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Correlations between imatinib pharmacokinetics, pharmacodynamics, adherence, and clinical response in advanced metastatic gastrointestinal stromal tumor (GIST): an emerging role for drug blood level testing?

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SUMMARY

Imatinib is the standard of care for patients with advanced metastatic gastrointestinal stromal tumors (GIST), and is also approved for adjuvant treatment in patients at substantial risk of relapse. Studies have shown that maximizing benefit from imatinib depends on long-term administration at recommended doses. Pharmacokinetic (PK) and pharmacodynamic factors, adherence, and drug–drug interactions can affect exposure to imatinib and impact clinical outcomes. This article reviews the relevance of these factors to imatinib's clinical activity and response in the context of what has been demonstrated in chronic myelogenous leukemia (CML), and in light of new data correlating imatinib exposure to response in patients with GIST. Because of the wide inter-patient variability in drug exposure with imatinib in both CML and GIST, blood level testing (BLT) may play a role in investigating instances of suboptimal response, unusually severe toxicities, drug–drug interactions, and suspected non-adherence. Published clinical data in CML and in GIST were considered, including data from a PK substudy of the B2222 trial correlating imatinib blood levels with clinical responses in patients with GIST. Imatinib trough

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CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

MvM and NW were solely responsible for the design of the review and collection of data. Both authors contributed equally to the writing and approved all drafts through the final manuscript.

plasma levels <1100 ng/mL were associated with lower rates of objective response and faster development of progressive disease in patients with GIST. These findings have been supported by other analyses correlating free imatinib (unbound) levels with response. These results suggest a future application for imatinib BLT in predicting and optimizing therapeutic response. Nevertheless, early estimates of threshold imatinib blood levels must be confirmed prospectively in future studies and elaborated for different patient subgroups.

Keywords

Gastrointestinal neoplasms; Sarcoma; Tyrosine kinase inhibitors; Pharmacokinetics; Pharmacodynamics; Drug monitoring; Dose-response relationship

INTRODUCTION

The introduction of imatinib mesylate (Gleevec®, Glivec®; Novartis Pharma AG, Basel, Switzerland) marked an important clinical step forward in the care of patients with advanced gastrointestinal stromal tumors (GIST). Imatinib, arguably the archetype for tyrosine kinase inhibitor (TKI) therapeutics, has provided unsurpassed long-term responses in clinical trials, extending survival almost three-fold compared with treatment prior to targeted therapy.[1–3] Still, pitfalls to achieving the best possible clinical outcome in individual patients exist, and maximizing long-term clinical benefit from imatinib may result from dose optimization and strategies to attain proper adherence to therapy. Drug concentrations appear to be associated with outcomes in GIST: low trough levels of imatinib are associated with significantly shorter times to progression.[4,5]

This review will examine current data on factors that affect exposure to and clinical outcomes with imatinib, including pharmacokinetic (PK) parameters and their variability among individual patients; the pharmacodynamics (PD) of imatinib, including its mechanism of action in inhibiting KIT and PDGFRα; drug–drug interactions; and adherence. Data on the potential utility of blood level testing (BLT) with respect to each of these factors will also be discussed.

IMATINIB IN GIST

GIST, with a yearly incidence of 10 to 20 cases per million inhabitants, comprise the most common sarcoma of the intestinal tract, accounting for 82% of all gastrointestinal (GI) mesenchymal neoplasms.[6] The development of GIST is generally driven by mutations in the *KIT* gene or, less commonly, the *PDGFRA* gene. More than half of GIST cases are found in the stomach; other sites include the small intestine (35%), colorectum (<5%), and rarely the esophagus, omentum, or mesentery.[6] GIST are found more often in adults older than 50 years of age, with a slightly greater preponderance in males than females in some series.[6,7]

Imatinib is a small-molecule TKI indicated for the treatment of adult patients with KIT-positive, advanced, unresectable malignant GIST as well as for adjuvant treatment of adult patients at substantial risk of disease recurrence following complete tumor resection.[8] Trials have demonstrated an unprecedented efficacy and tolerability of imatinib in patients with

advanced metastatic GIST.[2,3] Neoadjuvant imatinib has also been shown to be safe and efficacious in helping to achieve complete resection (R0, negative margins) and/or to reduce surgical morbidity.[9,10] Adjuvant imatinib was shown to improve recurrence-free survival (RFS) following primary resection.[11] Major treatment guidelines from the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) have each been updated to reflect these advances.[12,13]

Overview of considerations for optimizing imatinib treatment

The recommended starting dose for first-line imatinib in advanced GIST is 400 mg daily, although dose escalation to 800 mg daily is recommended for many patients who progress on imatinib.[12,13] Phase III studies comparing 400 with 800 mg daily in advanced disease have shown a progression-free survival (PFS) benefit with imatinib 800 mg daily for tumors with *KIT* exon 9 mutations.[14,15]

Continuous imatinib dosing is important in the management of advanced GIST. The French Sarcoma Group BFR14 study demonstrated that interruption of imatinib is associated with increased risk of relapse, even in patients who have achieved complete remission.[16] These results in GIST contrast with recent findings in chronic myelogenous leukemia (CML), in which it may be possible to discontinue imatinib treatment after a sustained complete molecular response has been achieved, particularly in patients pretreated with interferon.[17] Current ESMO and NCCN guidelines recommend that imatinib be continued indefinitely in advanced disease until disease progression, at which time using dose escalation of imatinib followed by sunitinib as indicated.[12,13]

PHARMACOKINETICS OF IMATINIB

The PK of imatinib have been assessed in studies in healthy subjects and in population PK studies in more than 500 patients with GIST or CML.[3,18–22] Imatinib is rapidly and completely absorbed from the GI tract, achieving a peak plasma concentration (C_{max}) within 2 to 4 hours following oral administration.[21] Imatinib's bioavailability is independent of food intake, and the mean absolute bioavailability of imatinib is 98%.[19,21] Imatinib undergoes rapid and extensive distribution into tissues, with minimal penetration into the central nervous system.[21] In the circulation, imatinib is approximately 95% bound to plasma proteins, principally albumin and α1-acid glycoprotein (AGP).[22,23] Imatinib undergoes metabolism in the liver via the cytochrome P (CYP) 450 enzyme system, with CYP3A4 being the primary isoenzyme involved.[21] The N-desmethyl metabolite CGP74588 is the major circulating active metabolite.[21,24] The elimination half-life for imatinib is approximately 16 to 18 hours.[21,22]

Pharmacokinetics in GIST Patients

The PK properties of imatinib in patients with CML and GIST are similar, with a few subtle differences. The C_{max} of imatinib at steady state in patients with GIST has been measured at 2.9 μg/mL compared with 2.3 μg/mL in patients with CML.[18,25] Also, the rate of clearance for imatinib is approximately 8% lower in patients with GIST than in patients with CML.[22] Small differences in PK properties between GIST and CML patient populations might be

attributable to factors that affect drug absorption or elimination, such as differences in liver function (advanced GIST patients commonly have liver metastases), or anatomical or functional abnormalities of the GI tract due to GISTrelated surgery on the liver, stomach, or intestines.[21,26] An alternate explanation may be differences in CYP isoenzymes that result in variable rates of drug metabolism or drug interactions, especially at the CYP3A4 level.[27]

Imatinib PK were evaluated in a substudy of the first 73 of 147 randomized patients with advanced GIST who were enrolled in the Phase II B2222 trial.[5] Large inter-patient variability in imatinib plasma exposure (coefficient of variation 40–50%) was observed (Table 1). These findings are consistent with results previously reported for patients with CML and GIST.[20,22] Figure 1 provides a graphic representation of this variability, described by percentile curves obtained from previously published PK data from patients with GIST.[22] Such variability in exposure underscores the potential impact of imatinib plasma concentrations on clinical outcomes in both GIST and CML.

