KATHY WILKINSON, RN, BSN, OCN®
ASSOCIATE EDITOR

Imatinib Mesylate

Monica P. Davey, RN, BSN, MEd, MBA

Drug name: Imatinib mesylate, formerly known as STI571, is manufactured as Gleevec™ (Novartis Pharmaceuticals Corporation, East Hanover, NJ).

Classification: Imatinib mesylate is a protein-tyrosine kinase inhibitor.

Indications: Imatinib mesylate is indicated in the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, the accelerated phase of disease, or in the chronic phase of disease after not responding to interferon-alpha therapy. Studies are being conducted to evaluate the drug in treating gastrointestinal (GI) stromal tumors (GIST, a form of sarcoma), small-cell lung cancer, prostate cancer, and glioblastoma.

Action: The translocation of genetic material between chromosomes 9 and 22 results in the formation of the Philadelphia chromosome, which is characterized by the creation of the BCR-ABL gene. This gene is transcribed into a protein with tyrosine kinase activity and causes abnormal cellular reproduction. Imatinib mesylate interferes with cellular proliferation and induces apoptosis of BCR-ABL cells. Also, in vitro, it interferes with the receptor tyrosine kinases for platelet-derived growth factor (PDGF), stem cell factor (SCF), and c-Kit and inhibits PDGF- and SCF-mediated cellular activity.

Metabolism: The major enzyme responsible for metabolism is CYP3A4. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism.

Excretion: Elimination is predominately in the feces, mostly as metabolites, with approximately 81% of the drug eliminated within seven days.

Half-life: The half-life of imatinib mesylate is approximately 18–22 hours.

Effect on blood counts: Neutropenia and thrombocytopenia are side effects of imatinib mesylate, and the frequency at which they occur is related to the stage of disease being treated. They are seen more frequently in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. Cytopenias also occur at a higher frequency at higher doses. Dose reduction or interruption is effective in managing most cases of cytopenia, and permanent discontinuation of drug therapy rarely is needed. The median duration of the neutropenic episodes is two to three weeks, and the median duration for thrombocytopenic episodes is three to four weeks (see Table 1 for recommended dose adjustments).

Adverse reactions and effects: Common drug-related adverse events include edema, elevation of liver function studies, muscle cramps, and GI irritation. Edema usually occurs in the periorbital area or lower limbs and is managed by holding the drug for two to three days, reducing the dose of the drug, or administering diuretics. Pleural effusion, ascites, pulmonary edema, and rapid weight gain with or without superficial edema have been reported. Fluid retention may be dose related, because it occurs more often at doses of 600 mg/day or more, or related to other factors; it occurs more frequently in patients in blast crisis and the elderly. Additionally, women report a slightly higher frequency of periorbital edema, headache, and fatigue than men. In clinical trials, the frequency of severe edema was 1%–5%.

Elevation of serum transaminase or bilirubin levels may occur and usually is managed with dose reduction or interruption of treatment. The median duration of these episodes is approximately one week. Treatment discontinuation may be necessary. In clinical trials, one patient who had been taking acetaminophen regularly for fever died of acute liver failure.

Muscle cramps, myalgias, arthralgias, musculoskeletal pain, and fatigue have been reported and are managed symptomatically. GI irritation in the form of nausea, vomiting, dyspepsia, and diarrhea sometimes occurs and is minimized if the drug is taken with food and a large glass of water. Skin rash with or without pruritis or pustules has been reported.

Interactions: The human P_{450} enzyme that metabolizes imatinib mesylate is CYP3A4. Therefore, caution is recommended when administering imatinib mesylate with inhibitors of the CYP3A4 family, as they may increase plasma imatinib mesylate concentrations. Substances that induce CYP3A4 activity may increase metabolism and decrease imatinib mesylate concentrations. Other drugs may have their plasma concentration levels altered by imatinib mesylate administration because imatinib mesylate is a competitive inhibitor of the CYP209 and CYP2D6 enzymes. Therefore, caution is recommended when administering drugs with these CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine). Imatinib mesylate may increase the concentration of other CYP3A4 metabolized drugs (see Table 2). Because warfarin is metabolized by enzyme CYP2C9, patients who require anticoagulation should receive low-molecular weight or standard heparin. Patients receiving imatinib mesylate also should refrain from taking acetaminophen because of the potential for liver failure, which was observed in one patient during clinical trials of the drug.

Route and dosage: The recommended dosage of imatinib mesylate is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The prescribed dose is administered orally, once daily with a meal and a large glass of water. The drug should not be taken with grapefruit or grapefruit-containing products or caffeine-containing products (these products also should be avoided for one hour before and after taking the drug). Patients should remain upright for one hour after drug ingestion.

Treatment with imatinib mesylate continues as long as the patient continues to benefit. The dose may be increased from 400 mg to 600 mg in patients with chronic phase disease or from 600 mg to 800 mg (given 400 mg twice daily) in patients in accelerated phase or blast crisis in the absence of

Monica P. Davey, RN, BSN, MEd, MBA, is a clinical research coordinator at the Fox Chase Cancer Center in Philadelphia, PA. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing *or the Oncology Nursing Society.*

Digital Object Identifier: 10.1188/02.CJON.118-120