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 favorability properties of the drug but also on its favorable therapeutic ratio and excellent pharmaceutical properties.

The key finding was an increase in imatinib clearance with time, mainly over the first 90 days, leading to a 30% decrease in drug exposure. This finding clearly shows the possibility of pharmacokinetic resistance in this disease. 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...
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? Eechoute 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. Eechoute 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.

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**References**

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