REVIEW ARTICLE

Signal Transduction Inhibitors (STI571): Molecularly Targeted Therapy

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The therapy of chronic myeloid leukemia (CML), characterized by the presence of the Philadelphia chromosome in the clonal hematopoietic stem cells, has changed dramatically in the last year with the development of a specific inhibitor of the BCR-ABL tyrosine kinase. This medication, STI571 or imatinib , was recently approved by the Food and Drug Administration for CML patients refractory or intolerant to interferon. The medication has the potential to rapidly reverse the clinical and hematologic abnormalities of CML and is the paradigm of molecularly targeted therapy. STI571 is the first agent in Oncology that directly targets the molecular basis of a malignant disease, changing the way that we will treat these conditions in the future. This new field of molecular and cellular biology has the possibility of controlling not only malignant conditions but also diseases treated by other medical specialties.

Key words: Chronic myeloid leukemia, Imatinib, Signal transduction inhibition, Tyrosine kinase

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder characterized by the presence of the Philadelphia chromosome. This traslocation between the breakpoint cluster region and Ableson (BCR and ABL) genes in chromosomes 22 and 9 respectively produces a BCR-ABL tyrosine kinase which characterizes the pathogenesis of this condition. The disease has an annual incidence of 1-2 cases per 100,000 per year and progresses through three distinct phases: a stable or chronic phase, accelerated phase and blast crisis (1). If the disease is not controlled, it inevitably progresses in a period of approximately 5 years to an acute leukemia, which is highly refractory to therapy.

Standard therapy of CML has consisted in the past in the control of the white blood cell count with agents such as busulfan and hydroxyurea. More recently, the use of alpha-interferon with or without cytarabine have improved the response, with a minority of patients obtaining complete cytogenetic remission (2). However, it was not until last year, that a medication called STI571 (imatinib; *Gleevec*) , with the potential to directly inhibit the BCR-ABL tyrosine kinase, was approved in a record time by the Federal Drug Administration (FDA). That medication has the potential to rapidly reverse the clinical and hematologic abnormalities of CML and is the paradigm of molecularly targeted therapy, a field that is expanding the possibilities to treat hematopoietic and solid cancers (3). We will discuss the interesting development of this novel drug and its potential uses in different neoplasias.

Design of STI571. Yaish et al in 1988 reported the first tyrosine kinase inhibitors, known as tyrphostins (4). Later work done by Ciba-Geigy researchers using screening compound libraries led to identification of the 2-phenylaminopyrimidine class of kinase inhibitors . Preclinical studies by Druker and others showed that the molecule was highly effective in blocking the tyrosine activity of BCR-ABL protein by blocking access of ATP to the kinase, inhibiting phosphorylation of any substrate (5,6). STI571 in addition to inhibiting the ABL kinase also had activity in the stem cell factor receptor (c-kit) and the platelet derived growth factor(7). This led Dr. Druker and colleagues, from the Oregon Health Science Center , to test STI571 in Phase I/II studies in patients with CML(8).

Clinical Studies.

Since 1998 evolved the trials by Druker et al, involving 83 patients with CML in the chronic phase who had failed alpha-interferon therapy and 58 patients with CML in blast crisis or Ph-chromosome positive acute lymphoblastic leukemia (9,10). In the first study, patients were treated with doses ranging from 25 to 1000 mg. No dose limiting toxicity was encountered and the threshold for the maximal effective dose was at 300 mg. Complete hematologic

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response was found in 98% of patients with major cytogenetic responses in 31%. In the other study, 38 patients with myeloid blast crisis and 20 with acute lymphocytic leukemia or lymphoid blast crisis were treated with doses ranging from 300 to 1000 mg, with a response of 55 and 70 % respectively.

The success of the above studies permitted multicenter trials in 6 countries with 532 patients in CML chronic phase refractory or intolerant to interferon. The patients were treated with 400 mg of STI571 daily, with 47% achieving major cytogenetic responses. In the accelerated phase of CML, 233 patients treated with 400 to 600 mg of STI571 achieved an hematologic response of 91%. Thirty percent of patients were alive at 14 months in a condition that with traditional chemotherapy offers a median survival of only 3 months.

The BCR-ABL tyrosine kinase inhibitor STI571 was well tolerated and had substantial activity even in those patients with a very poor prognosis and where in the past there was no effective therapy. This led the FDA to approve STI571 in May 2001 in a record review time of 3 months.

Toxicity of STI571. STI571 was usually well tolerated with mild to moderate nausea, diarrhea, myalgias and periorbital edema as the most frequent side effects. There has been a report of a fatal liver failure in a patient that was using concomitant high doses of acetaminophen. Myelosuppresion with decreases white blood cell counts and platelets were observed in 10-20 % of patients with blast and accelerated phases (10). This myelosuppresion is consistent with a therapeutic effect, as the Philadelphia positive clone contributes significantly to the hematopoiesis of these patients.

STI571- other uses. STI571 inhibits other kinases such as the stem cell growth factor (c-kit) and the platelet derived growth factor receptor (PDGFR). The gastrointestinal stromal tumors (GIST), a group of mesenchymal neoplasms that arise from precursors of the connective tissue cells of the gastrointestinal tract, express the c-kit oncogene (11). Due to the marked therapeutic effect of the medication in patients with advanced GIST tumors, the FDA also recently approved STI571 for this indication. STI571 is in evaluation in other tumors that express c-kit (CD117) or the PDGFR such as small cell lung cancer, glioblastomas, breast , prostate, liver, and lung cancer(12).

Conclusions

The introduction of STI571 has supported the model of CML pathogenesis and has led to a new paradigm for CML therapy. The future treatment of CML should led to the combination of STI571 with other agents and use in early disease. There had been several reports of drug resistance, by overexpresion of the BCR-ABL protein in the malignant cells, kinase domain mutations and additional cytogenetic abnormalities, for which possibly the agent has to be combined with other treatments. However, the success of STI571 has prompted investigators to identify the molecular targets of other diseases. The use of a number of disciplines, such as structural biology, computational chemistry, array screening asays, structurally directed medicinal chemistry and molecular and cellular biology, will permit using this new class of agents more effectively in the treatment of diverse conditions. Also, the analysis and validation of surrogate molecular endpoints, will be necessary in order to use these agents in a more rational way. STI571 is the first agent in oncology that targets directly the molecular basis of a disease instead of killing cells in a nonselective manner as in the past with the traditional chemotherapeutic drugs. There is no doubt that we have just seen the beginning of molecularly directed therapy that has applications not only in oncology, but also in other fields of medicine.

Resumen

La terapia para la leucemia crónica mieloide (CML), caracterizada por la presencia del cromosoma Philadelphia en las células clonales progenitoras, ha cambiado dramáticamente en el ultimo año con el desarrollo de un inhibidor específico en contra de la quinasa de tirosina BCR-ABL. Este medicamento, STI571 o imatinib, fue aprobado recientemente por la Administración de Drogas y Alimentos para pacientes con CML refractarios o intolerantes al interferón. El medicamento tiene el potencial de revertir rápidamente las anormalidades clínicas y hematológicas del CML y es el paradigma de la terapia dirigida por la biología molecular. STI571 es el primer agente en la oncología que directamente actúa contra la base molecular de una enfermedad maligna, cambiando la forma en que se tratarán estas condiciones en el futuro. Este nuevo campo de la biología molecular y celular tiene la posibilidad de controlar no solo condiciones malignas sino también enfermedades tratadas por otras especialidades médicas.

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