A NEW ERA IN ANTICANCER THERAPY

Bulgarian Pharmaceutical Association has granted Imatinib 1st prize for prescription drugs in 2008. This review addresses the role of imatinib in anticancer therapy. Imatinib is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing cells. It is currently marketed by Novartis as Gleevec (USA) or Glivec (Europe/Australia) as its mesylate salt.

IMATINIB - A NEW ERA IN ANTICANCER THERAPY

N. Danchev, I. Nikolova, G. Momekov
Medical University, Faculty of Pharmacy, Dept. “Pharmacology, Pharmacotherapy & Toxicology”, Sofia, Bulgaria
Correspondence to: Nikolai Danchev
E-mail: ndanchev@pharmfac.net

ABSTRACT

Imatinib, a synthetic tyrosine kinase inhibitor, is the first member of a new class of agents. The introduction of imatinib has brought a new era in anticancer therapy that is designed to interfere with a specific molecular target, usually a protein with a critical role in tumor growth or progression. Imatinib serves as a model for the development of other tyrosine kinase inhibitors and for targeted therapy in general.

Keywords: imatinib, STI571, tyrosine kinase inhibitors, anticancer therapy

Introduction

Conventional chemotherapy, although directed toward certain macromolecules or enzymes, typically does not discriminate effectively between rapidly dividing normal cells (e.g., bone marrow and gastrointestinal tract) and tumor cells, thus leading to several toxic side effects. Tumor responses from cytotoxic chemotherapy are usually partial, brief, and unpredictable. In contrast, targeted therapies interfere with molecular targets that have a role in tumor growth or progression. There are multiple types of targeted therapies available, including monoclonal antibodies, inhibitors of tyrosine kinases, and antisense inhibitors of growth factor receptors.

Imatinib mesylate is a recently developed oral anticancer agent rationally designed to selectively inhibit certain protein tyrosine kinases implicated in oncogenesis (4). Protein tyrosine kinases control the activation of signal transduction pathways that regulate critical cellular processes, such as growth, differentiation, and apoptosis. They are functionally dysregulated and overexpressed in a number of human cancers.

Imatinib is a synthetic tyrosine kinase inhibitor. It is specifically designed to inhibit the breakpoint cluster region (BCR)-Abelson (ABL) fusion protein that results from the chromosomal abnormality known as the Philadelphia chromosome.

History

In 1988, Yaish et al. (10) reported the first synthetic tyrosine kinase inhibitors, known as tyrphostins, which demonstrated specificity among different tyrosine kinases. Work done independently at Ciba-Geigy (now Novartis) using high throughput screening of compound libraries led to the identification of the 2-phenylaminopyrimidine class of kinase inhibitors. Using structure-activity relationships, these compounds were optimized against a variety of targets.

Molecular pharmacology

Protein kinases (PKs) are indispensable for numerous processes in the cell. These enzymes catalyze phosphorylation of different cellular substrates. Phosphorylation in turn regulates various cellular functions. Normally, their activity is stringently regulated.

However, under pathological conditions PKs can be deregulated, leading to alterations in the phosphorylation and resulting in uncontrolled cell division, inhibition of apoptosis, and other abnormalities and consequently to diseases. Inhibition of PKs has been shown to be a promising therapeutic strategy (2, 5).

Imatinib mesylate is a protein tyrosine kinase inhibitor. There are a large number of tyrosine kinase (TK) enzymes in the body, including the insulin receptor. Imatinib is specific for the TK domain in ABL, stem-cell factor receptor (c-Kit) and PDGF-R.

Imatinib is a selective inhibitor of the TK activity of BCR-ABL fusion gene (oncoprotein), the product of the Philadelphia chromosome. BCR-ABL tyrosine kinase is present in virtually

The molecule 2-phenylaminopyrimidine was then tested and modified by the introduction of methyl and benzamide groups to give it enhanced binding properties, resulting in imatinib.

Chemical structure of imatinib

STI571 (imatinib) was developed initially as a specific platelet-derived growth factor receptor (PDGF-R) inhibitor, but was also found to be a potent and selective inhibitor for ABL tyrosine kinases, including BCR-ABL. Its development is the template for rational drug design.

