Nursing Implications of Imatinib as Molecularly Targeted Therapy for Gastrointestinal Stromal Tumors

Jeanne M. Griffin, APRN, BC, MSN, OCN®, Myra St. Amand, RN, BSN, OCN®, and George D. Demetri, MD

T he scientific understanding and diagnosis of gastrointestinal stromal tumors (GISTs), a type of soft-tissue sarcoma, have increased dramatically in recent years. This research has translated into a molecular approach to anticancer therapy that has significantly altered the management of this challenging and often fatal cancer (Demetri et al., 2002). Before 2000, surgical resection was the only effective treatment option for GIST and no effective treatment had been found for patients with inoperable advanced or metastatic disease. Significant tumor regressions in GIST, long-term control of the cancer with prolongation of survival, and meaningful relief from the symptoms of advanced disease have been obtained with the oral drug imatinib mesylate (imatinib), known as Gleevec® in the United States and Glivec® in the rest of the world. Imatinib, produced by Novartis Pharmaceuticals in East Hanover, NJ, was called STI571 during research testing, (Demetri et al.; van Oosterom et al., 2001). Imatinib, which initially gained attention as a highly effective oral therapy for chronic myeloid leukemia (CML), now is approved to treat inoperable and/or metastatic GIST and presently is being tested in neoadjuvant and adjuvant settings for the management of GIST in its earlier stages.

Gastrointestinal stromal tumor (GIST), a form of soft-tissue sarcoma, is the most common noncarcinomatous tumor of the gastrointestinal tract. Despite its high incidence of recurrence, the malignant potential of GIST has been under-recognized. Advances in diagnostic technology since 2000 have led to increased diagnoses of GIST, suggesting that GIST is more common than previously suspected. Historically, the only treatment for GIST was surgical resection, but recent advances in the understanding of the pathogenesis of the disease have led to the development of a new treatment. A key factor in the growth and survival of cancerous GIST cells is the uncontrolled activation of a signaling enzyme known as KIT, a receptor tyrosine kinase, which becomes locked in an activated state. The abnormal signaling from the overactive KIT enzyme causes GIST cells to survive and proliferate uncontrollably. Imatinib mesylate is an oral drug designed to inhibit the kinase enzyme activity of KIT. Imatinib has been proven in several clinical trials to be effective against GIST and is currently the first-line medical therapy for malignant metastatic or recurrent GIST. Imatinib is administered as an outpatient oral drug and warrants nursing management with particular attention to potential side effects, significant drug interactions, monitoring, and patient education. This article—based on published trials and clinical experience—summarizes the nursing implications, clinical efficacy, and safety of imatinib as an effective and rationally targeted treatment for GIST.

Several factors influence nursing management of patients with GIST, including the high likelihood of disease recurrence, the need for long-term therapy of advanced disease stages, and...
the possibility of side effects with imatinib therapy. Care of patients with GIST must encompass clinical management, educational reinforcement, and long-term monitoring, and close attention must be paid to the psychosocial components of patients’ quality of life. This article is intended to assist nurses in meeting this challenge by providing a succinct overview of the key clinical features of GIST. The development of and clinical results obtained with imatinib for GIST therapy also are summarized. Nursing implications of GIST therapy are discussed based on the experience gained from several clinical trials performed at the authors’ institution, and a representative case study of the first patient with GIST to be treated with imatinib in the United States is presented.

Gastrointestinal Stromal Tumors

Pathogenesis and Epidemiology

GIST is a form of soft-tissue sarcoma that can occur anywhere along the gastrointestinal (GI) tract (see Table 1) and is the most common noncarcinomatous malignancy of the GI tract. The incidence and malignant potential of GIST are likely to be greater than previously suspected because GIST often was misidentified before the advent of a specific diagnostic marker (Miettinen & Lasota, 2001).

Increased understanding of GIST at the molecular level has led to improvements in the diagnosis and treatment of the disease. The majority of GIST cells expresses the KIT tyrosine kinase. KIT has a role in normal physiologic processes, such as hemotpoiesis, and in the growth and development of mast cells and interstitial cells of Cajal (ICC) (Heinrich et al., 2000). ICCs originate from mesenchymal cell progenitors and share features with GIST cells, including KIT expression (Kindblom, Remotti, Aldenborg, & Meis-Kindblom, 1998).

Most GISTs are characterized by abnormal activation of KIT (Hirota et al., 1998; Rubin et al., 2001), which promotes uncontrolled cell proliferation and prevents programmed cell death (apoptosis). KIT is encoded by the KIT proto-oncogene, and gain-of-function mutations in KIT (Fletcher et al., 2002; Miettinen, Majidi, & Lasota, 2002) lead to continuous unregulated activation of KIT (Hirota et al.; Lux et al., 2000; Rubin et al., 2001; Tuvesson et al., 2001). Mutated KIT has been found in approximately 90% of metastatic GISTs, but mutations have been reported in GISTs of all stages, even those thought to be benign (Andersson et al., 2002; Corless, McGreevey, Haley, Town, & Heinrich, 2002; Rubin et al., 2001). New treatments for GIST focus on inhibiting the excessive kinase activity of the KIT signaling enzyme.

