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SUPPLEMENT (SPECIAL ISSUE)

The role of imatinib plasma level testing in gastrointestinal stromal tumor

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Abstract The management of patients with gastrointestinal stromal tumor (GIST) has markedly advanced over the past 10 years. Imatinib has exceptional activity in controlling gastrointestinal stromal tumor (GIST) due to inhibition of the constitutively active conformation of KIT and PDGFRA which is found in the majority of patients with GIST. Although some patients may experience prolonged disease control while on imatinib, most patients will develop imatinib resistance within 2–3 years on therapy. A recent retrospective analysis demonstrated a relationship between imatinib plasma levels and progression-free survival in patients with advanced GIST. Plasma imatinib levels in this study were unrelated to the daily administered dose of imatinib. A prospective trial is underway in order to evaluate whether modification of imatinib dose to achieve a target imatinib plasma level will impact patient outcome when compared to standard imatinib dosing in GIST (http://www.clinicaltrials.gov, NCT01031628). This review will explore the current available data on the relationship between imatinib plasma levels, response to treatment, and other prognositic factors as well as discuss the implications of this data for possible future therapeutic approaches.

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Introduction

The understanding and management of gastrointestinal stromal tumor (GIST) has evolved tremendously over the past decade. With the identification of the molecular underpinnings of the disease, the identification of the high incidence of activating gain of function mutations in KIT, the development of both directed KIT inhibitors, imatinib, and broad spectrum tyrosine kinase inhibitors, sunitinib, the median overall survival of advanced GIST has gone from approximately 2 years to over 5 years [1, 2].

The field is continuing to build on this progress with continued investigation into the identification of kinase inhibitor resistance mechanisms and novel therapeutic targets, with the goal to continue to improve outcomes for patients with both localized and advanced GIST. In addition, recent work has suggested that there may be opportunities to maximize the benefit of the current approved treatments in individual patients. The goal of the current review is to discuss factors related to response to imatinib and the current available data regarding the role of imatinib levels in patients with gastrointestinal stromal tumor and how this may impact future treatment strategies.

GIST background and the role of imatinib in advanced GIST

Gastrointestinal stromal tumor is the most common mesenchymal tumor of the gastrointestinal track with an estimated 5,000 cases per year in the United States [3]. In a

landmark report in 1998, Hirota and colleagues [4] reported near universal expression of KIT in GIST as well as the presence of activating *Kit* mutations in GISTs. In Hirota's series of 49 GIST samples, 94% of cases expressed KIT. Mutations in the juxtamembrane domain of *KIT* were most common, resulting in constitutive ligand-independent activation of the KIT receptor tyrosine kinase leading to downstream signaling and uncontrolled cell proliferation. The tumorigenicity of *KIT* was confirmed when stable transfection of the mutant *KIT* cDNA induced malignant transformation of murine lymphoid cells. In the same year, work by Kindblom and colleagues confirmed the findings from Hirota et al., demonstrating 78 of 78 GISTs to be immunoreactive for KIT, with striking ultrastructural and immunophenotypic similarities with interstitial cells of Cajal, ICC [5]. This work supported the hypothesis that GIST may develop from the ICC or stem cells that differentiate toward ICC phenotype. Moreover, this observation confirmed KIT as an accurate diagnostic tool for GIST [5].

The next decade saw a phenomenal growth in the understanding of GIST biology and therapeutics. It began with a single patient who had chemotherapy resistant, metastatic GIST but developed a rapid and sustained response to imatinib, a small molecule tyrosine kinase inhibitor (TKI) with potent activity against the transmembrane receptor KIT [6]. Imatinib occupies the ATP-binding pocket of KIT preventing substrate phosphorylation and down-stream signaling, thereby inhibiting cell proliferation and survival. Early clinical results led to a large, randomized Phase II trial of imatinib in patients with metastatic or unresectable GIST, ultimately confirming the benefit and subsequent approval of imatinib for the treatment of advanced GIST by the US FDA in Feb 2002 [7]. Although imatinib leads to disease control in approximately 85% of patients with advanced GIST, imatinib resistance is a significant clinical issue, with a median progression-free survival of 18–24 months.

