Imatinib mesylate, a new drug for chronic myeloid leukemia in pediatric patients

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Background: **Imatinib mesylate (IM) is the greatest drug discovered in the past three decades. It is one of the new agents which have the potential to decrease therapy-related morbidities for patients with chronic myeloid leukemia (CML). As a tyrosine kinase inhibitor and a potential targeted model therapy, IM works through competitive inhibition of the ATP binding site of tyrosine kinase Bcr-Abl, the aberrantly expressed and constitutes active gene product of t(9;22) Philadelphia chromosome translocation.**

Data sources: **All literatures were from Pubmed and full text articles.**

Results: **IM induces major cytogenetic response in 60% of cases in chronic phase of CML and complete hematological response in 95%. IM can be used as the fist line treatment of CML. If the treatment is not successful within a year of treatment, the patient should be advised for marrow transplant. IM is also used in CML patients who are intolerant to interferon or have failed to interferon therapy. IM can induce high rates of cytogenetic and hematological responses in children in whom interferon treatment has failed. The hematologic toxic effects of IM are manageable.**

Conclusions: **IM plays a role in the treatment of CML both in adults and children. Usage of the agent awaits further elaboration of molecular biology of different cancers and specific targeted therapy.**

World J Pediatr 2007;3(2):110-114

Key words: **imatinib mesylate;**
chronic myeloid leukemia;
childhood cancers;
chronic leukemia

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Introduction

Chronic myeloid leukemia (CML) is a rare disease in childhood (2%-3% of childhood leukemias), therefore to perform a prospective trial is a difficult task. A variety of chemotherapy approaches to CML have been used in the past.[1] Among them, the potential curative therapy preserving the fertility is allogenic marrow transplant in children. Yet there is little information about interferon alpha or interferon alpha plus cytosine arabinoside therapy in children with CML. Imatinib mesylate (IM) has gone through the COG phase I trial in children and the COG phase II trial is now open to newly diagnosed patients of CML in children. This article is to make pediatricians understand the use of IM in the treatment of CML in children.

In the treatment of CML, IM was introduced by Novartis, USA. IM received the fastest approval for the treatment of CML in adults from the Food and Drug Administration (FDA) of USA in 2001.[2] The FDA approved IM for pediatric CML in 2003.[3]

Physical characteristics

IM is a yellowish white crystalline powder with a chemical name of 4-[(4-methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]-phenyl] benzamide methanesulfonate. Its molecular formula is $C_{29}H_{31}N_7O$ [CH_4SO_3] with a relative molecular mass of 589.7. It is slightly soluble to insoluble in neutral/alkaline aqueous buffers.

Mechanism of action[4]

The cause of CML is the translocation of regions of the BCR and ABL genes to form BCR-ABL fusion gene.[5] In at least 90% of the cases this event is a reciprocal translocation termed t(9;22), which forms the Philadelphia (Ph) chromosome.[6] The product of BCR-ABL gene, the BCR-ABL protein, is a constitutively active protein tyrosine kinase, which plays an important role in the regulation of cell growth.[5] IM, a protein-tyrosine kinase inhibitor, inhibits the BCR-ABL tyrosine kinase in the Philadelphia chromosome

positive CML cells, thus inhibiting proliferation and inducing apoptosis in BCR-ABL positive cell lines and leukemic cells.

In vivo, IM inhibits tumor growth of BCR-ABL transferred murine myeloid cells as well as BCR-ABL positive leukemia lines derived from CML patients.[4]

In vitro, IM not only suppresses the receptor tyrosine kinase in BCR-ABL positive leukemic cells but also tyrosine kinases for platelet growth factor (PDGF) and stem cell factor (SCF), C-kit. It also inhibits PDGF and SCF mediated cellular events.[4]

Pharmacokinetics and metabolism[4]

In healthy adult subjects and population pharmacokinetic studies, IM is well absorbed after oral administration, and the maximum plasma concentration (Cmax) is achieved within 2-4 hours. The mean absolute bioavailability for single oral dose is 98%. After oral administration, the elimination half lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. The mean imatinib area under the plasma concentration time curve (AUC) is increased proportionately with an increasing dose ranging from 25 to 1000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing and accumulation is 1.5-2.5 fold at a steady state when IM is dosed once daily. Ninety-five percent of IM is bound to plasma protein mostly to albumin and α_1 acid glycoprotein.

CYP3A4 is one of the human p450 cytochrome isoenzymes present in the mitochondria. CYP3A4 is the major enzyme responsible for the metabolism of IM. This enzyme metabolises IM to an active metabolite called N-demethylated piperazine derivative. This metabolite also shows potency similar to the parent compound i.e. IM. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

Elimination is predominantly in the feces, as metabolites. Studies on ^{14}C-labelled dose of imatinib have shown that approximately 81% of the dose can be eliminated within 7 days, and 68% of the dose is eradicated via feces and 13% via urine. Unchanged IM accounts for 25% of the dose (5% in urine and 20% in feces).

