

## Therapeutic Drug Monitoring of Imatinib—New Data Strengthen the Case

Ian Judson

A population pharmacokinetic study of imatinib in patients with gastrointestinal stromal tumor by Eechoute and colleagues has shown a significant increase in drug clearance over the first 3 months of treatment, resulting in a 30% decrease in drug exposure. This finding clearly shows the possibility of pharmacokinetic resistance in this disease. *Clin Cancer Res*; 18(20); 5517–9. ©2012 AACR.

In this issue of *Clinical Cancer Research*, Eechoute and colleagues (1) report on a population pharmacokinetic study of imatinib in patients with gastrointestinal stromal tumor (GIST). 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 for cancer, via inhibition of ABL in chronic myeloid leukemia (CML), and, principally, KIT in GIST. The dramatic success of imatinib depended not simply on its ability to inhibit the relevant target(s) but also on its favorable therapeutic ratio and excellent pharmaceutical properties. The drug has good oral bioavailability—98%—and an elimination half-life of approximately 18 hours, making it ideal for daily dosing (2). Subsequent studies showed little impact of food, age, race, gender, or body weight on the clearance of the drug, permitting it to be administered at a standard dose of 400 mg daily (3). 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 (4). The rapidity with which imatinib became licensed for CML and GIST reflects not only the favorable 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 (5).

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* (6), and patients with low imatinib trough levels are reported to have a reduced likelihood of remission and shorter progression-free survival (7). This has led to calls for therapeutic drug monitoring, in addition to the importance of knowing the genotype (8).

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, edema, and fatigue, become less severe over time (9), and it was reported in a retrospective population pharmacokinetic study that drug clearance increased after 12 months of exposure (10), which might account for the amelioration of toxicity with time. Subsequent pharmacokinetic studies failed to confirm this, either because repeat pharmacokinetic studies were conducted too early, for example, at 4 weeks in the case of the study by Demetri and colleagues (7), or because the study was conducted in patients who had been on treatment for varying periods of time, that is, a cross-sectional, rather than a prospective evaluation. For example, in the case of the cross-sectional study reported by Yoo and colleagues (11), most of the patients had already been on treatment for 5 months or more at the time of pharmacokinetic 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 (9).

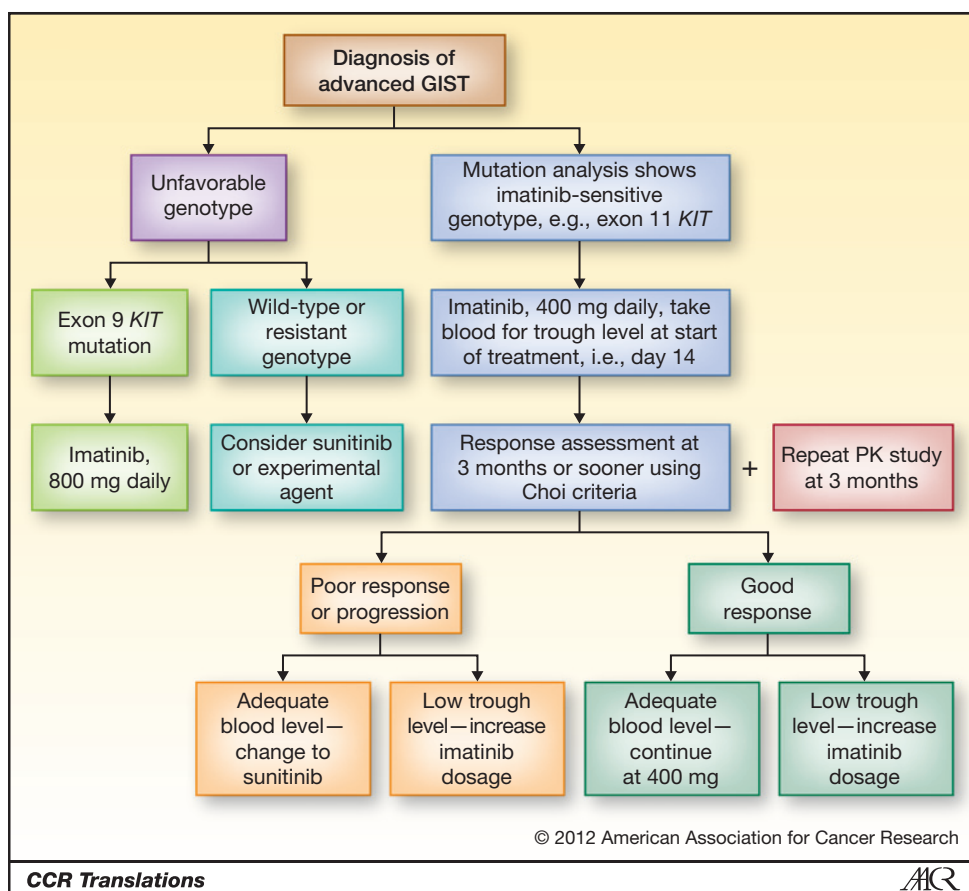
The study by Eechoute and colleagues was conducted prospectively, in a planned, meticulous fashion. This is the first such prospective population pharmacokinetic study of imatinib over time to be reported. Fifty patients with GIST being treated with imatinib for the first time had blood samples taken for full pharmacokinetic analysis at fixed time points: 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 seemed to plateau. This is