Population PK analyses in patients with advanced GIST have identified several variables as significant covariates for imatinib exposure and clearance, including white blood cell (WBC) counts, body weight, and granulocyte count, as well as AGP, albumin, and hemoglobin levels.[22,28,29] Additionally, a recent study found the *ABCB1* (*MDR1*) genotype, coding for the P-glycoprotein (P-gp) drug transporter, to be a significant covariate for imatinib clearance.[30] Some of these variables may change or normalize with improvement in the disease, thus having an impact on drug exposure and clearance. In fact, it has been shown that a trend exists toward increased imatinib clearance over time.[28,29] However, a progressive decline in adherence might be a confounding factor. In the B2222 PK substudy, the only two significant PK covariates for imatinib clearance and volume of distribution (Figure 2) were plasma albumin level and WBC, with age, gender, and body weight exerting only minimal effects.[5] A retrospective analysis conducted by Nolden and colleagues in 142 patients with metastatic GIST found that imatinib plasma levels ranged from 256 to 4582 ng/mL, with a first quartile cutoff of 851 ng/mL.[31] Imatinib plasma levels were shown to correlate with age, gender, imatinib dose, and response by Choi criteria. In addition, patients with *KIT* exon 9 mutations treated with a higher dose of imatinib had higher plasma levels of imatinib, and had a PFS similar to patients harboring *KIT* exon 11 mutations.

Imatinib tissue levels in GIST

Limited PK and PD data on imatinib tissue levels in GIST are available. Tissue distribution of imatinib occurs by both active and passive diffusion. Imatinib appears to be a substrate for some cellular influx transporters (OCT1 and OATP1A2) and efflux transporters (P-gp and breast cancer resistance protein).[32–39] Results from *in vitro* studies demonstrate involvement of both OCT1 and P-gp in active transport processes of imatinib, mediating the influx and efflux of the drug in cancer cells.[40] Recent findings indicate that expression of OCT1 in CML cells plays a role in determining clinical response to imatinib; higher pretreatment OCT1 expression has been correlated with improved rates of complete cytogenetic response.[38]

The rationale for increasing the dose of imatinib in select progressing patients rests in the potential for higher drug concentrations to overcome drug efflux mechanisms. Alternatively,

dose escalation may result in raising drug levels to within the therapeutic range conferred by secondary resistance mutations.[41]

Imatinib free concentrations

Recent results have demonstrated the importance of free drug concentrations of imatinib, the pharmacologically active fraction not bound by albumin or AGP, in considering exposure. The free area under the PK curve (AUC) for imatinib, which can either be measured directly or as the correction of the total drug concentration for binding to AGP, provides a valuable surrogate for cellular drug exposure.[22] Higher free AUC of imatinib has been shown to be a significant predictor of therapeutic response in patients with GIST.[42]

CORRELATING IMATINIB EXPOSURE WITH RESPONSE IN CML

Among patients with CML, significant correlations between imatinib trough plasma levels (C_{min}) and cytogenetic and molecular responses have been found.[43–45] In a PK/PD subanalysis of results from the International Randomized Interferon versus STI571 (IRIS) study, including 351 patients with chronic-phase (CP) CML, imatinib plasma C_{min} levels higher than 1000 ng/mL correlated significantly with improved rates of cytogenetic and molecular responses.[44] In the Tyrosine Kinase Dose Optimization Study (TOPS), evaluation of the effect of imatinib 400 mg bid compared with imatinib 400 mg daily in previously untreated patients with newly diagnosed CP CML showed that imatinib trough plasma levels were proportional to dose and stable over time despite high interpatient variability.[46] Patients with imatinib C_{min} in the lowest quartile showed a lower major molecular response rate (MMR) at 12 months, whereas patients in the highest C_{min} quartile showed a higher frequency of all grades of some adverse events.[46]

Another analysis pooled data from patients with newly diagnosed and previously untreated Ph+ CP CML from both the IRIS and TOPS trials. This study confirmed that higher steady-state imatinib levels correlated with better complete cytogenetic response (CCyR) and MMR, but also resulted in more Grade 3 and 4 treatment-related toxicities.[47] These results suggested a possible role for imatinib blood or plasma level testing in evaluating – as well as optimizing – responses in patients with CML.[44,46,47] In the case-control study by Singh and colleagues, mean plasma levels in non-responders were shown to be significantly lower than those in responders (413 vs 1380 ng/mL, respectively; P=0.002) in 40 patients with CML (20 responders and 20 non-responders to imatinib).[45] Based on these data, a subsequent receiver operating curve (ROC) analysis showed that a trough plasma level threshold higher than only 560 ng/mL could be sufficient to reduce the incidence of resistance (determined however only on a short-term basis).[48] Another recent study reported conflicting results, however, with no correlation found between imatinib levels and CCyRs at 1 year or between imatinib levels and major molecular responses after a median of 1298 days of therapy.[49] Additional studies in various CML patient populations, confirming the imatinib concentration-response relationship, continue to emerge in the literature.[50,51]

CORRELATING IMATINIB EXPOSURE WITH RESPONSE IN GIST

In GIST, important findings are emerging from studies examining the relationship between imatinib PK and response to treatment.[5,42,52] Correlations between free drug levels and side effects have also been observed.[29,42] In the PK substudy of B2222, correlations were based on imatinib C_{min} at steady state. Imatinib AUC, C_{max}, and C_{min} values were highly inter-correlated.[5] However, there was less variability in C_{min} over time compared with C_{max}, and C_{min} was more easily monitored than AUC. Figure 3 shows the distribution of patients by imatinib C_{min} level (divided into quartiles) at steady state (Day 29). This analysis revealed that patients with imatinib C_{min} above the lowest quartile threshold, 1100 ng/mL, had higher rates of objective response, with improved disease control and increased clinical benefit (Table 2). Overall, responding patients (complete response [CR], partial response [PR], or stable disease [SD]) had markedly higher median imatinib C_{min} (1446 ng/mL) than non-responders (1155 ng/mL), with significantly longer PFS associated with higher imatinib C_{min} as well (Table 2). No significant differences in median overall survival (secondary endpoint) were found between different imatinib C_{min} groups, perhaps due to the small numbers of patients in each group.[5] Combined, these findings suggest a minimal plasma threshold is necessary to achieve and maintain clinical response with imatinib in patients with GIST.

