Cancer Chemother Pharmacol (2001) 48 (Suppl 1): S77–S78
DOI 10.1007/s002800100310

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STI571, a tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia: validating the promise of molecularly targeted therapy

Abstract The deregulated tyrosine kinase activity of the Bcr-Abl fusion protein has been established as the causative molecular event in chronic myelogenous leukemia (CML). Thus the Bcr-Abl tyrosine kinase is an ideal target for pharmacologic inhibition. STI571 (formerly CGP57148B), is an Abl-specific tyrosine kinase inhibitor that in preclinical studies selectively kills Bcr-Abl-containing cells in vitro and in vivo. The results of clinical studies have demonstrated the potential of molecularly targeted therapies, and STI571 is emerging as a new therapeutic agent for CML.

Keywords Chronic myelogenous leukemia · Bcr-Abl · Tyrosine kinase · ST1571 · Targeted therapy

Introduction

The Bcr-Abl fusion protein, resulting from a (9;22) chromosome translocation, causes several types of leukemia. The 210-kDa form of Bcr-Abl is present in almost all patients with chronic myelogenous leukemia (CML) and a 185-kDa variant is present in approximately 20% of acute lymphoblastic leukemia (ALL) patients. The transforming function of Bcr-Abl requires tyrosine kinase activity of these Bcr-Abl fusion proteins, which is elevated compared with c-Abl [9]. Thus Bcr-Abl is an ideal candidate for a molecularly targeted therapeutic agent, and it is predicted that an inhibitor of the Bcr-Abl kinase would be an effective, selective therapeutic agent for the treatment of CML.

This work was presented at the 16th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Hematologic malignancies: pioneers in cancer therapy across the century from mustard to molecular targets and beyond," 27–28 October 2000, Nagoya, Japan.

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Designing a tyrosine kinase inhibitor

After identifying an appropriate molecular target, the next task is the design of an inhibitor of the enzyme. An initial lead compound was identified by researchers at Novartis (Basel, Switzerland) who screened a large compound library for in vitro inhibitors of protein kinases. In this case, the initial lead compound was a relatively weak inhibitor of protein kinase C-α and the platelet-derived growth factor receptor (PDGF-R) [10]. The activity of the 2-phenylaminopyrimidine series was optimized by synthesizing a series of chemically related compounds and analyzing the structure-activity relationship of each compound. The most potent molecules in the series were all dual inhibitors of the v-Abl and the PDGF-R kinases [1, 2]. STI571 (formerly CGP 57148B) emerged from these efforts as the lead compound for preclinical development. Its mechanism of action is schematically shown in Fig. 1.

Preclinical testing of STI571

STI571 has been tested in a number of preclinical models, including in vitro assays of enzyme inhibition, cellular assays of inhibition of kinase activity and proliferation, and in vivo assays of tumor formation [4]. These studies demonstrated that STI571 inhibits all Abl kinases at submicromolar concentrations, including p210Bcr-Abl, p185Bcr-Abl, v-Abl, and the c-Abl tyrosine kinase [5]. Numerous tyrosine and serine/threonine protein kinases have been tested for inhibition by STI571, and except for the PDGF-R and the c-Kit tyrosine kinases, no others are inhibited [4, 5].

At concentrations of 1 and 10 μ*M*, STI571 kills or inhibits the proliferation of all Bcr-Abl-expressing cell

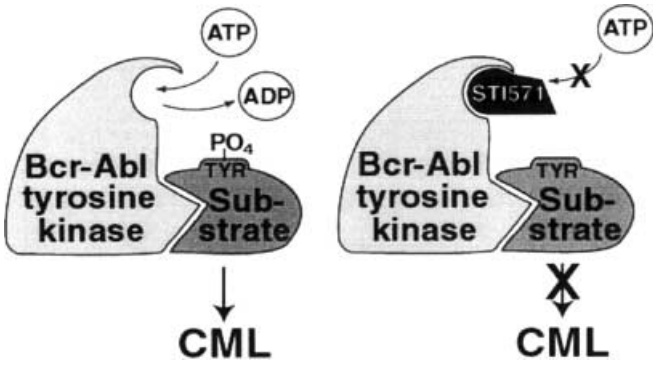

Fig. 1 Schematic representation of the mechanism of action of STI571. The Bcr-Abl tyrosine kinase is a constitutively active kinase that functions by binding adenosine triphosphate (ATP) and transferring phosphate from ATP to tyrosine residues on various substrates. This activity causes excess proliferation of myeloid cells characteristic of CML. STI571 functions by blocking the binding of ATP to the Bcr-Abl tyrosine kinase, thus inhibiting the activity of the kinase. In the absence of tyrosine kinase activity, substrates required for Bcr-Abl function cannot be phosphorylated