Dosage in children

Sugawara et al[5] investigated pharmaco kinetics using 230 mg/m^2 of IM in a 6-year-old child with CML and found that the area under the concentration time curve was inferior to that for adult patients in the 400 mg/d group. They concluded that suboptimal plasma concentration might be related to resistance to IM and/or blast crisis.[5]

The recommended dosage in pediatric patients is 260 mg/m^2 and 350 mg/m^2 equivalent to the adult dose of 400 mg/day for chronic phase and 600 mg/d for accelerated/blast crisis phases of CML, respectively.[6]

Drug interaction[4]

Drugs that increase imatinib plasma concentration

Ketoconazole, itraconazole, erythromycin and clarithromycin inhibit the P450 isoenzyme (CYP3A4), therefore there is a significant increase in exposure to imatinib when co-administered with these drugs.

Drugs that may decrease imatinib plasma concentration

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma levels. The CYP3A4 inducers include dexamethasone, phenytoin, carbamezepine, rifampicin, and phenobarbitol, which may decrease the concentration of imatinib.

Drugs that may have their plasma concentration altered by imatinib

IM increases the mean Cmax and AUC of simvastatin (simvastatin is a CYP3A4 substrate).

When IM is administered with cyclosporine or pimozide, CYP3A4 substrates that have a narrow therapeutic window; their levels may be increased.

IM will increase the plasma concentration of CYP3A4 metabolized drugs like triazolo-benozodiazepines, dihydropyridine and calcium channel blockers, etc.

Since warfarin is metabolized by CYP2C9, patients who require anticoagulation should receive low-molecular weight or standard heparin while on IM.

Indications and usage

Imatinib mesylate is indicated for patients with CML in chronic phase, accelerated phase or blast crisis. It is also indicated for patients in chronic phase of CML after use of interferon.

Definition of response

Hematological remission response

All responses need to be confirmed after ≥4 weeks. Complete hematological response (CHR) is defined by the following parameters: white blood cells <10 × 10^9/L; platelet <450 × 10^9/L; myelocyte and metamyelocyte <5% in peripheral blood, no blasts and promyelocyte in peripheral blood, and basophils <20% with no extramedullary involvement.

Cytogenetic response

A major cytogenetic response (MCR) combines both complete and partial response. Complete cytogenetic response is defined when there are 0% ph^+ metaphases and partial response is defined when there are 1%-35% ph^+ metaphases in marrow culture. Complete cytogenetic response is to be confirmed by a second bone marrow cytogenetic evaluation performed at least one month after initial bone marrow study.

Dose adjustment for hepatotoxicity

If the level of bilirubin is increased more than 3 times the upper limit of normal (IULN) or that of liver enzymes more than 5 times ULN, IM is stopped. When the level of bilirubin has been less than 1.5 times IULN and the level of transaminases to less than 2.5 times IULN, administration of IM can be continued at a reduced daily dose.

Dose adjustment for neutropenia and thrombocytopenia

Dose adjustment for neutropenia and thrombocytopenia can be done (Table).

Side effects

Fluid retention and edema are mostly seen in patients below 65 years of age and in those who have received higher doses of IM. The patients should be monitored for an expected weight gain. When severe fluid retention occurs, diuretics are required in 1% to 2% of patients treated with IM.[7]

Diarrhoea, abdominal pain, dyspepsia are common gastrointestinal side effects.

Since neutropenia or thrombocytopenia is encountered frequently, regular hemography should be done. Accelerated phase CML or in blast crisis is more often seen in patients. The events can be managed with either a reduction of the dose or an interruption of the treatment with IM.

Hepatotoxicity may occasionally be severe. Liver function should be monitored before initiating therapy or during therapy. Markedly elevated levels of transaminase or bilirubin occurs in 1.1%-3.5% of patients. They can be managed with a reduction of the dose or interruption of the treatment.

Renal toxicity is defined as raised level of creatinine (grade 3), which can be seen in 1.2% of patients with CML in myeloid blast crisis and 1.3% in an accelerated phase during the treatment with IM.

Carcinogenesis, mutagenesis, impairment of fertility[8]

To date, there is no objective evidence of impaired spermatogenesis in men with CML. Women with CML treated with IM should be aware of the potential teratogenecity of IM and should be counseled to use effective contraceptive method throughout the treatment.