Results from the PK analysis conducted by Widmer and colleagues in Switzerland that examined the relationship between imatinib free plasma levels and response similarly demonstrated the importance of adequate drug exposure in achieving and maintaining therapeutic response, as well as a significant correlation between imatinib exposure and incidence of adverse events.[42] A prior analysis in 58 patients with GIST or CML evaluated imatinib PK using a non-linear mixed-effects population model (NONMEM®); free drug exposures (expressed as AUC) were estimated.[22] Among those patients with GIST, higher imatinib-free AUC was a significant predictor of therapeutic response (odds ratio ±standard error [SE]: 2.6±1.1; P=0.026 by logistic regression). This PK model also allows the extrapolation of random sampling results (i.e. obtained from blood samples taken at any time after the last drug dose) in terms of free C_{min} using a Bayesian maximum *a posteriori* estimation.[53]

Correlating imatinib exposure and response by mutational subtype

Imatinib response in GIST varies based on the type of activating mutation(s) present.[2,15,54,55] Mutational analysis of tumors from the large European Organisation for Research and Treatment of Cancer–Australasian Phase III trial, comparing response and survival following either standard-dose (400 mg daily) or high-dose (800 mg daily) imatinib, found that the presence of *KIT* exon 11 mutation was the strongest predictor of response and disease stabilization in patients with GIST.[15] Tumors with *KIT* exon 9 mutation were associated with significantly poorer PFS on standard-dose therapy, which was not observed in *KIT* exon 11 or wild-type (WT) tumors.[15] Similar results were reported from the North American Southwest Oncology Group S0033 Phase III trial, in which *KIT* exon 9 and WT genotypes predicted poorer response and shorter time to progression versus *KIT* exon 11 mutations; there was some evidence of improved response in those with exon 9 mutant

genotypes who received high-dose imatinib.[55] The MetaGIST analysis of both Phase III studies of imatinib indicates that imatinib 800 mg daily significantly improved PFS in high-risk patients whose GIST harbored a *KIT* exon 9 mutation in contrast to those that harbored other mutations.[14]

In the B2222 PK substudy, presence of *KIT* exon 11 mutation predicted improved rates of clinical benefit with imatinib exposure greater than 1100 ng/mL.[5] In 39 patients with *KIT* exon 11 mutations evaluated by C_{min} quartile (as shown in Table 3), patients in the upper quartiles had significantly higher rates of overall objective clinical benefit: 100% achieved either CR, PR, or SD compared with 67% (6/9) for those in quartile (Q) 1 (P=0.0001 between Q1 and Q2–Q4, Chi-square test).[5] There were too few patients with *KIT* exon 9 mutations to be able to draw any conclusions with respect to this subgroup. Results from the Swiss analysis by Widmer and colleagues found the strongest associations between free plasma concentrations and response among patients whose tumors harbored *KIT* exon 9 mutations or WT KIT.[42] In a more recent analysis, the relationship between extrapolated free C_{min} and response in GIST was shown to be especially relevant in patients whose tumors contain a *KIT* exon 9 mutation or are WT (Figure 4).[53] Because of the limited number of patients included in the analysis, such results should be considered with caution and will have to be confirmed in further studies. In addition, using free imatinib levels derived from a per-sample analysis in these two Swiss analyses by Widmer and colleagues may have led to an over-powered analysis, as this method ignores intra-patient correlation.[42,53] Extrapolation of free concentrations also still remains to be confirmed formally by direct measurement of free plasma levels of imatinib in patients' blood. Further studies are also required to ascertain whether reproducible PD differences exist between subgroups of patients with different *KIT* mutations and to identify minimum effective concentrations for these subgroups.

Results from the French Database

The French database for imatinib BLT includes patients from BFR14, and Bui and colleagues again demonstrated significant inter-patient variability in imatinib trough levels.[52] However, in contrast to earlier findings by Widmer and colleagues, this study found that imatinib C_{min} levels among GIST patients tended to be lower than trough levels among CML patients, suggesting more rapid clearance in the GIST patient population.[22,42] Other preliminary results from Bui and coworkers showed that long-term survivors tended to have higher imatinib trough concentrations than more recently treated patients (Figure 5). Nevertheless, no definitive conclusions concerning trough levels and long-term survival can be made at this time.[52]

ADHERENCE WITH IMATINIB

Because imatinib therapy requires daily administration, maintaining proper adherence may take on a greater significance in patients with GIST, as discontinuation of imatinib is associated with loss of remission and a shorter time to relapse, even in patients who have achieved CR when imatinib is discontinued. This is supported by the Phase III French Sarcoma Group BFR14 Study evaluating the effect of imatinib interruption in responding patients (CR, PR, or SD) after different periods of treatment.[16,56,57] Three-and 5-year results

from the study indicate that discontinuation of imatinib is associated with rapid progression.[56] Conversely, in CML, early studies showed that discontinuation of imatinib may be feasible after sustained complete molecular response has been achieved, especially in those pretreated with interferon.[17] Yet, discontinuation of imatinib has been associated with relapse in some patients with CML; however, previous best responses can be achieved following imatinib re-introduction.[58] Results obtained after discontinuation of imatinib in CML are not fully concordant; nevertheless, continuous administration may be appropriate for most patients. Better adherence appears also to be associated with significantly lower resource utilization and costs in CML patients.[59]

Oral cancer therapies, such as imatinib, have become increasingly common in oncology practice. Although these therapies offer patients the convenience of self-administration at home, evidence suggests that adherence to oral cancer therapies is far from optimal.[60–62] For example, in one study, drug serum level monitoring revealed that patients with hematologic cancers overestimated their compliance with allopurinol by a factor of two.[60] Serum samples showed that the control group (baseline levels of compliance) were fully compliant 16.8% of the time, whereas patient self-reports showed a compliance rate of 53.8%.

Evidence for suboptimal adherence with imatinib therapy

A number of recent studies have examined adherence to imatinib therapy among patient populations with either GIST or CML; all documented surprisingly high rates of non-adherence.[61–63] Results from one study by Tsang and colleagues indicated that adherence to imatinib declines markedly with time on therapy.[62] Researchers tracked patient prescription data for 4043 patients receiving imatinib for CML or GIST for 24 months. The study evaluated *compliance*, defined as the dose of imatinib taken versus the dose prescribed, and *persistency*, defined as the time in days that each patient remained on therapy. The overall rate of compliance for both patient groups was 75% (78% in CML and 73% in GIST patients). Total (100%) compliance was achieved by only half of the patients. During the course of the 24-month study, average persistency was 255 days. As seen in other disease categories in which adherence has been studied, the authors found a high and stable level of persistency early in the treatment course, followed by a steady decline (Figure 6).[62]

Another study by Feng and coworkers examined prescription data for 320 patients who received imatinib therapy for CML or GIST during a period of 12 months. The average rate of full compliance was 76%. More than a quarter of patients (28%) interrupted therapy for at least 30 consecutive days.[61]

The Adherence Assessment with Glivec®: Indicators and Outcomes (ADAGIO) study was an observational, open-label trial conducted in 169 patients with CP CML who received imatinib.[63] Levels of non-adherence were examined using structured patient interviews, intuitive ratings by patients and physicians, and pill counts. The study found that approximately one-third of patients exhibited non-adherent behavior. Patterns of under- and overtaking medication were evident using pill-count data, with perfect adherence reported in only 14.2% (23/162) of patients.