Prognostic factors for recurrence after complete resection of localized GIST

There are a number of prognostic factors which have been identified for risk of recurrence following complete resection of localized GIST. An NIH consensus conference incorporated tumor size and mitotic rate in order to develop a four tiered risk stratification system [3]. In this system, tumors which are >10 cm and/or have >5 mitoses/50hpf are noted to have the highest risk of recurrence, whereas tumors which are less than 5 cm or have a mitotic rate <5/50hpf are deemed low risk. Subsequently, Meittenin et al. [8] have developed a system which includes site of primary tumor, in addition to size and mitotic rate [3]. This is important as it has been increasingly apparent that site of primary tumor independently impacts risk of recurrence with tumors in the small bowel having a higher risk of recurrence than tumors which originate in the stomach.

In addition to clinical factors, mutation status of the primary tumor has demonstrated prognostic value. For example, deletions affecting codons 557 and/or 558 of exon 11 of KIT have been identified as an independent risk for recurrence after resection of primary localized GIST [9, 10].

Factors which predict response to imatinib

As discussed above, imatinib is a small molecule tyrosine kinase inhibitor with potent activity against the transmembrane receptor KIT, PDGFRa,b ABL kinase and chimeric BCR-ABL fusion oncoprotein product of chronic myeloid leukemia. Approximately, 85% of GISTs are associated with a *KIT* mutation in either the exons 9, 11, 13 or 17. Exon 11 mutations occur in approximately 65% of all cases, followed by exon 9 mutations (15%), exon 13 (1%) and 17 (1%) of tumors each [11–13]. It is estimated that approximately 5% of GIST harbor *PDGFRA* mutations, while the remaining 7–13% of GISTs are designated "wild-type" for both *KIT* and *PDGFRA* [14].

Clinical trials have demonstrated the importance of primary mutation status as it relates to response to imatinib. Patients with primary exon 11 mutation in the *KIT* gene of their GIST have been shown to have longer PFS and OS when treated with imatinib as compared to patients with primary mutations of exon 9, or KIT wild-type GIST [2, 15]. A large European phase III trial has suggested that patients with primary exon 9 KIT mutations in their GIST may benefit from high-dose imatinib (800 mg/day) as initial therapy, as compared to 400 mg per day [16]. These results were recently confirmed in a large meta-analysis which combined datasets from both the large Phase III North American trial and the large Phase III European-Asian-Australian trial comparing imatinib 400 mg per day to imatinib 800 mg per day in patients with advanced GIST [17]. In this analysis, there was no difference in either progression-free survival or overall survival for the patients with primary exon 11 mutations in their GIST when comparing those who received imatinib 400 mg per day with those who received imatinib 800 mg per day. There was, however, a small, but significant advantage in progression-free survival for patients with primary exon 9 mutations in their GIST when treated with high-dose imatinib. There was no difference in overall survival for the population, which was likely a result of the crossover design of the trial which allowed patients who were

randomized to imatinib 400 mg to crossover to 800 mg per day at the time of disease progression. Approximately, 30% of patients will regain disease control at the time of dose escalation [18]. In addition, mechanisms of resistance to imatinib resistance vary based on the primary mutation type once again emphasizing the heterogeneity in GIST as a disease [19]. Specifically, tumors with primary exon 11 mutations are frequently found to have secondary kinase mutations at the time of imatinib resistance. Secondary kinase mutations appear to be less common in tumors with primary exon 9 mutations. These data suggest that there may be a difference in the degree of imatinib exposure needed to control tumors with different kinase mutations.

