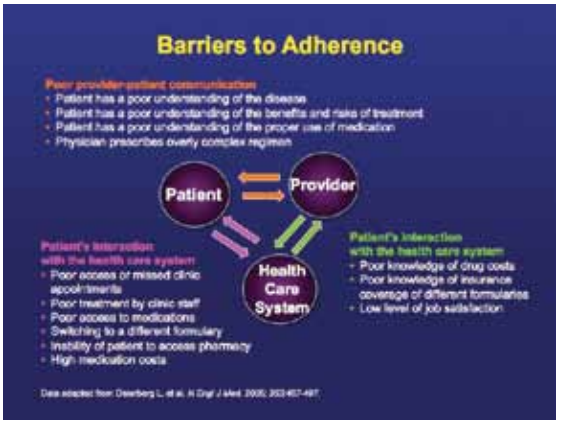

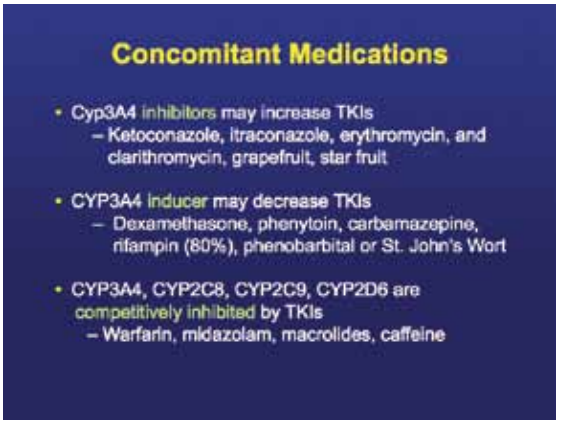

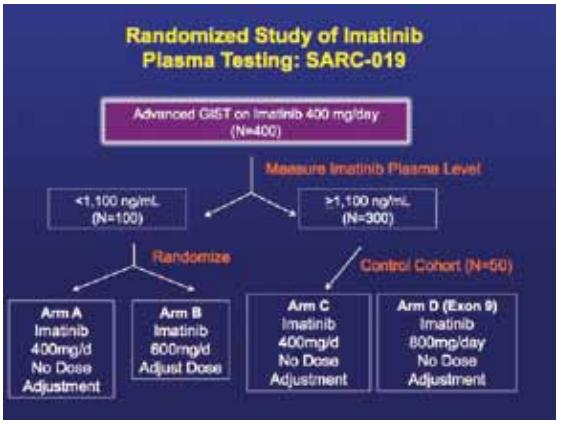

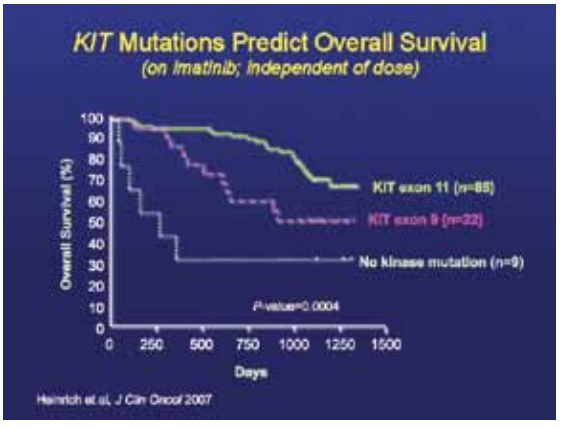

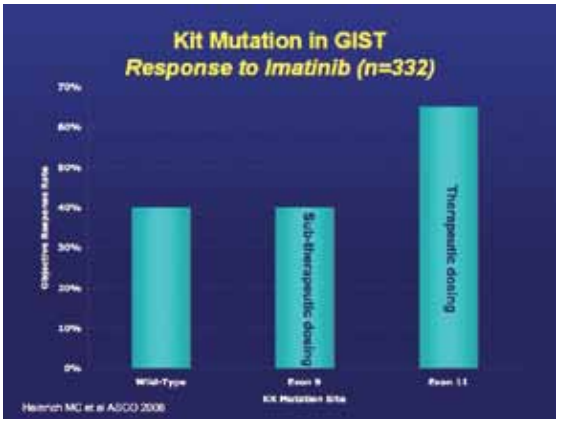

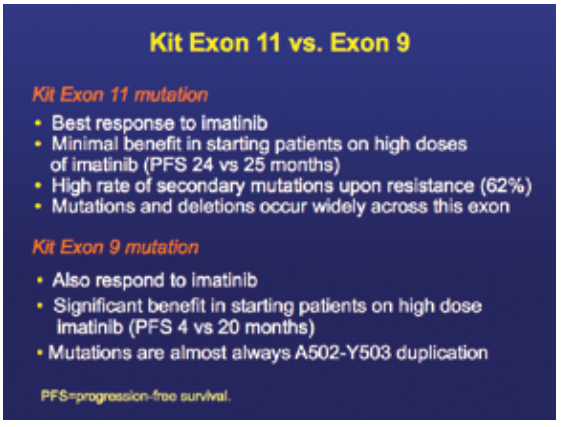

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