Glivec® (Gleevec®, Imatinib, STI571)
A Targeted Therapy for Chronic Myelogenous Leukemia

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1. CONCEPT AND TARGET SELECTION: BCR-ABL

Chronic myelogenous leukemia (CML) is a clonal hematological disorder characterized by a reciprocal translocation between chromosomes 9 and 22 (1,2) known as the Philadelphia (Ph) chromosome. The molecular consequence of this interchromosomal exchange is the creation of the bcr-abl gene coding for a protein with elevated tyrosine kinase activity. The demonstration that the expression of Bcr-Abl is both necessary and sufficient to cause a CML-like syndrome in murine bone marrow transplantation models (3–5) and the finding that the tyrosine kinase activity of Bcr-Abl is crucial for its transforming activity (6), has established the enzymatic activity of this deregulated protein as an attractive drug target addressing Bcr-Abl-positive leukemias. For the first time,
a drug target was identified that very clearly differed in its activity between normal and leukemic cells. It was conceivable that this enzyme could be approached with classical tools of pharmacology since its activity, the transfer of phosphate from adenosine triphosphate (ATP) to tyrosine residues of protein substrates, could clearly be described and measured in biochemical as well as cellular assays. Furthermore, cell lines were available that were derived from human leukemic cells that had the same chromosomal abnormality. Such cell lines were instrumental for in vitro and animal studies that laid the groundwork for the clinical trials. So, the essential tools were assembled to go forward aiming at identifying potent and selective inhibitors of the Abl tyrosine kinase.

2. MEDICINAL CHEMISTRY: DEVELOPMENT OF AN ABL TYROSINE KINASE INHIBITOR

The starting point for the medicinal chemistry project that led to the synthesis of Glivec was the identification of a lead compound from a screen for inhibitors of protein kinase C (PKC). This compound, a phenyl-amino pyrimidine derivative, had very promising “lead-like” properties (7,8) and had a high potential for diversity, allowing simple chemistry to be applied to produce compounds with more potent activity or selectivity. A high cellular PKC inhibitory activity was obtained with derivatives bearing a 3'-pyridyl group at the 3 position of the pyrimidine (Fig. 1A). During the optimization of this structural class, it was observed that the presence of an amide group on the phenyl ring provided inhibitory activity against tyrosine kinases, such as the Bcr-Abl kinase (Fig. 1B). At this point a key observation from analysis of structure–activity relationship (SAR) was that a substitution at position 6 of the diamino phenyl ring abolished PKC inhibitory activity completely. Indeed, the introduction of a simple “flag-methyl” led to loss of activity against PKC, whereas the activity against protein-tyrosin kinases was retained or even enhanced (Fig. 1C). However, the first series of selective inhibitors originally prepared showed poor oral bioavailability and low solubility in water. The attachment of a highly polar side chain (an N-methylpiperazine) was found to dramatically improve both solubility and oral bioavailability. To avoid the mutagenic potential of aniline moieties, a spacer was introduced between the phenyl ring and the nitrogen atom. The best compound from this series was the methyl piperazine derivative originally named STI571 (imatinib, now known as Glivec® or Gleevec®), which was selected as the most promising candidate for clinical development (Fig. 1D) (9,10).

Docking studies (11) and X-ray crystallography (12,13) showed that binding of Glivec occurs at the ATP binding site. Analysis of the crystal structure showed that Glivec inhibits the Abl kinase by binding with high specificity to an inactive form of the kinase. The need for the kinase to adopt this unusual