Structural studies of Imatinib in complex with its targets in CML and GIST: the molecular basis for selectivity and resistance.

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Glivec™ (Imatinib, STI571) is a drug targeted against Bcr-Abl kinase for the treatment of chronic myelogenous leukemia (CML) and against cKit kinase for the treatment of gastrointestinal stromal tumors (GIST). The impressive response rate of patients treated with STI571 in the early phase of CML showed the feasibility of using ATP-competitive inhibitors in the chronic treatment of molecularly defined cancers. However, CML patients treated in the later phases (accelerated and blast crisis), tend to develop resistance and relapse. Resistance is now also being found in GIST patients.

The unique binding mode of STI571 to the kinase domain of the target is key to the excellent selectivity and thus tolerability of the drug, but it also the source of the susceptibility to resistance. STI571 binding is dependent on the conformational state of the protein and on contacts with residues that are not important for the function of the protein. Mutations that affect the conformational state or the binding site will therefore result in STI571 resistance. Although there are probably several different mechanisms leading to patient relapse, mutations are found in more than 50 % of cases.

Structural biology has been used to gain a better understanding of the role of these mutations in resistance. This provides a basis for the design of more potent inhibitors that might overcome or avoid the devlopment of resistance and the design of inhibitors that are active against mutants. However, it is unlikely that one single inhibitor will be effective and it will be necessary to use multiple compounds to target different conformations or different mutants of Abl kinase, or other downstream targets.