Impact of imatinib level on response: CML

Imatinib mesylate was initially developed for the treatment of chronic myelogenous leukemia, CML, due to its ability to inhibit the BCR-ABL fusion protein [20]. Recently, two studies evaluating the relationship between imatinib trough levels (Cmin) and cytogenetic and molecular responses in CML have been reported [21, 22]. Picard et al. [21] reported 68 pts who had been treated with imatinib, 400 or 600 mg/day for at least 12 months. Imatinib trough levels were measured and retrospectively correlated with response. Interpatient trough imatinib plasma levels were noted to be highly variable ranging from 181 to 2,947 ng/ml, consistent with previous reports. Patients receiving imatinib 400 mg per day demonstrated with a mean imatinib levels of 1,058 ± 557 ng/ml and those receiving 600 mg per day demonstrated 1,444 ± 710 ng/ml [21]. When comparing patients who responded with those that did not, trough imatinib plasma levels were noted to be significantly higher in the group of patients with molecular and cytogenetic responses [21]. This was independent of daily dose received, 400 mg or 600 mg daily. In addition, Picard et al. [21] suggested that the threshold for trough imatinib levels should be set above 1,002 ng/ml in vivo in order to maximize response in CML. Larson et al. [22] confirmed these findings in a larger retrospective study of 351 patients with CML. In this study, trough imatinib plasma levels available on d29 of treatment were correlated with patient outcomes after 5 years of imatinib therapy. In this larger analysis, high exposure to imatinib as measured by trough level resulted in better cytogenetic and molecular responses and improved event-free survival [22]. Once again, significant interpatient variation in imatinib trough level was seen. Because of this, patients were grouped in quartiles to assess general impact of trough imatinib levels on clinical endpoints. The authors found that patients in the lowest quartile were more likely to discontinue therapy due to "lack of effectiveness" than those in the higher quartiles [22]. In addition, the imatinib trough levels among patients who achieved a complete cytogenetic response (CCyR) were significantly higher than those for patients who did not achieve a CCyR, with reported mean values of 1,009 ± 544 ng/ml and 812 ± 409 ng/ml, respectively [22].

Impact of imatinib level on response: GIST

Although early studies suggested lack of a correlation between imatinib levels (bound or unbound) to response in GIST, more recently, as in CML, studies in larger populations of GIST patients have indeed demonstrated a relationship between imatinib exposure and outcome [23–25].

Demetri et al. [24] reported a retrospective analysis of 73 patients with advanced GIST who had been randomized to either imatinib 400 or 600 mg/day on the pivotal Phase II trial in GIST, B2222. Trough levels of total plasma imatinib and its major metabolite CGP745888 were drawn on day 1 and day 29. Median follow-up for clinical endpoints is over 5 years. As in the CML population, significant interpatient variability existed for drug levels at both the 400 and the 600 mg dose level. In addition, there was no clear correlation between daily dose (400 vs. 600 mg) and trough imatinib levels [24]. Due to this large variability, patients were grouped in quartiles and outcomes were correlated to trough imatinib level. Interesting, the lowest quartile imatinib trough level was very similar to the CML population, <1,100 ng/ml. Patients in the lowest imatinib quartile (<1,100 ng/ml) had a significantly shorter time to progression (11.3 months) when compared to patients in the upper three quartiles (30.6 months, $P = 0.0029$) [24]. Patients with exon 11 mutation in the upper three quartiles (trough imatinib > 1,100 ng/ml) had a significantly higher clinical benefit rate than patients with exon 11 mutation in the lowest quartile. There were not sufficient data available for patients with exon 9 or wild type to make any conclusions regarding whether drug levels had an impact on clinical outcome [24].

A recent paper by Widmer et al. [25] again demonstrated a relationship between higher imatinib exposure (AUC free imatinib) and likelihood of response to imatinib [11]. Notably, in this exploratory analysis, the dose–response relationship seemed to vary based on mutational status of the GIST, with the exon 9 patients possibly requiring higher imatinib exposure than patients whose tumor harbored an exon 11 mutation. Although these data are based on small numbers of patients, this does seem to support the data from the metaGIST analysis, suggesting that patients with exon 9 mutation may benefit from a higher dose of imatinib, although this finding requires confirmation in larger and prospective datasets [17].