Factors contributing to non-adherence

Factors associated with non-adherence in the study conducted by Feng and colleagues included increasing age (older than 51 years), gender (female), higher number of concomitant medications, and complications of disease or therapy.[61] In the ADAGIO study, factors associated with non-adherence to imatinib therapy included increased age, increased time since diagnosis, increased duration of imatinib treatment, and improved health at study enrollment.[63] Several other factors are recognized as important contributors to non-adherence with drug therapy, including lack of understanding of the importance of adherence to achieving and maintaining response; drug-related side effects; miscommunication between the patient and physician; environment-related factors, such as social, family, and patient attitudes toward treatment, as well as financial constraints; and presence of cognitive impairments or psychopathologies.[64]

THERAPEUTIC DRUG MONITORING IN THE MANAGEMENT OF GIST

Blood level testing to maintain defined therapeutic drug levels is not commonly used in oncology at present. However, it is employed for this purpose in several other medical disciplines, including organ transplant, cardiology, neurology, psychiatry, and infectious disease (especially in HIV/AIDS, a disease with a pharmacotherapeutic model that roughly resembles GIST and CML). BLT is generally termed “therapeutic drug monitoring” in these settings.[65]

Findings from recent studies have improved our understanding of the relationship between imatinib exposure and clinical outcomes, but the putative plasma threshold for clinical benefit for patients with GIST remains a subject of investigation. Nevertheless, drug level monitoring in certain clinical situations as a mean of preventing low drug exposure has proven valuable, giving the health care provider a tool for identifying patients with suboptimal drug exposure so that possible causes can be investigated. PK/PD results from the B2222 substudy have provided initial data for defining optimal plasma levels for imatinib in GIST: plasma imatinib concentrations greater than 1100 ng/mL may increase the likelihood of durable disease control. Imatinib blood concentrations lower than this level may warrant investigation into possible causes of low drug exposure. The utility of imatinib BLT for ensuring optimal drug exposure has already been suggested in CML.[66,67]

Practical issues in BLT

Current applications for BLT during imatinib therapy include lack of therapeutic response, severe toxicities, drug–drug interactions, and non-adherence. BLT may also be important in patients who have undergone major gastrectomy, to ensure optimal treatment with imatinib.[26] The potential role of BLT in optimizing therapeutic response is still investigational, however, despite preliminary estimates of minimum imatinib blood levels that correlate with improved clinical outcomes (C_{min} >1110 ng/mL).[5] However, threshold blood levels at trough remain to be prospectively and retrospectively evaluated in larger studies and defined for each major GIST mutational subtype. Further studies also may help determine whether a correlation exists between suboptimal exposure and the development of resistance. The correlation of imatinib blood levels with surrogate disease markers, blood

cell counts, and phosphate levels may be useful in guiding therapy, particularly in the adjuvant setting. Other areas of investigation include the predictive value of imatinib free concentrations compared with total imatinib concentrations, the relationship between imatinib blood and tissue levels, the relationship between blood levels and the portion of the intestinal tract resected, and the importance of pharmacogenetic factors in drug exposure. Further explorations of concentrations–toxicity relationship are also warranted. Moreover, the development of mathematical algorithms will enable the drawing of samples at time points not strictly corresponding to the trough level, thus, providing a wider sampling window.[68] However, current recommendations proposed by Wang and colleagues for imatinib sampling are 24 hours post-dose for imatinib 400 mg daily dosing and 12 hours postdose for imatinib 400 mg twice-daily dosing. Finally, the sampling tube required may depend on the laboratory involved in the measurement.

Imatinib blood level testing in the French database study revealed that attaining good adherence was problematic: the authors concluded that in four of seven patients who had very low trough levels, poor adherence played a role.[52]. Although non-adherence appears to be a significant problem with oral cancer treatments such as imatinib, drug monitoring can be useful in detecting suspected cases of non-adherence, hopefully avoiding prolonged suboptimal responses by ensuring minimal therapeutic plasma levels of imatinib.[52] Although BLT may be useful, it is important to consider that measured drug blood levels are indicative only of short-term compliance and may not reflect adherence during any prolonged period prior to testing. Also, BLT may indeed be subject to a confounding “white coat” effect when used to assess adherence.[69]

Major cancer treatment centers in Europe, in collaboration with the manufacturer of imatinib, have developed a testing protocol for monitoring plasma levels in cancer patients.[70] This effort is focused on developing a database of imatinib plasma level measurements to verify therapeutic plasma thresholds in various indications and to identify and certify laboratories to provide proper testing services. Certification of testing laboratories is done by a designated central laboratory, which implements a cross-check of results to ensure consistency with testing standards. Additionally, the central laboratory administers a system of regular quality-control checks.

The currently preferred analytical method used for imatinib BLT is liquid chromatography–tandem mass spectrometry (LC-MS/MS). It provides a rapid, efficient, and simple means of quantifying imatinib in plasma.[71] The method has been shown to be precise, sensitive, and accurate. LC-MS/MS assays are presently being developed to cover other major TKIs.[72,73] Although LC-MS/MS is the preferred method for imatinib BLT, cost considerations may prohibit its use in certain settings. High-performance liquid chromatography–ultraviolet techniques have also been published, making the assay accessible by any laboratory or institute not equipped with sophisticated and costly LC-MS/MS apparatus.[74,75]

In addition to its usefulness in optimizing exposure to imatinib, BLT may also serve the same purpose with newer TKIs. Second-line agents such as sunitinib (Sutent®; Pfizer Inc; New York, NY) and other investigational, newer-generation TKIs, for example, nilotinib (Tasigna®; Novartis Pharma AG) and dasatinib (Sprycel®; Bristol-Myers Squibb; New

York, NY), have been shown to be useful in patients who are intolerant/resistant to imatinib and/or sunitinib.[76–78] BLT may be applicable to these agents, but clinical PK/PD analyses correlating efficacy with drug exposure as have been done with imatinib are still lacking.

CONCLUSIONS

Long-term studies of imatinib have documented impressive rates of response and survival. Nevertheless, achieving optimal clinical benefit from imatinib depends on optimal dosing and good adherence. Exposure to imatinib and subsequent impact on therapeutic benefit can be affected by factors such as individual patient variability in absorption, distribution, and metabolism, because of genetic or demographic differences, or because of anatomical or GIST-related surgery abnormalities of the GI tract. Other specific factors, such as drug interactions or environmental influences may also have an impact on drug exposure, thus compromising response.

BLT may be useful in predicting and optimizing therapeutic response. Data from some PK studies indeed show that low plasma exposure is associated with a trend toward lower rates of objective response and faster development of resistance or progressive disease. Although retrospective analyses of data from the B2222 PK substudy have provided a preliminary estimate of a minimum threshold blood level for imatinib in GIST (1100 ng/mL), convincing results from prospective studies are needed before BLT becomes a routine part of imatinib therapy for patients with GIST. Furthermore, these studies would also help determine suitable blood levels for different patient subgroups (in term of minimal, as well as maximal levels). To that purpose, in CML, a randomized controlled trial (Imatinib COncentration Monitoring Evaluation study) has just started in Europe.[79] For GIST, studies such as the Sarcoma Alliance for Research through Collaboration (SARC) Imatinib BLT Study (SARC-019)[80] may provide clearer, more definitive answers.

Monitoring imatinib blood or plasma levels appears to be a useful tool for investigating cases of suboptimal therapeutic response, potential drug–drug interactions, toxicities that are unusually severe for the dose of imatinib taken, and suspected non-adherence. A low blood level may indeed provide health care providers with a means of initiating a discussion of the importance of adhering to imatinib as prescribed. Establishing a baseline imatinib trough level 1 month after treatment initiation could serve as a reference point for later measurements, and it may help guide optimal imatinib blood levels throughout treatment in cases of clinical concern. The outcome of ongoing prospective trials will be necessary for clinicians to define the exact role of BLT for imatinib and other TKI treatment optimization.