Lactating mothers

It is not known whether IM or its metabolites are excreted in human milk. However, lactating rats when administered IM at 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/d based on the body surface area, showed extensive excretion of IM and its metabolites in milk. Women should be advised against breast feeding while taking IM.

Studies in children

The incidence of CML in pediatric patients is 1%-2% of all pediatric cancers,[9] or around 5-10 cases per year per million population as defined by the Delhi Cancer Registry.[9]

The safe and effective treatment of CML with IM has been highlighted by the ever increasing number of abstracts and papers by pediatricians working even in developing nations like Turkey and Iran.

Pediatric CML seen in the tertiary care centers in Delhi and vellore often have been treated successfully with IM (personal communication). An Indian study in adult patients by Deshmukh et al[10] from Tata Memorial Hospital reported that 23.3% of 174 patients with CML in various phases achieved MCR after treatment with IM.

Table. Dose adjustments for neutropenia and thrombocytopenia

Chronic phase CML (starting dose 400 mg)	ANC $<1.0 \times 10^9$/L and/or platelets $<50 \times 10^9$/L	1. Stop IM until ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L 2. Resume treatment with IM at dose of 400 mg 3. If recurrence of ANC $<1.0 \times 10^9$/L and/or platelets $<50 \times 10^9$/L, repeat step 1 and resume IM at reduced dose of 300 mg
Accelerated phase CML and blast crisis (starting dose 600 mg)	ANC $<0.5 \times 10^9$/L and/or platelets $<10 \times 10^9$/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of IM to 400 mg 3. If cytopenia persists for 2 weeks reduce further to 300 mg 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop IM until ANC $\geq 1 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and then resume treatment at 300 mg

In one study, IM was used in lymphoid blast crisis in CML in a child aged 12 years and CHR and MCR were achieved after 6 weeks of chemotherapy (personal communication). To determine the optimal dose, dose limiting toxicities and pharmacokinetics of IM in children with refractory or recurrent Philadelphia chromosome positive (Ph^+) leukemia, Champagne et al[6] studied children on IM. Oral IM was well tolerated at doses ranging from 260 to 570 mg/m^2. Doses ranging from 260 to 340 mg/m^2 provided systemic exposure similar to those for adult patients who were treated with daily doses of 400-600 mg/m^2, respectively. Pharmacokinetic analysis showed marked variability of parameters in patients. A pediatric patient with atypical CML who had been treated successfully achieved cytogenetic and molecular remission with IM.[11] The Memorial-Sloan Kettering Cancer Center at New York has also reported IM in the treatment of Philadelphia-chromosome positive leukemia in children aged 20 months to 12 years. IM was found effective in inducing undetectable residual disease in a small cohort of pediatric patients.[12]

A survey conducted by Children's Oncology Group to determine contemporary view on the use of IM in children among hemato-oncologists and hematopoietic stem cell transplant physicians[13] revealed that when the child was newly diagnosed with CML in chronic phase and had a human leukocyte antigen (HLA)-matched related donor, 60% of the hemato-oncologists would propose the use of IM prior to hematopoietic stem cell transplant. If there was a HLA-matched-unrelated donor, the hemato-oncologists proposed to use IM in 91% of the cases. If there was a newly diagnosed case of CML in chronic phase with only unrelated donor, again the hemato-oncologists would expect to see response to IM in 60% of the cases. Therefore, there is an increased preference to the use of IM in both adults and children, as it is a relatively non-toxic drug. The effectiveness of IM is also equally good, but the durability of the long-term results in the treatment of CML remains unknown.

Studies in adults

Since the USA's FDA approval of IM, IM has been used extensively in adults. The trials of IM in adults have gone through Phases I, II and III, and they have shown excellent survivals.[14,15]

The British Society for Hematology believed that imatinib mesylate should be broadly prescribed by UK hematologists as it is a highly effective agent in the treatment of CML. IM is indicated for the following CML patients:[7] newly diagnosed patients with CML; those who are intolerant to IFN; those who achieved hematological control but without a major cytogenetic response after one year treatment with IFN; patients with increased Ph^+ metaphases after treatment with IFN; patients in accelerated or blast transformation phases should be given IM until further progression.

Other uses of IM

Maki[16] used IM for innovative systemic therapy for sarcomas. IM has marked effect on gastrointestinal stromal tumor and leiomyosarcoma.[17] It is also used in the treatment of clonal eosinophilic disorders including systemic mastocystosis,[18] idiopathic hypereosinophilic syndrome,[19] and advanced myelofibrosis.[20] IM can reduce CML-associated bone marrow fibrosis.[21]

Funding: None.
Ethical approval: Not needed.
Competing interest: None declared.
Contributors: TV and SR wrote the manuscript. TV is the guarantor of the article.

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Received December 18, 2006
Accepted after revision March 31, 2007