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Nilotinib

A Viewpoint by Philipp le Coutre

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Treatment of chronic myeloid leukaemia (CML) with the 2-phenylaminopyrimidine derivative imatinib introduced the concept of targeted therapy into cancer treatment. Imatinib almost selectively inhibits the constitutive tyrosine kinase activity of BCR-ABL, an oncoprotein that is known to be the causative molecular player in CML, and resulted in a marked improvement in haematologic response, such that almost all (98%) newly diagnosed patients achieved a complete haematologic remission. Moreover, in many of these patients, imatinib is associated with a 1000-fold decrease in BCR-ABL transcript levels.

Nevertheless, in patients in the advanced stages of CML, accelerated phase and blast crisis, clinical results with imatinib have been less favourable, with significant relapse rates in the first year of treatment. Additionally, almost simultaneously with the observation of the remarkable clinical results in chronic-phase CML patients, both preclinical and clinical evidence of various mechanisms of resistance to imatinib, primarily in the advanced stages of the disease, were reported. Those mechanisms of resistance can be point mutations or amplifications of the target kinase BCR-ABL. Both of these mechanisms reactivate BCR-ABL through phosphorylation, ultimately leading to the leukaemic phenotype.

In addition to imatinib resistance, adverse effects may also hamper optimal treatment and therapeutic success. Although adverse effects associated with imatinib are often mild and less frequently observed than with conventional antileukaemic agents, they are increasingly becoming the focus of clinical considerations in the optimal management of CML patients. In particular, muscular cramps, fluid retention and skin rashes are the most common adverse effects associated with imatinib therapy.

Strategies to overcome primary and secondary resistance to imatinib in CML include dose escalation, combination therapy with classical antitumour agents or allogeneic stem cell transplantation. However, the specific nature of the mechanisms of resistance to imatinib also suggests a need to improve upon the concept of targeted therapy. Nilotinib (formerly AMN107) is a 2-phenylaminopyrimidine derivative structurally related to imatinib but different with regards to binding affinity and specificity to the target structure. While six hydrogen bonds are required to stabilize the binding of imatinib in the BCR-ABL tyrosine kinase domain, a proper fit of nilotinib depends on only four hydrogen bonds.

Both substances have target specificity restricted to the BCR-ABL, proto-oncogene protein c-KIT and platelet-derived growth factor receptor (PDGF-R) kinases. The chemical alterations in the design of nilotinib resulted in approximately a 30-fold decrease of the 50% inhibitory concentration (IC_{50}) in wild type BCR-ABL positive cells in favour of nilotinib (25 nmol/L) versus imatinib (669 nmol/L). Therefore, nilotinib more effectively inactivates the BCR-ABL kinase and has only a small effect on c-KIT and PDGF-R compared with imatinib.

Preclinical data obtained in cells transfected with BCR-ABL point mutations that result in imatinib resistance showed activity of nilotinib in 32 of 33 cell lines. These observations reflected the stronger binding affinity of nilotinib, and encouraging pharmacokinetic data derived from a phase I trial confirmed that a dosage regimen of 400 mg twice daily (total daily dosage of 800 mg) provided plasma concentrations that exceeded these IC_{50} values in the absence of severe toxicities.

The following two observations are noteworthy at this early stage of available phase II data of nilotinib in patients with Philadelphia chromosome-positive (Ph+) CML: (i) imatinib-resistant or -intolerant patients show remarkable haematologic and cytogenetic response rates; and (ii) these responses are accompanied by a favourable toxicity profile. However, longer follow-up periods and larger patient populations are required to better understand the definite role for nilotinib in the treatment of Ph+ CML. ▲