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Review paper

STI571 (imatinib mesylate): the tale of a targeted therapy

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STI571 (imatinib mesylate) is an example of the successful development of a targeted agent. Its target is the constitutively active tyrosine kinase (p210$^{bcr-abl}$) in a hematologic neoplasm, chronic myelogenous leukemia (CML). The results in early clinical trials were remarkable and led to rapid approval by the Food and Drug Administration for clinical use of the STI571 in CML. This article reviews the pre-clinical and clinical development of this agent and also discusses some of the prevailing theories to explain the emerging problem of resistance. Future directions for this drug, possibly directed at other targets, are also discussed. [© 2002 Lippincott Williams & Wilkins.]

Key words: Imatinib mesylate, STI571, targeted therapy.

Introduction

Signal transduction inhibitor (STI) 571 (imatinib mesylate) is one of the first examples of agents targeted to a molecular abnormality in neoplasms, in this case the neoplasm is chronic myelogenous leukemia (CML). The discovery of the Philadelphia chromosome in 1960 by Nowell and Hungerford was the first step in identifying the target for CML.[1,2] Rowley later showed that the abnormal chromosome was due to a reciprocal translocation between chromosome 9 and 22, and subsequent studies found that the *abl* oncogene from chromosome 9 is fused to the *bcr* gene of chromosome 22.[2] The protein resulting from this fusion gene can be of different molecular weights depending on the breakpoint of chromosome 9, but the 210-kDa protein is a constitutively active tyrosine kinase (p210$^{bcr-abl}$) that appears to be essential in causing the clonal expansion of myeloid cells in CML. This protein is seen in approximately 95% of all patients with CML. Druker was instrumental in working with Ciba-Geigy (now Novartis) to promote the idea of screening for compounds that inhibit the tyrosine kinase activity of the *bcr–abl* gene product.[1] These efforts led to the development of a 2-phenylaminopyrimidine compound initially called CGP 57148B, later known as STI571, that was a specific inhibitor of the Abl and platelet-derived growth factor receptor (PDGF-R) tyrosine kinases.[3] STI571 works by blocking the ATP-binding site of the p210$^{bcr-abl}$ tyrosine kinase, which in turn prevents the kinase from phosphorylating substrates. The substrates prevented from being activated by STI571 initiate a cell-signaling process leading to the proliferation of myeloid leukemic cells seen in CML.[4]

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Pre-clinical development

In vitro studies demonstrated that STI571 was a specific inhibitor of the tyrosine kinase activity of Bcr–Abl (p210 and p185), PDGF-R, kit, Tel–Abl fusion protein and Tel–PDGF-R fusion protein, and had little effect on other tyrosine kinases.[5,6] In addition to inhibiting the function of specific proteins, STI571 was shown to selectively inhibit the growth of leukemic cells containing the Bcr–Abl fusion protein without affecting normal cells lacking the protein.[7,8] There was also evidence from these *in vitro* studies suggesting prolonged exposure was necessary for optimal effect. The specificity of this compound and its lack of effect on normal cells *in vitro* was important for further development of the drug. If STI571 proved to be a nonspecific inhibitor of tyrosine kinases, it would also inhibit necessary cell-signaling activity and be clinically impossible to use. The promising *in vitro* studies led to animal *in vivo* experiments to further explore the potential benefits and side effects of the drug. Studies in mice showed that with continuous exposure, STI571 could completely eradicate Bcr–Abl-containing tumors[9,10] with minimal toxicity. The disease was

eliminated without damage to the normal tissues in the host—the ultimate goal of targeted therapy.

Clinical trials and Food and Drug Administration (FDA) approval

The phase I trial[11] began in June 1998 and finished in May 2000. The 83 patients enrolled had chronic phase Philadelphia chromosome-positive CML and were either unable to tolerate interferon (IFN)-α or their disease was IFN-α refractory. STI571 was given daily in a dose-escalation manner from 25 to 1000 mg. The 400 mg dose level produced a mean maximal steady-state concentration of 4.6 μM with a half-life of 13–16 h. The concentration achieved at this dose exceeded the concentration required for *in vitro* cell death of Bcr–Abl-containing cells and the half-life supported a once-daily dosing schedule. No dose-limiting toxicities were observed, but common toxicities were myalgias, edema, diarrhea, thrombocytopenia and neutropenia. Cutaneous reactions such as exfoliative dermatitis, rash and exanthematous pustulosis have also been reported, and seem to have a dose–response relationship with STI571.[12] The responses seen in this trial were remarkable. Ninety-eight percent of patients treated with 300 mg/day or more had complete hematologic responses that occurred within 2–3 weeks. Major cytogenetic responses (less than 35% Philadelphia chromosome-positive) were seen in 31% of patients and 13% were complete cytogenetic responses (0% Philadelphia chromosome-positive). Responses have been maintained in 51 of the 53 patients with a median follow-up time of 265 days.

Due to the results seen in the initial phase I trial in patients with chronic CML, a parallel study[13] was developed to include adults in myeloid or lymphoid CML blast crisis and patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). Fifty-eight patients enrolled and 38 were in myeloid blast crisis, while the remaining 20 were in lymphoid blast crisis (patients with ALL were placed in this group). The dose-escalation ranged from 300 to 1000 mg based on results from the initial phase I study. Compared to the previous study, toxicities were similar, varying mainly in severity. Toxicities that appeared to be exacerbated at comparable dose levels and had a dose–response relationship were nausea, vomiting, neutropenia, thrombocytopenia and rash. The complete hematologic response rate in the myeloid group was 32% (12 of 38) with 13% of these patients relapsing in less than 1 year. The complete hematologic response rate in the lymphoid group was 20% (four of 20) with 15% of these patients relapsing in the same time period. The results for Philadelphia chromosome-positive ALL patients were similar to the overall lymphoid group. The rate and pace of the relapses tempered the enthusiasm of the initially high response rates. The resistance to STI571 in the blast phase is a topic of much interest and will be discussed in a later section.