Influence of pharmacogenomic and biologic factors on imatinib levels

As has been noted in both the GIST and CML populations, there is significant interpatient variability in imatinib trough levels for a given imatinib dose [21, 22, 24]. Judson et al. [26] have also demonstrated significant variability in oral imatinib clearance, and perhaps an association between pharmacokinetic parameters and hematologic toxicity, although the explanation for this variability is not well understood.

Imatinib pharmacokinetics have been studied extensively [27]. Imatinib has >90% bioavailability following oral administration. Imatinib is extensively metabolized by the cytochrome *P*450 system, and it is felt that CYP3A is primarily responsible for the metabolism of imatinib to its major metabolite CGP74588. Imatinib is a substrate of ABCB1 and ABCG2 and has been shown to be extensively bound to alpha1-acid glycoprotein (AGP) [27, 28].

Previous studies have evaluated the impact of pharmacogenomic factors on imatinib pharmacokinetics to evaluate whether these factors may account for some of the reported variability in imatinib pK. In a subset of GIST patients, Gardner et al. [29] evaluated the correlation between imatinib pharmacokinetics and 9 allelic variants in 7 genes thought to be related to imatinib pharmacokinetics: adenosine triphosphate–binding cassette transporters (ABCB1 and ABCG2) and enzymes (cytochrome P450 [CYP] 2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5). Interestingly, the authors found that common genetic variants of these genes did not have a significant impact on the pharmacokinetics of imatinib [29].

Petain et al. developed a unique covariate model to evaluate the effect of both biologic and pharmacogenomic factors concurrently with regard to imatinib pharmacokinetics in adults and children. This model included effect of age, body weight, sex, albumin, alpha1-acid glycoprotein (67 pts) and 8 polymorphisms *ABCB1, ABCG2, CYP3A4, CYP3a5 and APG* (46 pts). Interestingly, when considering the factors included in the model, biologic factors appeared to have a stronger influence on imatinib pharmacokinetics than pharmacogenomic factors. Specifically, albumin, body weight and APG (not *APG*) were associated with imatinib plasma level. Age alone was not found to be a significant covariate in this model when the other factors were included. The authors notably point out that in the current era of molecularly targeted therapy where a certain degree of exposure may be needed to inhibit a relevant target, drug levels may indeed be of more relevance than fixed dosing, particularly when considering agents where the recommended dose was identified without a classic determination of maximally tolerated dose (MTD) [28, 30].

The most detailed analysis of impact of clinical and biologic factors on imatinib levels was recently published by Yoo et al. [31]. In this analysis, the authors correlated imatinib trough level to clinical characteristics in 107 pts being treated with imatinib for GIST in Korea. Doses ranged from 300 mg per day to 800 mg per day, although the majority of pts received 400 mg per day ($n = 92$). Seventy-four percent of patients were receiving imatinib for metastatic GIST, while 26% were receiving imatinib adjuvantly. As has been reported previously, there was significant interpatient variability of imatinib trough levels. Also, there was no significant difference in mean trough between patients treated with 400 mg per day compared to patients treated with 600 mg per day. Patients treated at 800 mg per day did have a significantly higher Cmin when compared to those treated at 400 mg per day ($P < 0.001$). This finding is relevant as this is the first published study in GIST to report levels in patients treated with imatinib 800 mg per day. Multivariate analysis was performed on factors found during univariate analysis to be associated

