Imatinib Mesylate: A Designer Drug

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Abstract
Molecularly targeted therapy is a novel approach in cancer treatment. Imatinib, a specific tyrosine kinase inhibitor, since its inception in 1990s, has become the first-line drug in management of chronic myelogenous leukemia (CML) chronic phase. It has also shown promising results in treatment of gastrointestinal stromal tumors, clonal eosinophilic disorders and Philadelphia chromosome positive acute lymphatic leukemia. The efficacy of imatinib has geared up further research into development of designer drugs with molecular targets. This review gives a comprehensive description of the development, biology, utility, dosing, and limitations of imatinib mesylate.

INTRODUCTION
Several drugs have been used to treat chronic myelogenous leukemia (CML) including cytotoxic drugs such as busulfan, hydroxyurea, and cytosine arabinoside (ara-C). Treatment of CML is difficult, especially in the accelerated phase and blast crises. Imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, produces high response rates in patients with CML.1,2 It has also been used in several other cancers.

HISTORY
Imatinib was identified in late 1990s. Imatinib, a 2-phenylaminopyridine derivative, was given the name STI571 when it was under early development. STI stands for Signal Transduction Inhibitor and represents the action of the drug to inhibit enzymes called tyrosine kinase inhibitors.3 It is currently marketed its mesylate salt, imatinib mesylate. It is a new promising drug, used for targeted therapy especially in CML.

Pharmacokinetics/Metabolism: The chemical formula of imatinib is C_{29}H_{31}N_{7}O.CH_{4}SO_{3}. The bioavailability of the drug after oral administration is 98%. There is a 1.5- to three-fold drug accumulation at steady-state after once-daily dosing in CML patients.4 Metabolic degradation of imatinib occurs in the liver and main metabolite, N-demethylated derivative, is also active. Mean plasma terminal elimination half-lives were 13.5 ± 0.9 h for imatinib, 20.6 ± 1.7 h for CGP74588, N-desmethyl metabolite, in a study of the drug metabolism.5 The major route of elimination is in the bile, only a small portion is excreted in urine. Imatinib is mostly eliminated as metabolites, only 25% is eliminated unchanged.

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CLINICAL USES
Use in CML: This targets a tyrosine kinase that is the protein produced by a DNA translocation (the “Philadelphia chromosome”) that appears central to the CML disease process. There are a large number of TK enzymes in the body. Imatinib is specific for the TK domain in abl (the Abelson proto-oncogene), c-kit and PDGF-R (platelet derived growth factor receptor).4 The Philadelphia chromosome leads to a fusion protein of abl with bcr (breakpoint cluster region), termed bcr-abl. As it is a continuously active tyrosine kinase, imatinib decreases bcr-abl activity.

A phase II clinical trial was conducted in 39 Japanese patients in the first chronic phase of CML.7 Hematologic complete response was obtained in 92.3% of the patients, complete cytogenetic response (CR) was obtained in 43.6%, and major partial CR was obtained in 20.5% of the patients. Although 29 of 39 patients required an adjustment of dosing because of grade 3 or 4 adverse events, most of the events were reversible.

Imatinib has passed through Phase III trials for CML, and has been shown to be more effective than the previous standard treatment of interferon-alpha and cytosine arabinoside. In a study by O’Brien et al.,8 the response to imatinib alone versus interferon-alpha combined with low-dose cytarabine was compared (553 patients in each group). At 18 months, the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 96.7 percent in the imatinib group and 91.5 percent in the combination-therapy group (P<0.001). Imatinib was better tolerated than combination therapy. The US FDA has approved imatinib for first line treatment of CML.9

Imatinib has been found to be effective even in patients presenting in blast crises though less effective than in
chronic phase CML. In a recent Indian report, 174 patients in chronic phase received imatinib mesylate in the dose of 400 mg daily, while those in accelerated phase and blast crisis received 600 to 800 mg daily. Of the 97 patients with chronic phase, 49 patients (50.5%) achieved a major (major + complete) cytogenetic response. Of the 47 patients in accelerated phase, 10 patients (21.3%) achieved a major cytogenetic response and in 30 patients with blast crisis, 7 (23.3%) achieved a major cytogenetic response.

In cost effectiveness analysis, in most cases, imatinib was both less costly and more efficacious than BMT in the 2-year treatment of Ph [+ ] CML. Previously established poor prognostic significance of marrow fibrosis in CML is less relevant with imatinib therapy. Data on treatment of CML with imatinib in pediatric patients is limited. HLA-matched myeloablative transplantation offers a high rate of cure in the pediatric population.