**Author's Affiliation:** Sarcoma Unit, Royal Marsden Hospital, Fulham Road, London, United Kingdom

**Corresponding Author:** Ian Judson, Royal Marsden Hospital, Institute of Cancer Research, Sycamore House, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom. Phone: 44-20-8722-4303; Fax: 44-20-8642-7979; E-mail: Ian.Judson@icr.ac.uk

**doi:** 10.1158/1078-0432.CCR-12-2570

©2012 American Association for Cancer Research.



**Figure 1.** Proposed draft scheme about how therapeutic drug monitoring might work in practice. Note that there are many uncertainties, such as the correct treatment of certain unfavorable genotypes, the optimum time for response assessment, and the 3-month trough level associated with poorer outcome, which require further research. PK, pharmacokinetic.

extremely important, as it not only vindicates the early report of increased clearance with time, providing a clear explanation for the improvement in drug tolerance, but also 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? Echoute and colleagues did not find evidence for a change in metabolic elimination. Imatinib is metabolized 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 (12); hence, increased liver metabolism would not be expected to result in decreased imatinib efficacy. Echoute and colleagues also studied the burden of metastatic liver disease and concluded that this could not explain the magnitude of change in clearance observed. They suggest that the difference could lie in absorption, but alterations in drug transporters over

time have not been shown and it could be that disease-related factors play a major role. For the moment the mechanism remains unresolved.

About how the data should be used, it is clear that if therapeutic drug monitoring is to be considered, trough levels need to be measured at or after 3 months—after this increase in drug clearance has occurred. Furthermore, prospective analyses of imatinib efficacy in relation to pharmacokinetics will be required, using later time points, as the threshold for benefit may need to be adjusted in comparison with the data from the B2222 study reported by Demetri and colleagues (7). 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 resistant exon 9 mutant *KIT* tumors, or if the dosage decreases, for example, to 600 mg, it 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.

#### Disclosure of Potential Conflicts of Interest

I. Judson has received honoraria from Novartis, Pfizer, and PharmaMar for speaking engagements and attendance at advisory board meetings and

received departmental funding for clinical trials with agents for the treatment of gastrointestinal stromal tumor from Novartis, Pfizer, Merck, Morphotek, and Bayer.

Received August 7, 2012; accepted August 8, 2012; published OnlineFirst August 17, 2012.

#### References

1. Eechoute K, Fransson MN, Reyners AK, de Jong FA, Sparreboom A, van der Graaf WT, et al. A long-term prospective population pharmacokinetic study on imatinib plasma concentrations in GIST patients. *Clin Cancer Res* 2012;18:5780–7.
2. Peng B, Dutreix C, Mehring G, Hayes MJ, Ben-Am M, Seiberling M, et al. Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol* 2004;44:158–62.
3. Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005;44:879–94.
4. Judson IR. Imatinib for patients with liver or kidney dysfunction: no need to modify the dose. *J Clin Oncol* 2008;26:521–2.
5. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004;22:3813–25.
6. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. *J Clin Oncol* 2010;28:1247–53.
7. Demetri GD, Wang Y, Wehrle E, Racine A, Nikolova Z, Blanke CD, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol* 2009;27:3141–7.
8. von Mehren M, Widmer N. Correlations between imatinib pharmacokinetics, pharmacodynamics, adherence, and clinical response in advanced metastatic gastrointestinal stromal tumor (GIST): an emerging role for drug blood level testing? *Cancer Treat Rev* 2011;37:291–9.
9. van Oosterom AT, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001;358:1421–3.
10. Judson I, Ma P, Peng B, Verweij J, Racine A, di Paola ED, et al. Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. EORTC Soft Tissue and Bone Sarcoma Group. *Cancer Chemother Pharmacol* 2005;55:379–86.
11. Yoo C, Ryu MH, Kang BW, Yoon SK, Ryoo BY, Chang HM, et al. Cross-sectional study of imatinib plasma trough levels in patients with advanced gastrointestinal stromal tumors: impact of gastrointestinal resection on exposure to imatinib. *J Clin Oncol* 2010;28:1554–9.
12. Nikolova Z, Peng B, Hubert M, Seiberling M, Keller U, Ho YY, et al. Bioequivalence, safety, and tolerability of imatinib tablets compared with capsules. *Cancer Chemother Pharmacol* 2004;53:433–8.