These promising phase I studies led to four phase II studies whose interim results were reported in abstract form in December 2000 at the American Society of Hematology Meeting, and involved chronic-phase CML,[14] accelerated-phase CML,[15] myeloid blast crisis CML[16] and Philadelphia chromosome-positive adult ALL.[17] These results, in general, confirmed the response rates and toxicities seen in the phase I trials in a larger group of patients.

Overall, the response rates compared to standard therapy for the different phases of CML are impressive. The toxicities also appear to be minimal, well tolerated and less severe than the toxicities seen with standard therapies. These results prompted the FDA to accelerate approval for STI571. FDA approval for all three stages of CML [chronic (after IFN failure), accelerated and blast] was received on 10 May 2001, an astonishing 1 year after the completion of the initial phase I study and less than 3 months after the review began.

Possible mechanisms of resistance to STI571

As mentioned previously, the only relapses on treatment occurred in the blast and accelerated phases, and several theories regarding this resistance to STI571 have evolved. *bcr–abl* appears to be the critical oncogene in CML, but it is possible that as the disease evolves, other oncogenes drive proliferation of the malignant clone.[18] If this were the case, the specificity of STI571 would cause it to become ineffective. Another possibility is that the *bcr–abl* gene is mutated and/or amplified, rendering it resistant to inhibition.[19] If a mutation causes alteration of the ATP binding site, the drug would be rendered ineffective. However, overexpression of the $p210^{bcr-abl}$ tyrosine kinase may possibly be overcome by increasing the dose. Elements outside of the cell may also be contributing factors. One such theory is increased production of α_1-acid glycoprotein, a plasma protein, directly or indirectly caused by higher tumor burdens will result in increased drug–protein binding. This would mean a lower

concentration of drug would be available to block the ATP-binding site of the p210$^{bcr–abl}$ fusion protein.[20,21] If this occurs, drugs that competitively bind to the α_1-acid glycoprotein may allow for increased 'free' levels of STI571 and increase its efficacy. Alternatively, this resistance mechanism might call for an intermittent parenteral dosing scheme that would saturate the α_1-acid glycoprotein binding sites.

Other targets

Kit tyrosine kinase

The results in CML have prompted investigators to look for other targets for STI571 and one in particular looks to be as promising as p210$^{bcr–abl}$, i.e. c-*kit*. c-*kit* is a proto-oncogene that encodes a receptor tyrosine kinase (Kit) whose ligand is stem cell factor (SCF). Kit is expressed on mast cells, melanocytes, hematopoetic cells, the interstitial cells of Cajal and in 89–100% of gastrointestinal stromal tumors (GISTs).[22] Mutations in c-*kit* likely cause Kit to become constitutively active in GIST cells independent of its SCF ligand. Tumor formation results and thus presents another ideal target for STI571. This was initially demonstrated in a case report[23] and is now being evaluated in a phase II trial. Interim results were reported in abstract form to the American Society of Clinical Oncologists in 2001[24] and were astonishing for a tumor known to be unresponsive to cytotoxic chemotherapy. Patients were placed on 400 or 600 mg: 54% (19 of 35) had partial responses, 34% (12 of 35) had stable disease and no patients have relapsed after a response. Toxicities included tumor hemorrhage, abdominal pain and electrolyte disturbances. If these results are durable, FDA approval of STI571 for another indication is on the horizon.

The Kit tyrosine kinase is also expressed in 70% of small cell lung cancers and STI571 has been shown to be cytostatic to various small cell lines.[25] Although there is the concern that there are a number of signals that initiate the growth of small cell lung cancer, 'adjuvant' approaches after induction of maximal cytotoxic response is of interest.

PDGF-R

Glioblastoma cell lines have been inhibited in xenograft models by STI571 and this may be due to its action on the PDGF-R.[26] This is an incurable tumor and if STI571 could provide any response or even stable disease it would be welcome. There are currently no phase II clinical trials in progress.

PDGF-R may also be expressed on tumor-associated endothelial cells and STI571 may inhibit local tumor invasion[27,28] by inhibition of the receptor on these cells. Uehara *et al*.[27] demonstrated this in abstract form in prostate cancer and bone metastasis, raising the possibility of using STI571 in the treatment and prevention of metastatic disease.

Tel–PDGF-R

This fusion protein is created by translocation between chromosome 5 and 12, and is seen in chronic myelomonocytic leukemia. There is data that suggests that cells expressing this protein are inhibited by STI571[28] and present yet another possible therapeutic use for the drug.

Other possibilities

Other possibilities include combinational strategies with classic cytotoxic agents such as IFN-α, daunorubicin, doxorubicin and others. Synergy is seen with some of these agents *in vitro*.[28] Clinical trials investigating some of these combinations are currently being conducted.

The future

The war on cancer has had advances in its strategic plan recently, but the battle for their implementation continues. Molecularly targeted therapies will provide a new weapon in the armamentarium that hopefully will be selective and the development of STI571 has shown us that such weapons can be lethal to neoplastic cells while sparing others. However, unlike CML and GIST, most neoplasms will likely have more than one or two signals that drive them, and developing weapons will require understanding and characterizing the targets for each tumor, keeping in mind that this enemy is agile and may change targets repeatedly.

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