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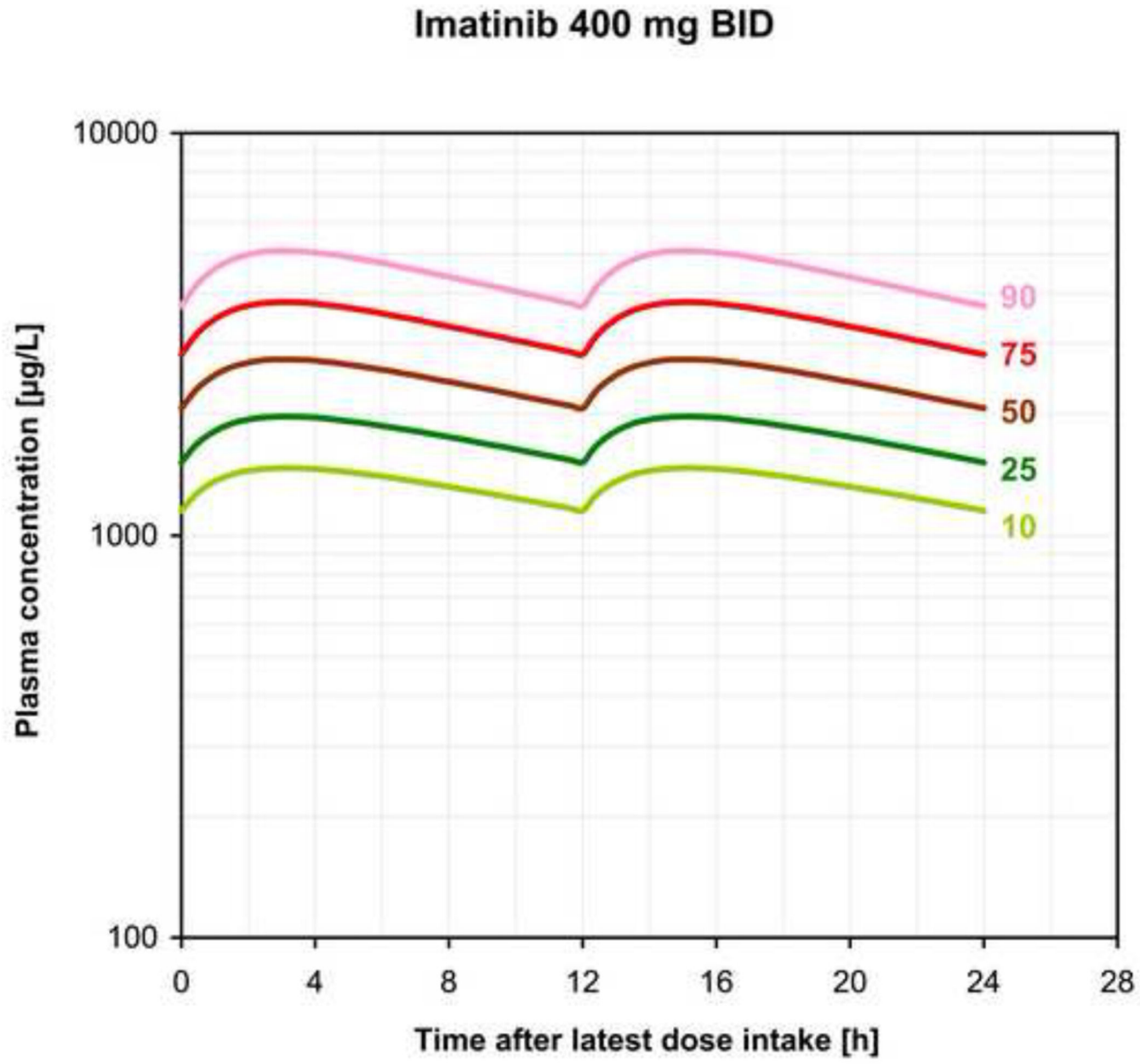
SEARCH STRATEGY AND SELECTION CRITERIA

A non-biased search of the chronic myelogenous leukemia and gastrointestinal stromal tumors literature was performed, and pertinent articles identified on PubMed were considered. References listed in relevant articles were searched as well. Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English were included.



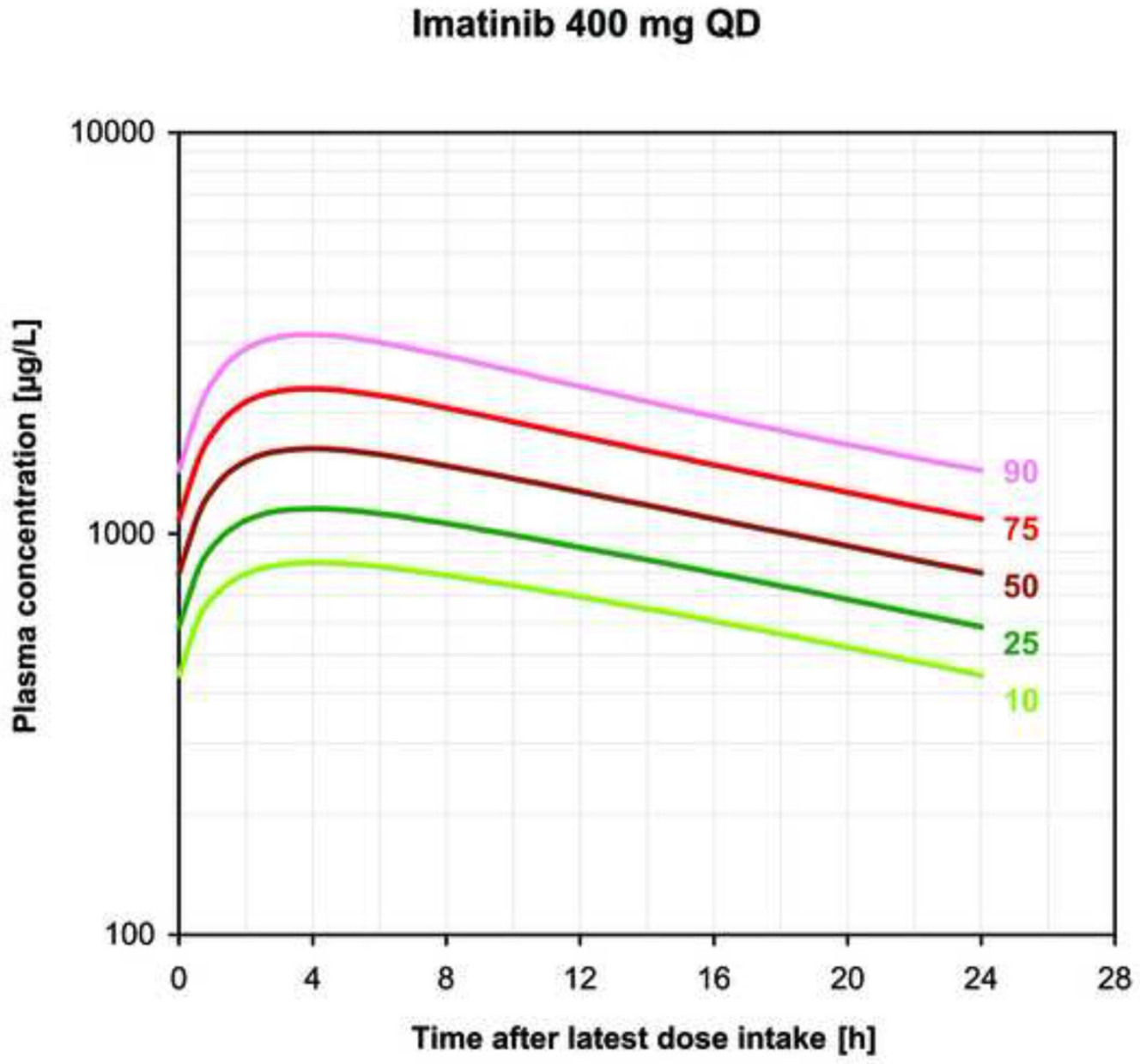


Figure 1. Imatinib exposures and expected concentrations

Predicted from a population PK model in GIST patients receiving imatinib 400 mg or 800 mg (400 mg bid) daily, the percentile curves quantify expected dispersion for individual drug levels. With 400 mg qd, 25% of patients attain C_{min} >1100 ng/mL (top panel). With 400 mg bid, >90% of patients exceed this threshold (bottom panel). Curves were drawn from previously published PK data.[22]