Use in gastrointestinal stromal tumors (GISTS): Gastrointestinal stromal tumor (GIST) is a neoplasm of the gastrointestinal tract, mesentery, or omentum that expresses the protein-tyrosine kinase KIT. Most small GISTs (<5 cm and especially <2 cm) with low rate of mitosis (<5 dividing cells per 50 high-power fields) are benign and—after surgery—do not require adjuvant therapy. The 5-year survival rate ranges from 50% to 65% after complete resection of a localized primary GIST. Larger GISTs (>5 cm), and especially when the cell division rate is high (>6 mitosis/50 HPF), may disseminate and/or recur. Until recently, advanced GISTs were notorious for being resistant to chemotherapy, with a treatment success rate of <5%. Recently, imatinib, also a c-kit tyrosine kinase inhibitor is found to be useful in treating GISTS, leading to a 40-70% response rate in metastatic or inoperable cases. It has increased the 1-year survival rates in high risk GISTS to more than 90% and also improved the 5-year survival rates after surgical resection.

Ph+ ALL: This form of adult acute leukemia has worst prognosis with low responses to intensive chemotherapy and high degree of early refractory relapse. However, imatinib has been found to be a promising drug in this type of ALL. In a recent study by Lee and colleagues in 29 patients with Ph+ ALL, sequential chemotherapy and imatinib was given prior to transplantation. After a median follow-up period of 25 months, the estimated probability of disease free survival and overall survival was 78% and relapse rate was low at 4%.

Clonal eosinophilic disorders/Other cancers: Mutations involving the platelet-derived growth factor receptor genes (PDGFA and PDGFRB) have been pathogenetically linked to clonal eosinophilias, and their presence predicts complete as well as durable treatment responses to imatinib mesylate. These disorders include systemic mastocytosis, chronic eosinophilic leukemia, chronic myelomonocytic leukemia, and atypical chronic myeloproliferative disorder. Presence of either PDGFA or PDGFRB mutations warrants the use of imatinib in clonal eosinophilia. In HES, prednisone, hydroxyurea, and interferon-alpha constitute first-line therapy, whereas imatinib, cladribine, and monoclonal antibodies to either interleukin-5 (mepolizumab) or CD52 (alemtuzumab) are considered investigational.

Imatinib is under trial for use in some other malignancies. In a case of chronic neutrophilic leukemia, after failure of alpha interferon and hydroxyurea therapy, a durable and complete clinical and cytogenetic remission was induced by imatinib at dose of 400 mg daily. Imatinib in combination with hydroxyurea shows promise as therapy for grade IV progressive glioblastoma multiforme (GBM). Patients experiencing response or stable disease yielded a combined clinical benefit rate of 57%.

Preparations and storage

The approximate cost of strip of 10 capsules/tablets is Rs 600-1000. The tablets are stored at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). They should be protected from moisture.

Precautions

This medication is not recommended for use during pregnancy. It is not known whether this drug passes into breast milk. Because of the potential risk to the infant, breast-feeding is not recommended while using this drug. Patients on this drug should avoid activities such as contact sports to minimise the risk of getting cut, bruised or injured and maintain good personal hygiene.

The drugs that may necessitate dosage adjustment or special monitoring during treatment with imatinib include antifungals like itraconazole or ketoconazole; antibiotics like clarithromycin, erythromycin or troleandomycin; rifampicin/ rifabutin; prednisolone and dexamethasone; anticonvulsants like phenytoin, carbamazepine, clonazepam, or phenobarbital; antihypertensives like nifedipine, amlodipine, felodipine, isradipine, nimodipine; anti-anxiety agents like alprazolam, diazepam, or triazolam; cholesterol-lowering drugs like lovastatin, atorvastatin, or simvastatin and cyclosporin, pimozide, warfarin etc.

**Dosage And Administration**

The recommended dose of imatinib mesylate is 400 mg/day for adult patients in CML chronic phase and 600 mg/day for CML accelerated phase/blast crisis. For children with Ph+ chronic phase CML, recurrent after transplantation or who are resistant to interferon-alpha therapy, the recommended dose is 260 mg/m²/day. For gastrointestinal stromal tumors, the recommended dose is 400 mg/day or 600 mg/day for adults with unresectable and/or metastatic, malignant GISTs. The dose...
should be given with large glass of water. In children once daily dose may be given or split into two. If patient is unable to swallow the tablets, these may be dissolved in water or apple juice (50-100ml). There is limited experience in children less than 3 years age, and should be avoided at this young age.

In adult CML cases, the dose may be increased/doubled in the absence of severe adverse events and severe non-leukemia related neutropenia/thrombocytopenia in the following circumstances: progression of disease (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of therapy; or cytogenetic response after 6-12 months of therapy; or loss of an earlier hematologic or cytogenetic response. In children, dose may be increased to 340 mg/m²/day, if clinically indicated. Patients on high doses of imatinib can develop increased iron levels and other exogenous sources should be limited.

