

A new mutation affecting the ATP pocket of kit receptor in patients with GIST showing acquired resistance to Imatinib: a coupled experimental and modeling investigation

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A new era of targeted cancer therapy was inaugurated with the approval of Imatinib mesylate (or STI 571/Gleevec) for the treatment of chronic myeloid leukemia (CML). STI-571 is a phenyl-aminopyrimidine compound, initially identified from a high-throughput screen for inhibitors of protein kinase C and subsequently found to be a potent and selective inhibitor of the Abl, platelet-derived growth factor beta-receptor, and kit tyrosine kinases. Imatinib binds in a pocket close to the ATP-binding site of the Abl catalytic domain, and effectively inhibits Abl kinase activity in vitro and in vivo at concentrations of 0.1-1.0 microM.

One year after its approval by FDA and EMEA for CML treatment, in 2001 Imatinib was also approved for advanced gastrointestinal stromal tumors (GISTs) chemotherapy.

GISTs are the most common mesenchymal tumors of the gastrointestinal tract; they represent a spectrum of tumors, ranging from benign to highly malignant. The application of Imatinib to GIST was a direct result of (1) its selective inhibition of the kit receptor tyrosine kinase, which is constitutively active in most GISTs, (2) its efficacy and minimal toxicity in patients with CML, (3) the parallels between the pathogenesis of GIST and CML, and (4) the lack of effective alternative treatments for metastatic GISTs.

In CML, Imatinib is highly effective both in early and late stages of the disease.

Nonetheless, several relapses do occur after initial response, despite continued treatment. In patients who developed resistance to Imatinib, reactivation of the Bcr-Abl signaling was observed, due to either a secondary mutation, resulting in a missense substitution of a residue belonging to the drug binding site and critical for binding, or to a progressive Bcr-Abl gene amplification. In GISTs, primary resistance seems to involve at least 15% of patients with advanced disease, and its occurrence could be correlated with different c-kit mutations.

At the National Institute for the Study and Cure of Cancer of Milan, among a series of 105 patients enrolled in a Phase III, prospective controlled trial on Imatinib in advanced GISTs, a point mutation in exon 14, observed only in Imatinib nonresponding metastases, was identified for the first time. This mutation, T2030C, results in the corresponding protein mutation T670I, belonging to the ATP pocket of the kit receptor.

In this work, we present the results obtained from the application of combined detailed molecular modeling and experimental investigation techniques to the study of the interactions between T670I and Imatinib.