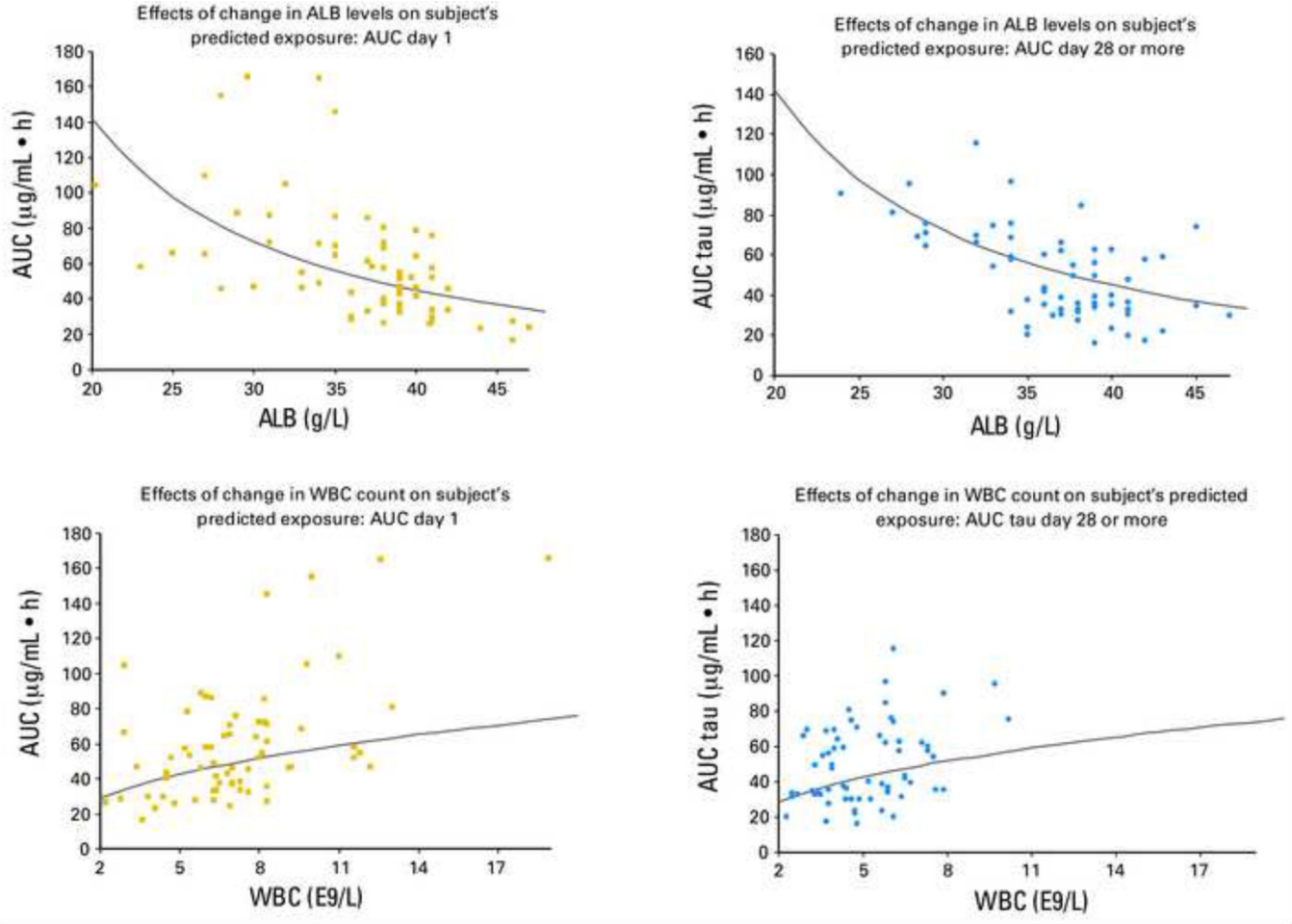


Figure 2. Effects of albumin (ABL) and WBC on model predicted AUC_{∞} Day 1 and single-dose AUC^{24} at steady state (Day 29)

[5] Plasma albumin and WBC counts were the only two significant PK covariates identified for imatinib clearance and volume of distribution in the B2222 PK substudy.

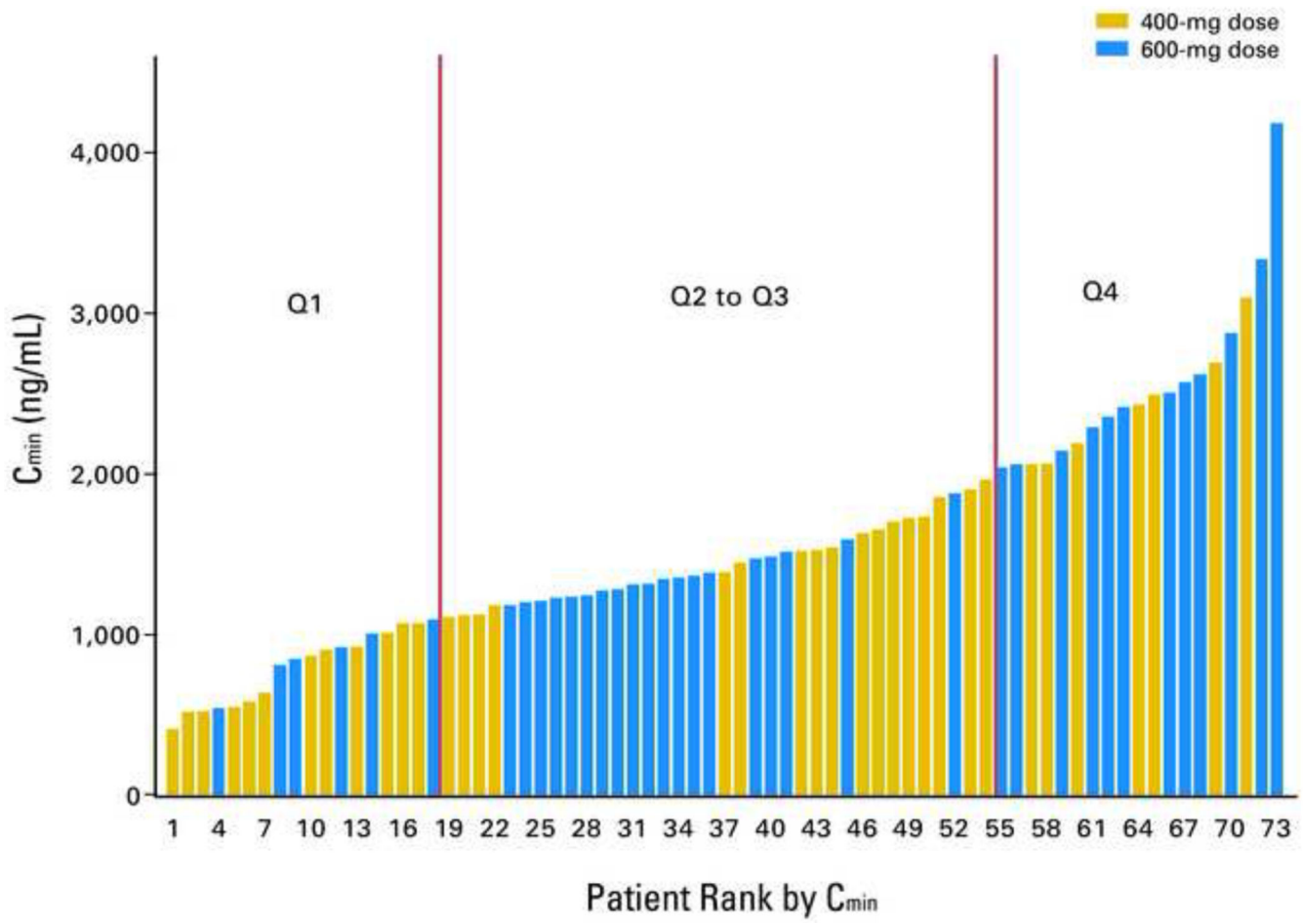


Figure 3. Distribution of patients by imatinib C_{min} level at steady state (Day 29)