Imatinib received FDA approval in May 2001. On the same month it made the cover of TIME magazine as the “magic bullet” to cure cancer.
all patients with chronic myelogenous leukemia (CML) and some patients with acute lymphoblastic leukemia (ALL); it is considered the abnormality that causes CML. The compound has also shown high activity in blocking the tyrosine kinase activity of c-Kit and PDGF-R. The ability of imatinib to inhibit BCR-ABL tyrosine kinase activity is related to its occupancy of the kinase pocket of the protein, which blocks access to ATP and prevents substrate phosphorylation. Imatinib has been shown to induce apoptosis or growth arrest in hematopoietic cells expressing BCR-ABL (3, 9).

Imatinib also inhibits the ABL protein of non-cancer cells but cells normally have additional redundant tyrosine kinases which allow them to continue to function even if ABL tyrosine kinase is inhibited. Some tumor cells, however, have a dependence on BCR-ABL. Inhibition of the BCR-ABL tyrosine kinase also stimulates its entry in to the nucleus, where it is unable to perform any of its normal anti-apoptotic functions.

**Therapeutic uses**

Imatinib is indicated for the treatment of:

- Newly diagnosed patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (8);
- Patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy;
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL);
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) (8).

**Place In Therapy**

The choice between drug therapy (imatinib) and transplantation for newly diagnosed patients with chronic phase, Philadelphia positive, CML is becoming increasingly difficult. In the era of imatinib, patients with a high likelihood of success (younger patients with matched siblings donors or patients with an insufficient response to imatinib) may be the ones selected for early transplantation. Long-term follow-up is need to assess the tolerability and duration of responses to imatinib (1, 6).

**Drug interactions**

The metabolism of imatinib is largely dependent on CYP3A4. Concomitant administration of CYP3A4 inhibitors (e.g. ketoconazole, erythromycin, grapefruit and grapefruit juice) may increase and CYP3A4 inducers (e.g. Hypericum perforatum, carbamazepine, dexamethasone, Phenobarbital, phenytoin, rifabutin, rifampin), may decrease imatinib systemic exposure (Cmax and AUC). Conversely, imatinib may inhibit the metabolism of CYP3A4 substrates (e.g. simvastatin), thereby increasing their exposures. Furthermore, imatinib has been shown to be a potent competitive inhibitor of CYP2C9, CYP2D6 and CYP3A4; concomitant imatinib administration may result in elevated blood concentrations of drugs that are substrates of these enzymes. Imatinib may increase systemic exposure to paracetamol by inhibiting its O-glucuronidation (7).

**Side effects**

Imatinib is effective and generally well tolerated overall in clinical trials. Adverse events were fairly common, but most of them were mild to moderate in severity. Since the ligand of c-Kit is a stem cell factor, which is important for hematopoiesis, one of the major side effects of imatinib is grade 1 or 2 myelosuppression, commonly seen in patients who are given imatinib. The most serious side effect is a reduction in red blood cell count and inflammation of the skin in the form of rashes. Since molecular targeting drugs link to the specific target site, it would seem that treatment would have minimal or no side effects due to the cytostatic properties. However, side effects are encountered, which should be taken into consideration prior to prescription in order to avoid serious setbacks which might culminate in fatal conditions.

**Conclusions**

Imatinib is a novel, molecularly targeted anticancer drug that demonstrates remarkable clinical activity in patients with CML, GIST, and other tumors caused by imatinib-specific abnormalities of PDGF-R and c-Kit. Experience to date has demonstrated that the earliest possible initiation of treatment with imatinib and the use of full therapeutic dosages are crucial to achieving optimal clinical responses.

The introduction of imatinib has brought a new era in anticancer therapy that is designed to interfere with a specific molecular target, usually a protein with a critical role in tumor growth or progression. This approach differs from the more empirical approach used in conventional cytotoxic chemotherapy, which has remained the mainstay of anticancer drug use over the past several decades. Targeted therapy has the potential to reduce or eliminate many of the present problems in the field of cytotoxic chemotherapy, such as the production of serious host-cell toxicity. Unfortunately, several of the present-generation small molecule tyrosine kinase inhibitors used in targeted therapy have their drawbacks and limitations and have more similarities than differences to the current cytotoxic drugs. However, knowledge of their effects will facilitate the development of improved targeted agents that can circumvent these limitations. Imatinib serves as a model for the development of other tyrosine kinase inhibitors and for targeted therapy in general.

**REFERENCES**