Strategies to overcome resistance to targeted protein kinase inhibitors.

Selective inhibition of protein tyrosine kinases is gaining importance as an effective therapeutic approach for the treatment of a wide range of human cancers. However, as extensively documented for the BCR-ABL oncogene in imatinib-treated leukaemia patients, clinical resistance caused by mutations in the targeted oncogene has been observed. Here, we look at how structural and mechanistic insights from imatinib-insensitive Bcr-Abl have been exploited to identify second-generation drugs that override acquired target resistance. These insights have created a rationale for the development of either multi-targeted protein kinase inhibitors or cocktails of selective antagonists as antitumour drugs that combine increased therapeutic potency with a reduced risk of the emergence of molecular resistance.

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