lines tested to date [4, 5]. In contrast, a variety of immortalized or transformed cell lines that do not express Bcr-Abl are not sensitive to STI571 [5]. In colony-forming assays using CML bone marrow or peripheral blood samples, the addition of STI571 decreases the number of colonies formed and may select for the growth of Bcr-Abl-negative progenitor cells [3, 5]. Minimal inhibition of the colony-forming potential of normal bone marrow has been observed [3, 5]. Thus STI571 appears to be selectively toxic to cells expressing the constitutively active Bcr-Abl protein tyrosine kinase. Antitumor activity has been observed in syngeneic or nude mice injected with Bcr-Abl-expressing cells and then treated with STI571 [5, 8].

Phase I trials of STI571

Based on the preclinical data and lack of significant toxicity in animals, a phase I clinical trial was conducted in CML patients who had failed other treatment options. All patients in the chronic phase ($n = 31$) achieved hematologic remissions after therapeutic dose levels were reached. With prolonged (≥5 months) therapy, an increasing proportion of these patients demonstrated cytogenetic responses, including several individuals with complete disappearance of the Philadelphia (Ph) chromosome [7].

STI571 has also shown activity as a single agent in CML patients in blast crisis and in Ph^+ ALL patients [6]. Although the responses tended not to be durable, 20% of myeloid blast crisis patients had ongoing responses between 6 months and 1 year of therapy. As almost all CML patients express Bcr-Abl, a protein unique to tumor cells, this disease has provided an ideal opportunity to test the concept that drugs targeted against a tumor-specific abnormality have therapeutic utility. Ongoing studies are directed at optimizing the use of this agent, analyzing the dose-response relationships with Bcr-Abl tyrosine kinase inhibition, and analyzing the mechanisms of relapse in patients in blast crisis.

References

1. Buchdunger E, Zimmermann J, Mett H, Meyer T, Muller M, Regenass U, Lydon NB (1995) Selective inhibition of the platelet-derived growth factor signal transduction pathway by a protein-tyrosine kinase inhibitor of the 2-phenylaminopyrimidine class. Proc Natl Acad Sci USA 92:2558
2. Buchdunger E, Zimmermann J, Mett H, Meyer T, Müller M, Druker BJ, Lydon NB (1996) Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. Cancer Res 56:100
3. Deininger MW, Goldman JM, Lydon N, Melo JV (1997) The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells. Blood 90:3691
4. Druker BJ, Lydon NB (2000) Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J Clin Invest 105:3
5. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB (1996) Effects of a selective inhibitor of the ABL tyrosine kinase on the growth of BCR-ABL positive cells. Nat Med 2:561
6. Druker BJ, Kantarjian H, Sawyers CL, Resta D, Fernandes-Reese S, Ford J, Talpaz M (1999) Activity of an Abl specific tyrosine kinase inhibitor in patients with Bcr-Abl positive acute leukemias, including chronic myelogenous leukemia in blast crisis. Blood 94:697a
7. Druker BJ, Talpaz M, Resta D, Peng B, Buchdunger E, Ford J, Sawyers CL (1999) Clinical efficacy and safety of an Abl specific tyrosine kinase inhibitor as targeted therapy for chronic myelogenous leukemia. Blood 94:368a
8. le Coutre P, Mologni L, Cleris L, Marchesi E, Buchdunger E, Giardini R, Formelli F, Gambacorti-Passerini C (1999) In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. J Natl Cancer Inst 91:163
9. Lugo TG, Pendergast AM, Muller AJ, Witte ON (1990) Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. Science 247:1079
10. Zimmermann J, Caravatti G, Mett H, Meyer T, Muller M, Lydon NB, Fabbro D (1996) Phenylamino-pyrimidine (PAP) derivatives: a new class of potent and selective inhibitors of protein kinase C (PKC). Arch Pharm 329:371