[5] Vertical lines represent 25% and 75% percentiles. 400 mg group (n=34): 11 patients are in quartile 1 (Q1), 16 in Q2–Q3, and 7 in Q4. 600 mg group (n=39): 7 patients are in Q1, 20 in Q2–Q3, and 12 in Q4.

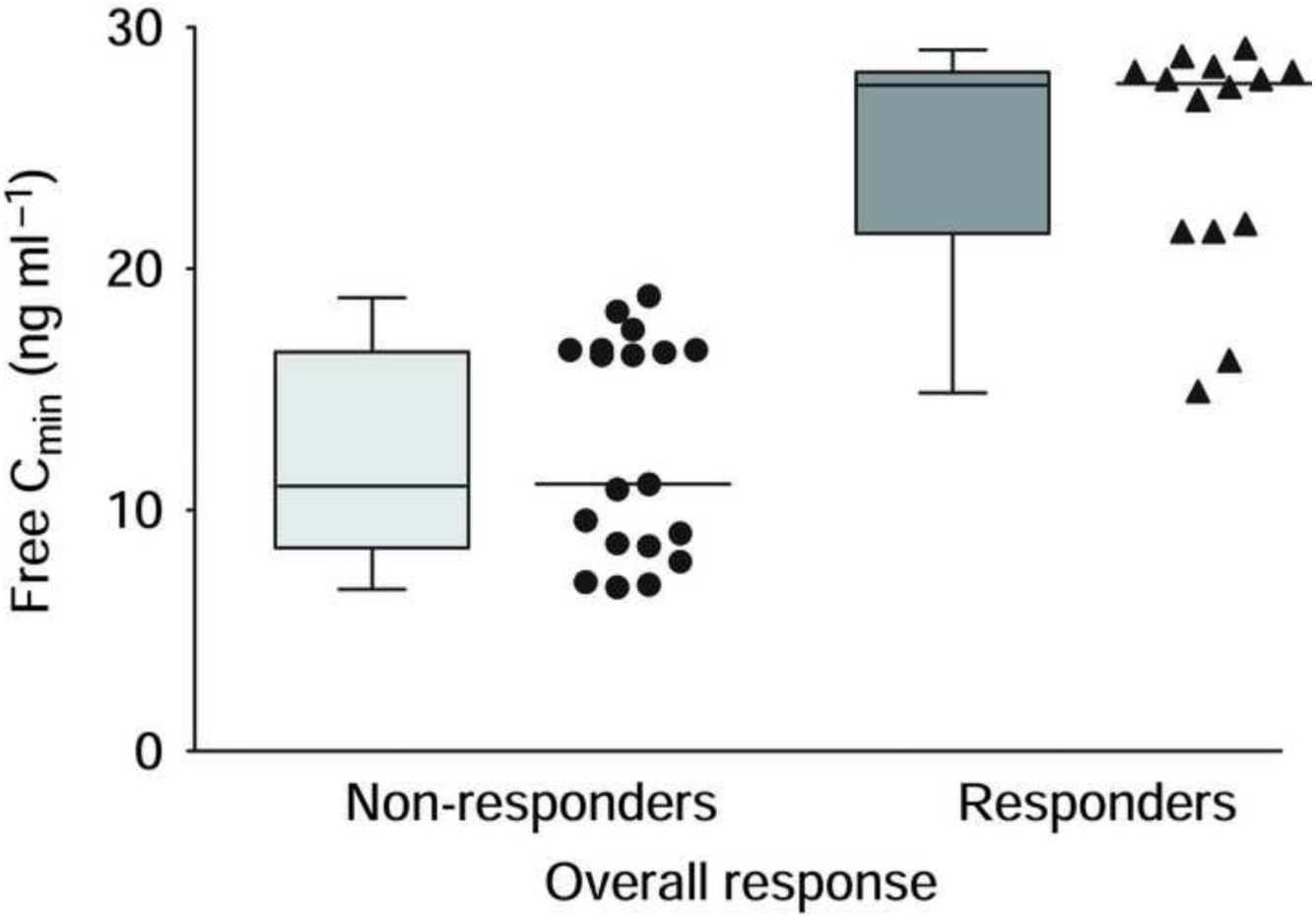


Figure 4. Free imatinib trough levels (C_{min}) according to therapeutic response in exon 9 mutated or WT *KIT* patients

[53] Box plots and individual values of free C_{min}: responders were complete response, partial response, or stable disease; n=14; median = 25.7 ng/mL. Non-responders were progressive disease; n=19; median = 10.1 ng/mL.

