Therapeutic drug monitoring of imatinib – new data strengthen the case

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Running title: Pharmacokinetics of imatinib in GIST

Prof Judson has received honoraria from Novartis and Pfizer for speaking engagements and attendance at advisory boards and departmental funding for clinical trials with agents for the treatment of gastrointestinal stromal tumor from Novartis, Pfizer and Bayer.
Summary

A population pharmacokinetic study of imatinib in patients with gastrointestinal stromal tumor by Eechoute et al has demonstrated a significant increase in drug clearance over the first 3 months of treatment, resulting in a 30% decrease in drug exposure. This clearly demonstrates the possibility of pharmacokinetic resistance in this disease.

Main text

In this issue of Clinical Cancer Research Eechoute et al report a population pharmacokinetic study of imatinib in patients with gastrointestinal stromal tumor. Their findings have important implications for the optimum dosing of the drug and the possibility that for some patients, imatinib resistance may have a pharmacokinetic explanation.

The tyrosine kinase inhibitor imatinib represents one of the best examples of the molecularly targeted therapy of cancer, via inhibition of ABL in chronic myeloid leukemia (CML), and, principally, KIT in gastrointestinal stromal tumor (GIST). The dramatic success of imatinib depended not simply on its ability to inhibit the relevant target(s) but also on its favourable therapeutic ratio and excellent pharmaceutical properties. The drug has good oral bioavailability, i.e. 98%, and an elimination half-life of approximately 18 hours, ideal for daily dosing. Subsequent studies showed little impact of food, age, race, gender or bodyweight on the clearance of the drug, permitting it to be administered at a standard dose of 400 mg daily. In addition, impaired renal or hepatic function does not cause a significant alteration in clearance and it is rarely necessary to adjust imatinib dosage except in the case of severe renal impairment. The rapidity with which imatinib became licensed for CML and GIST reflects not only the favourable properties of imatinib as a drug but also the fact that in both diseases the key molecular driver, a translocation involving BCR and ABL in the case of CML and an activating mutation in KIT in the case of GIST, is crucial to the growth and survival of the cancer cells in the vast majority of patients and remains so virtually throughout the evolution of the disease.

However, there is evidence that imatinib dosage is important, in that a higher dose of imatinib is more effective against GIST driven by the relatively rare exon 9 mutation in KIT and patients with low imatinib trough levels are reported to have a reduced likelihood of remission and shorter progression-free survival. This has led to calls for therapeutic drug monitoring, in addition to the importance of knowing the genotype.

It was reported early in the development of imatinib for the treatment of GIST that a number of side effects, such as skin rash, nausea, oedema, fatigue etc, become less severe over time and it was reported in a retrospective population pharmacokinetic study (PK) that drug clearance increased after 12 months of exposure, which might account for the amelioration of toxicity with time. Subsequent PK studies failed to confirm this, either because repeat PK were performed too early, e.g. at 4 weeks in the case of the Demetri study, or because the study was performed in patients who had been on treatment for varying periods of time, i.e. a cross-sectional, rather than a prospective evaluation. For example, in the case of the cross-sectional study reported by Yoo et al, most of the patients had already been on treatment for 5 months or more at the time of PK analysis, hence any increase in clearance with...
time might already have occurred. However, this study did report some important findings including reduced imatinib trough levels in patients who had had a major gastric resection and an association between imatinib clearance and albumin levels, as previously suggested. 

The study by Eechoute et al. was performed prospectively, in a planned, meticulous fashion. This is the first such prospective population PK study of imatinib over time to be reported. Fifty patients with GIST being treated with imatinib for first time had blood samples taken for full PK analysis at fixed time points, i.e. on the first day of treatment, then at 1, 6 and 12 months. In addition, blood for trough levels was taken on day 14 and monthly throughout treatment. The volume of liver metastatic disease was measured. The key finding was an increase in imatinib clearance with time, mainly over the first 90 days, leading to a 30% decrease in imatinib exposure. After 3 months the clearance appeared to plateau. This is extremely important, since it not only vindicates the early report of increased clearance with time, providing a clear explanation for the improvement in drug tolerance, but underlines the fact that for some patients this reduction in drug exposure could be enough to render the drug ineffective, perhaps especially those patients who have had a major gastric resection. The volume of metastatic liver disease had a small impact, but nowhere near sufficient to account for the change in imatinib clearance observed.

What are the possible explanations for increased imatinib clearance with time and the implications of this finding for the future use of the drug? Eechoute et al. did not find evidence for a change in metabolic elimination. Imatinib is metabolised in the liver by CYP3A4 to its principal metabolite CGP74588. However, the ratio of parent compound to metabolite did not change with time, suggesting that liver metabolism was unaltered. In addition, CGP74588 has an even longer elimination half-life than imatinib and is also equipotent as a tyrosine kinase inhibitor, hence increased liver metabolism would not be expected to result in decreased imatinib efficacy. They also studied the burden of metastatic liver disease and concluded that this could not explain the magnitude of change in clearance observed. They suggested that the difference could lie in absorption, but alterations in drug transporters over time have not been demonstrated and it could be that disease-related factors play a major role. For the moment the mechanism remains unresolved.

As to how the data should be utilised; it is clear that if therapeutic drug monitoring is to be considered, trough levels need to be measured at or after 3 months, i.e. after this increase in drug clearance has occurred. Furthermore, prospective analyses of imatinib efficacy in relation to PK will be required, utilising later time points, since the threshold for benefit may need to be adjusted in comparison with the data from the B2222 study reported by Demetri et al. A possible scheme for integrating genotype and pharmacokinetic data in determining the appropriate imatinib dosage is proposed in Fig 1. Currently the key unknown factor is precisely what imatinib trough level would predict for poor outcome following 3 months of treatment and the majority of the increase in imatinib clearance has occurred. It is also unknown whether an increase in imatinib dosage to 800 mg would be required, as in the treatment of the relatively resistance exon 9 mutant KIT tumors, or if less dose increases, e.g. to 600 mg, might be sufficient to bring plasma levels into the optimum therapeutic range. What is undoubtedly the case is that increases in imatinib dosage may be justified for some patients with a poor response to imatinib or the early development of drug resistance and in some cases resistance may have a pharmacokinetic explanation.
References


Legend to Figure 1

Proposed draft scheme as to how therapeutic drug monitoring might work in practice. Note that there are many uncertainties, such as the correct treatment for certain unfavourable genotypes, the optimum time for response assessment, etc., the 3 month trough level associated with poorer outcome, which require further research.
Diagnosis of advanced GIST

Unfavorable genotype
- Exon 9 KIT mutation
  - Imatinib 800 mg daily
- Wild type or resistant genotype
  - Consider sunitinib or experimental agent

Mutation analysis shows imatinib sensitive genotype, e.g., exon 11 KIT
- Imatinib 400 mg daily, take blood for trough level at start of treatment, i.e., day 14
- Response assessment at 3 months or sooner using Choi criteria
  + Repeat PK study at 3 months

Poor response or progression
- Adequate blood level – change to sunitinib
- Low trough level – increase sunitinib dosage

Good response
- Adequate blood level – continue at 400 mg
- Low trough level – increase imatinib dosage

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