Side effects of imatinib therapy: The commoner side effects are listed in Table 1. The patient should be told to contact the physician in the event of fever, cough, sore throat, burning micturition, breathlessness or bleeding manifestations. Lokeshwar et al. reported a 46-year-old woman with chronic phase CML, treated with imatinib who developed severe pancytopenia associated with fever, chest infection and bleeding after 6 weeks of therapy. A BM biopsy revealed hypoplasia (BM cellularity < 5%). She died of pulmonary mucormycosis. Dermatological toxicity from imatinib use has been reported in an Indian study.

In event of toxicity, dose adjustment or temporary stoppage of therapy may be needed. If a severe non-hematologic adverse event develops (such as severe hepatotoxicity or severe fluid retention), imatinib should be withheld until the event has resolved. If elevations in serum bilirubin >3 times upper limit of normal (ULN) or in hepatic transaminases >5 times ULN occur, imatinib should be withheld until bilirubin values have returned to <1.5 x ULN and transaminase levels to <2.5 x ULN. If ANC is <1.0 x 10⁹/L and/or platelets is <50 x 10⁹/L, stop imatinib until ANC ≥1.5 x 10⁹/L and platelets ≥75 x 10⁹/L. If recurrence occurs, stop and resume at reduced dose. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop imatinib until ANC ≥1 x 10⁹/L and platelets ≥20 x 10⁹/L and then resume at 300 mg daily dose.

Resistance to imatinib and other tyrosine kinase inhibitors: Resistance to imatinib has been reported. Management of resistance may include therapeutic strategies such as dose escalation to achieve individual optimal levels, combination therapy, as well as treatment interruption. PKC412 inhibitor has been found to be effective against imatinib-resistant mutants. PKC 412 is an fms-like tyrosine kinase 3 (FLT3) inhibitor. The FLT3 receptor has been identified as a potential target for therapy of acute myeloid leukemia (AML). The result of FLT3 internal tandem duplication (ITD) or activating loop mutations is the constitutive activation of the kinase. Other FLT3 inhibitors include CEP 701 and SU 5416. Similarly VEGF has been implicated in tumor angiogenesis and may act through autocrine and paracrine mechanisms. The tyrosine kinase inhibitors used for VEGF inhibition include SU 5416, SU 1248, PKC 412, and PTK 787 etc. Combination of these drugs with cytoreductive chemotherapy leads to better response and decreased emergence of resistant clones. Patients who become refractory on imatinib may also respond to SU11248. In preliminary studies, the combination of rapamycin to imatinib acts synergistically to overcome moderate resistance to imatinib.

To conclude, imatinib mesylate is an example of the paradigm of successful targeted therapy through tyrosine kinase inhibition. It has convenient mode of administration and gives beneficial results in most cases, especially in CML, though its action is not limited to this disease alone. A proper follow up minimizes side effects and helps in detection of resistance to the drug. Since tyrosine kinases play critical role in neoplastic process in many human cancers, success of imatinib has instigated a tremendous effort to develop targeted PTK therapy based on the presence of over 40 chromosomal translocations that lead to deregulation of 12 different PTK associated with various hematologic malignancies.

Table 1: The side effects/adverse reactions noted on imatinib therapy for cancer

<table>
<thead>
<tr>
<th>More Common Side Effects</th>
<th>Less Common Side Effects</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>Heartburn/dyspepsia</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Weight gain</td>
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<tr>
<td>Swelling around the eyes or feet (edema)</td>
<td>Itching</td>
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<tr>
<td>Muscle cramps</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Constipation</td>
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<tr>
<td>Low platelet with increased bleeding risk</td>
<td>Low blood level of potassium</td>
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<tr>
<td>Low WBC count with increased infection risk</td>
<td>Fluid in the lining of the lungs</td>
</tr>
<tr>
<td>Muscle aches and pains</td>
<td>(pleural effusion), heart (pericardial effusion), or abdomen (ascites)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Pancreatitis</td>
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<tr>
<td>Tiredness (fatigue)</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Joint and bone pain</td>
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<tr>
<td>Abdominal pain</td>
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</tbody>
</table>

Note: liver damage has been rarely reported.

REFERENCES

30. Dengler J, von Bubnoff N, Decker T, Peschel C, Duyster J. Combination of imatinib with rapamycin or RAD001 acts synergistically only in Bcr-Ab1-positive cells with moderate resistance to imatinib. Leukemia 2005; (Epub ahead of print).