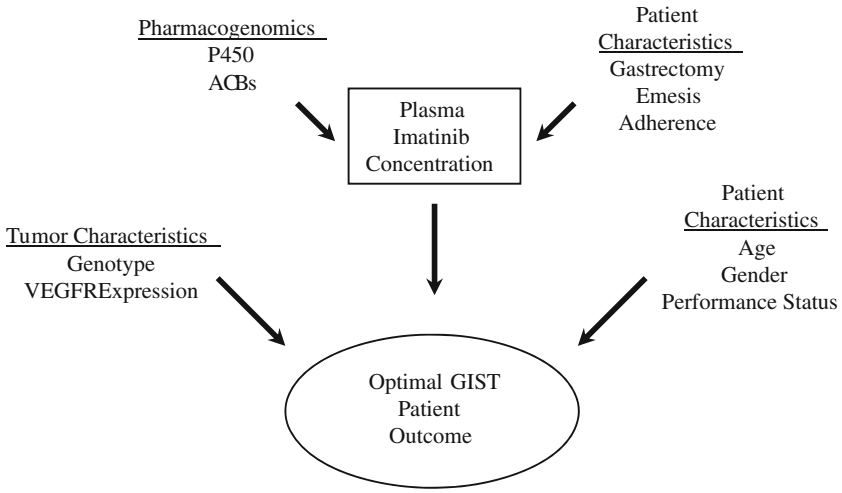

Fig. 1 The optimally targeted therapy of patients with GIST is a complex interplay of patient characteristics and tumor characteristics

with imatinib trough. These included, age, sex, BSA, hemoglobin concentration, albumin concentration, creatinine clearance, and previous major gastrectomy. The authors found that albumin concentrations ($P = 0.001$), creatinine clearance ($P = 0.002$), and previous major gastrectomy ($P = 0.003$) were significant, independent covariates associated with imatinib trough. Unfortunately, outcome data were not reported.

Other studies evaluating clinical prognostic factors have suggested that low baseline hemoglobin and high baseline neutrophil count were associated with earlier resistance to imatinib in a multivariate model. Of note, in this model, albumin was not identified as an independent prognostic factor [32]. In this large study of 818 pts treated in the Euro-Aus Phase III trial, imatinib blood levels were not included; thereby, this data are not able to determine whether there is a relationship between these factors and imatinib plasma levels.

Summary

In summary, the understanding of GIST on a molecular level has allowed for the development of rationally targeted and highly effective therapies for advanced disease. Recent data have suggested that there is a relationship between imatinib exposure, as measured by trough level, and response in patients with advanced GIST. Interestingly, there are a number of factors that affect imatinib plasma levels as well as the targeted imatinib plasma trough level for a given patient. Both clinical factors (extent of gastrointestinal surgery, renal function and albumin levels) and key metabolic enzymes affect imatinib plasma levels in this patient population. Additionally, the proposed target imatinib plasma level may vary based on the specific *KIT* gene mutation being targeted, especially in the case of *KIT* exon 9 mutation. Thus, there may be a complex interplay between *KIT* genotype, patient clinical characteristics and imatinib plasma levels that significantly influence patient outcomes (Fig. 1). A prospective study is underway in patients with advanced GIST in order to determine whether dose adjustment utilizing a target imatinib level of >1,100 ng/ml will improve outcome in patients with advanced GIST (Fig. 2; http://www.clinicaltrials.gov, NCT01031628). This understanding is critically important in order to optimize first-line therapy with imatinib in this patient population.

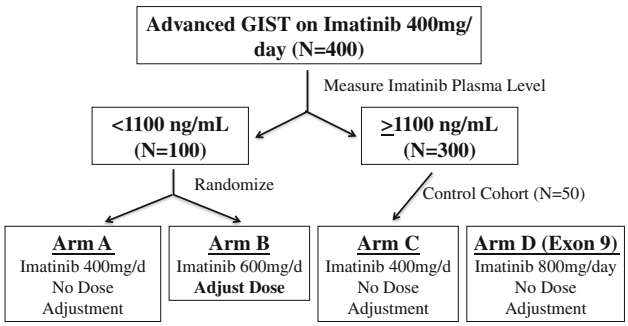

Fig. 2 Schema for ongoing randomized Phase III trial evaluating dose adjustment of imatinib in patients with metastatic GIST, NCT01031628. Patients with tumors which harbor an exon 9 mutation will be assigned to Arm D and may be dose escalated to imatinib 400 mg BID independent of imatinib blood level

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