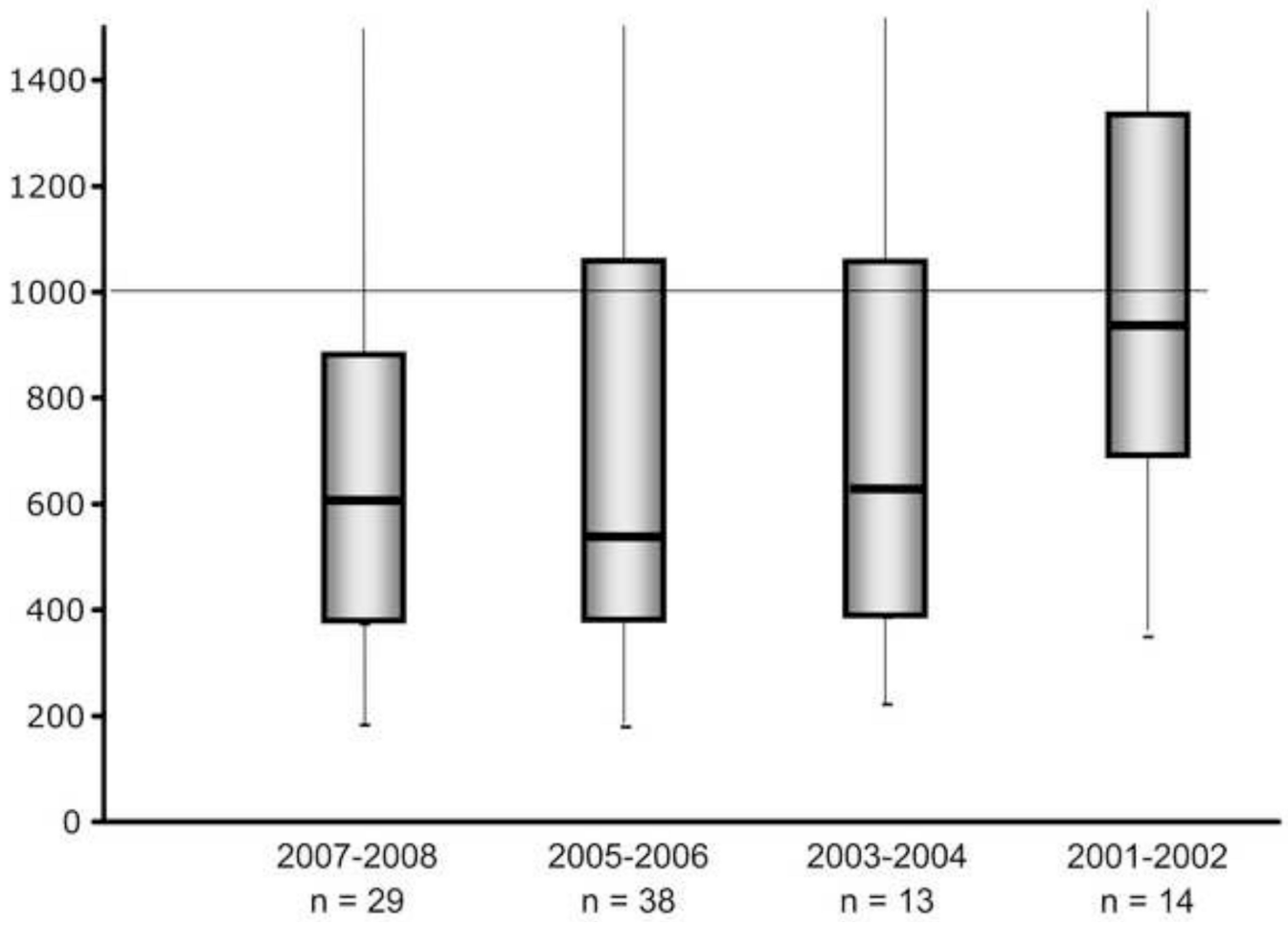


Figure 5. French database: imatinib C_{min} according to time under treatment

[52] Results from French Database showing that long-term survivors tend to have higher imatinib concentrations compared with those who had initiated treatment more recently.

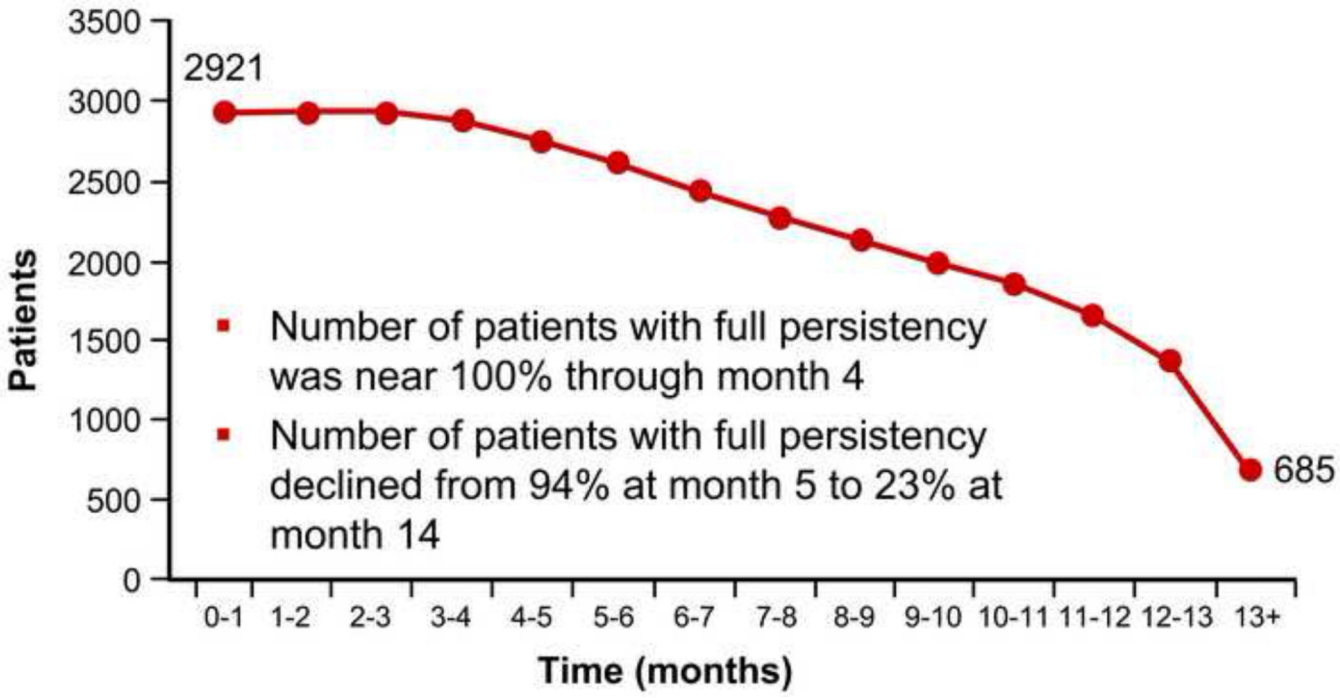


Figure 6. Imatinib adherence

[62] Higher and stable level of persistency through Month 4 followed by a steady decline in adherence.

Table 1

Study B2222: Imatinib pharmacokinetic parameters at steady state.[5]

Parameters	**400 mg qd Mean ± SD (CV%) (n=34)**	**600 mg qe Mean ± SD (CV%) (n=39)**
AUC, µg*hr/mL	56.4 ± 23.9 (42.5%)	64.3 ± 27.1 (42.2%)
C_{max}, ng/mL	3405 ± 1434 (42.1%)	3868 ± 1574 (40.7%)
C_{min}, ng/mL	1530 ± 666 (43.6%)	1752 ± 794 (45.3%)
CL/F, L/hr	8.84 ± 4.87 (55.1%)	10.9 ± 4.43 (40.6%)
$T_{1/2}$, hr	19.3 ± 2.2 (11.5%)	19.5 ± 2.8 (14.3%)

qd, once daily; SD, standard deviation; CV%, percentage coefficient of variation.

Table 2

Response and time to progression by imatinib C_{min} quartile.[5]

	PK C_{min} quartiles (n=73)		
Response	**Q1 (n=18) n (%)**	**Q2–Q3 (n=36) n (%)**	**Q4 (n=19) n (%)**
CR + PR + SD*	12 (67)	29 (81)	16 (84)
CR + PR†	8 (44)	24 (67)	14 (73)
Median TTP, months‡	11.3	30.6	33.1

*Chi-square test comparing two groups: C_{min} <Q1 vs C_{min} ≥Q1; *P*=0.177;

†Chi-square test comparing two groups: C_{min} <Q1 vs C_{min} ≥Q1; *P*=0.0601;

‡*P*=0.0105 and *P*=0.0029 between Q1 and Q2–Q4, hazard ratio=0.418 with 95% CI (0.231, 0.756).

Table 3

Overall objective clinical benefit (CR+PR+SD) by imatinib C_{min} quartile for *KIT* exon 11 patients.[5]

	PK C_{min} Quartiles (n=39)		
Response	**Q1 (n=9) n (%)**	**Q2–Q3 (n=17) n (%)**	**Q4 (n=13) n (%)**
CR + PR + SD	6 (67)	17 (100)	13 (100)

Chi-square test comparing two groups: C_{min} <Q1 vs C_{min} ≥Q1; *P*=0.009.