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Imatinib Mesylate

A Viewpoint by Allan van Oosterom

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Imatinib mesylate (imatinib) is a novel orally available inhibitor of specific protein tyrosine kinases. Protein kinases are enzymes transferring phosphate from adenosine triphosphate (ATP) to specific amino acids on substrate proteins. Phosphorylation of these proteins leads to activation of signal transduction pathways with a critical role in a number of biological processes such as cell growth, differentiation and apoptosis. Several protein kinases are deregulated and overexpressed in human cancers and are thus attractive targets for selective pharmacologic inhibitors. Imatinib functions through competitive inhibition of ATP binding to the tyrosine kinase enzyme, which leads to the inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction in chronic myeloid leukaemia (CML), activated KIT tyrosine kinase in gastrointestinal stromal tumours (GIST), and the receptor for platelet derived growth factor (PDGF) in dermatofibrosarcoma protuberans (DFSP).

In patients with CML imatinib is rapidly absorbed after oral administration and a mean maximal concentration of 2.3 mg/L (4.6 μM) was reached at steady state following once-daily administration of 400mg. The half-life of imatinib in the circulation ranged from 13–16 hours; the level increased by a factor of 2–3 at steady state with once-daily dosing. The mean plasma trough concentration was around 1.5 μM at 24 hours after the administration of 400mg at steady state. This amount exceeded the concentration required for the inhibition of cellular phosphorylation by BCR-ABL, KIT and PDGF-α, but not of many other tyrosine kinases.

Imatinib is well tolerated with modest adverse effects, and only occasional grade 3 and 4 nausea, vomiting, myalgia and diarrhea. The maximum tolerated dose is 800mg daily. Previously the only treatment option for locally advanced and metastatic GIST was surgery, since cytotoxic drugs were effective in less than 10% of patients. Response rates for imatinib in all reported studies are above 50%, and over 75% of our own patients are still on treatment after one year since an additional 25% show clinical benefit not meeting the criteria of response. From the longest ongoing studies we know that after 2 years about 60% of patients are still on drug.

In conclusion, imatinib is a new very effective drug for patients with specific cancers (CML, GIST, DFSP) when their disease has the relevant target present. It is well tolerated; however, long term effects are still awaited since as yet no patient has been on the drug for longer than 2.5 years. ▲