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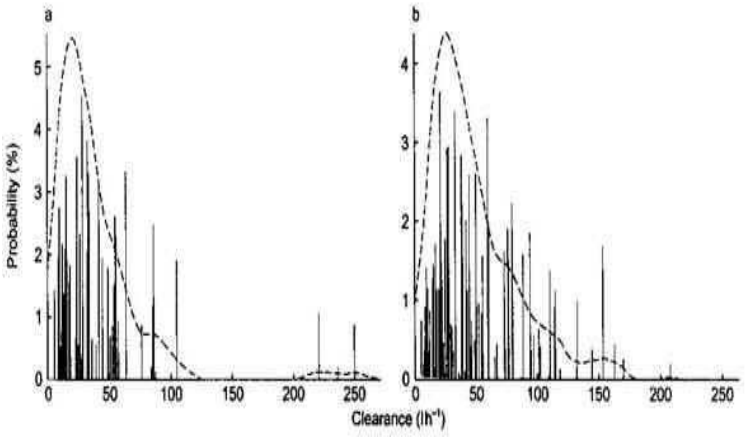
IMATINIB INFORMATION SHEET

PREAMBLE

Despite the excellent efficacy of imatinib, cases of treatment failure or suboptimal response have been reported for patients with CML. Cellular mechanisms of resistance to imatinib and drug efflux mediated by P-glycoprotein have been identified as possible mechanisms. Another hypothesis to explain variable responses to imatinib therapy lies in the substantial pharmacokinetic variability of imatinib (Figure). In the top panel low exposure to the drug in plasma can cause low intracellular exposure and therapeutic failure. The bottom panel illustrates that applied pharmacokinetic studies can identify adequate systemic exposure to the drug in patients exhibiting therapeutic failure suggesting another mechanism, for example drug efflux effect at the cell surface, that might explain the resistance to therapy. In the former case drug dose could be optimised to improve therapeutic response, however, in the latter case optimising imatinib therapy may have no effect and an expensive, ineffective therapy could be switched based on this evidence. Furthermore, there is some evidence to suggest that pharmacokinetic parameters vary with therapy duration. One study has shown that imatinib clearance tends to increase over a period of 12 months treatment with the drug, suggesting that patients with adequate systemic exposure early in a treatment regimen may fail therapy over time if drug exposure is not monitored and corrected.



Clin Pharmacokinet 2005; 44(4): 349-366.

CONCENTRATION- EFFECT RELATIONSHIP

A recent study demonstrated that trough (sample taken just before the next dose) imatinib plasma concentrations were associated with cytogenetic and molecular response in CML. A patient with a trough imatinib plasma concentration >1000 ng/mL is 8 times more likely to experience a therapeutic effect compared with patients who have concentrations below this effect target. Furthermore, GIST patients with a trough imatinib plasma concentration <1100 ng/mL had lower rates of clinical benefit and faster time to progression of disease.

References: Blood 109(8): 3496-99; 2007, *Blood* 111(8):4022-8; 2008

THERAPEUTIC RANGE

Suggested target for effect is >1000 ng/mL for CML Suggested target for effect is >1100 ng/mL for GIST Toxicity: monitor patient carefully if trough imatinib plasma concentration exceeds 2000 ng/mL.

A target for toxicity has not been defined; however, fluid retention, rash, myalgia and anaemia appear to be more common at higher imatinib concentrations. *Blood* 111(8):4022-8; 2008; *Clin Cancer Res* 12(20):60-73-78; 2006.

SAMPLE COLLECTION, TRANSPORT AND COST

- Wait at least 4 days after commencing/changing therapy to reach steady state before collecting blood for analysis.
- Blood samples for TDM can be collected earlier if efficacy or toxicity are concerns.
- Collect a 5 mL EDTA (purple top) tube 24 hours (or 12 hours if twice daily dosing) after the dose (i.e. trough collection, just before the next dose). Do not use tubes with gel separator as gel can bind drugs giving a falsely low result.
- Separate plasma and send in an Eskie with an ice brick. If sample transport delayed for 12 h, freeze sample as soon as possible after collection and send frozen.
- Medicare recharge where applicable (Medicare rebate is $35; Medicare request form must accompany sample).