Clinical Use of Tyrosine Kinase Inhibitors: Therapy for Chronic Myelogenous Leukemia and Other Cancers

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Since the initial discovery of tyrosine-specific protein kinases encoded by transforming viruses and their normal cellular homologues, there has been a great deal of interest in understanding their role in cancer and exploring their potential as therapeutic targets. Several approaches confirmed the role of tyrosine kinases in virtually every aspect of cellular transformation including cell cycle progression, increased survival in response to apoptotic challenge, neovascularization, and aberrant gene expression (for review, see Ref. 1). This information suggested that the diverse spectrum of tyrosine kinases and their association with specific malignancies offered multiple targets for chemotherapeutic intervention. However, exploitation of these enzymes as specific tumor targets has only recently been realized, and clinical application of tyrosine kinase-targeted therapy is a new and growing field (2–4).

Initial discovery of small molecules that interfered with ATP binding or utilization represented a major breakthrough in tyrosine kinase-targeted therapy (5). Subtle but measurable distinctions in the ATP binding pocket of tyrosine kinases were exploitable, and specificity for individual kinases (or related enzymes) could be engineered into small molecules with characteristics of conventional chemotherapeutic agents [molecular size, bioavailability, and cell and tissue uptake (5–8)]. The key to successful development of small molecular kinase inhibitors has been in providing selective and potent inhibition of an oncogenic target. In some cancers, unregulated or aberrant expression of a single tyrosine kinase underlies transformation (9, 10), providing great opportunities for targeted therapy with tyrosine kinase inhibitors.

CML² is characterized in >95% of patients by the presence of the Philadelphia chromosome, representing a reciprocal translocation of chromosomes 9 and 22 (11, 12). This translocation results in altered control of the c-abl tyrosine kinase and expression of a protein, termed bcr-abl, with exons derived from the c-abl gene and bcr locus (12). The resultant chimeric protein expresses unregulated tyrosine kinase activity, and studies have shown that its kinase activity is important in the etiology of CML and other diseases (13). Therefore, bcr-abl kinase inhibition may have a direct impact on CML and other diseases.

After collection of the structural, enzymatic, and molecular characteristics of tyrosine kinases, a 2-phenylaminopyrimidine derivative was characterized for its ability to inhibit v-abl, c-abl, and bcr-abl tyrosine kinase activity through competitive ATP binding pocket interactions (14, 15). The compound STI571 emerged from these studies, and its in vitro and in vivo efficacy in inducing apoptosis or suppressing clonogenic leukemic cell growth suggested that it might be therapeutically useful for treatment of CML (15–17). Whereas selective kinase inhibition underlies its basic mechanism of action, the apoptotic response to STI571 in bcr-abl-positive cells is not completely understood. Transfer of total dependence of CML progenitors on bcr-abl signaling for their sustained growth or survival may be an important consideration in the clinical responsiveness to this drug. STI571 has been introduced into Phase I trials at three centers in the United States with very promising early results (18). The drug is administered p.o., and biologically effective levels are pharmacologically achievable. Preliminary clinical responses were noted in both the chronic and the more advanced stages of the disease. It is anticipated that STI571 will impact the treatment of CML and may stimulate greater interest in the clinical use of tyrosine kinase inhibitors.

As suggested in earlier and more recent reports, STI571 may be useful in other malignancies, including leukemias characterized by expression of an alternate molecular form of bcr-abl (p190bcr-abl) and those expressing protein tyrosine kinases with ATP binding pockets structurally similar to c-abl (10, 14). Studies of STI571 activity on an available spectrum of tyrosine kinase targets suggested that c-kit and platelet-derived growth factor receptor kinases are also inhibited by STI571, with affinities similar to those described for the bcr-abl family of kinases (14, 15). Therefore, patients with tumors supported through activation or expression of one of these kinases may also benefit from STI571 therapy. In this regard, the report of c-kit expression in small cell lung cancer and its inhibition by STI571 published in this issue of Clinical Cancer Research demonstrates the potential to treat seemingly unrelated cancers with a selective kinase inhibitor (19). Other tumors dependent on platelet-derived growth factor receptor signaling (i.e., high-grade glioma) may also be targets for STI571 therapy.

Development of kinase targeting inhibitors represents a monumental research effort that is beginning to shown good clinical promise. Limited spectrum specificity and dependence of tumors on an activated or unregulated protein kinase for an oncogenic contribution will continue to be most important considerations in the design, testing, and efficacy of these inhibitors.

References


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