Presentation and Prognosis

Fifty percent of patients with GIST present with large tumors and metastatic disease (Kindblom et al., 2002; Miettinen et al., 2001). Small GISTs often are found incidentally during surgery, endoscopy, digital rectal examination, or autopsy. Common signs and symptoms associated with GISTs include abdominal discomfort or pain, a sensation of abdominal fullness, nausea, vomiting, anorexia, weight loss, and urinary problems (Blanke, Eisenberg, & Heinrich, 2001; Crosby et al., 2001; Joensuu et al., 2002; Judson, 2002; Miettinen & Lasota, 2001). Some GISTs are detected as palpable abdominal masses, and GI tract bleeding frequently is the first sign of a GIST. Slow tumor bleeding can cause anemia and related symptoms, such as pallor, weakness, and fatigue (Joensuu et al., 2002). Forty percent of patients present with acute hemorrhage in the intestinal tract or peritoneal cavity from tumor rupture and tissue perforation (George & Desai, 2002). GISTs also can cause altered bowel function, bowel obstruction or perforation, dysphagia, jaundice, and fever (Joensuu et al., 2002).

All GISTs should be regarded as having some degree of malignant potential and be classified as low, intermediate, or high risk, rather than as malignant or benign (Fletcher et al., 2002; Judson, 2002). GISTs that are most likely to be malignant have increased mitotic activity (>5 mitoses per 50 high-power fields [HPFs] and larger tumor size [>5 cm]). Singer et al. (2002) found that spindle-cell histology and a lesser degree of mitotic activity (<3 mitoses per 30 HPFs) are two prominent, independent prognostic factors favoring recurrence-free survival in patients with GIST. GISTs located in the esophagus, lower intestinal tract, omentum, or mesentery (Fletcher et al.; Miettinen, Majidi, et al., 2002) are associated with a poorer prognosis than those arising in the stomach (Joensuu et al., 2002).

The five-year survival rates for patients with primary malignant GISTs vary widely and have been reported to be 28%–60% (Joensuu et al., 2002). Among patients undergoing surgery for GIST (including resection of primary and recurrent disease), approximately 35%–65% are alive five years postsurgery; survival rates associated with recurrent disease are at the lower end of the range, and metastatic disease typically leads to death within two years of diagnosis of metastasis (Roberts & Eisenberg, 2002). The median survival time for patients with primary GIST is approximately 60 months (DeMatteo et al., 2000). Before the availability of effective, molecularly targeted drug therapy, median survival was 9–23 months for patients with metastatic and/or recurrent GIST (DeMatteo et al., 2000).

Diagnosis and Treatment

KIT expression in GISTs can be identified by antibodies to the CD117 antigen, which is currently a diagnostic marker for GIST (Fletcher et al., 2002; Miettinen, El-Rifai, Sobin, & Lasota, 2002). Positive CD117 staining, in conjunction with tissue that exhibits characteristic GIST histologic features, such as spindle-cell or epithelioid morphology, confirms the GIST diagnosis (Fletcher et al.). This testing should be performed for all mesenchymal tumors of the GI tract, omentum, and mesenteries; for spindle-cell and epithelioid tumors of the liver; and for unclassified abdominal tumors of unknown origin (Miettinen, El-Rifai, et al.). Clinicians must recognize that occasionally any test

---

**Table 1. Gastrointestinal Stromal Tumor in Depth**

<table>
<thead>
<tr>
<th>GIST Overview</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of GIST in population</td>
<td>–</td>
</tr>
<tr>
<td>1–2 per 100,000; slight preponderance in males</td>
<td>–</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>–</td>
</tr>
<tr>
<td>Median = 60</td>
<td>–</td>
</tr>
<tr>
<td>Range = 16–94</td>
<td>–</td>
</tr>
<tr>
<td>Frequency of GIST among tumors</td>
<td>–</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>5–6</td>
</tr>
<tr>
<td>Gastrointestinal mesenchymal tumors</td>
<td>80</td>
</tr>
<tr>
<td>Anatomical location of GISTs</td>
<td>–</td>
</tr>
<tr>
<td>Stomach</td>
<td>70</td>
</tr>
<tr>
<td>Small intestine</td>
<td>20–40</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>5–15</td>
</tr>
<tr>
<td>Esophagus</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Omentum</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Mesentery and peritoneum</td>
<td>Very rarely</td>
</tr>
<tr>
<td>Disease status at presentation</td>
<td>–</td>
</tr>
<tr>
<td>Primary</td>
<td>46</td>
</tr>
<tr>
<td>Metastatic</td>
<td>47</td>
</tr>
<tr>
<td>Locally recurrent</td>
<td>7</td>
</tr>
</tbody>
</table>

GIST—gastrointestinal stromal tumor

Note. Based on information from Blanke et al., 2001; DeMatteo et al., 2000; Joensuu et al., 2002; Miettinen & Lasota, 2001.
Imatinib inhibits the activity of these protein tyrosine kinases by binding to their kinase domain, thereby inhibiting signaling activity within malignant cells and promoting cell death (Savage & Antman, 2002).

Identification of the molecular cause of CML provided the conceptual underpinnings for this therapeutic approach. CML is caused by the activation of an intracellular protein tyrosine kinase, Bcr-Abl (Daley, Van Etten, & Baltimore, 1990; Rowley, 1973). Inhibition of Bcr-Abl tyrosine kinase activity by imatinib has been shown to be effective and well tolerated and lead to an improved quality of life in the treatment of CML. Imatinib currently is indicated for all phases of CML and is the pharmacotherapy of choice for the disease (Hahn et al., 2003; O’Brien, Guilhot, et al., 2003; Peggs & Mackinnon, 2003).

Results from trials with patients with CML and experiments in vitro showed that anti-proliferative and apoptotic effects of imatinib on GIST cells provided the rationale for using imatinib as a potential treatment for GIST (Demetri et al., 2002; Heinrich et al., 2000; Tuveson et al., 2001).

Clinical Experience With Imatinib

The success of a single-patient, proof-of-concept trial prompted the initiation of formal clinical testing of imatinib in patients with advanced GIST (Joensuu et al., 2001). Imatinib doses up to 400 mg twice daily were well tolerated in the phase I dose-finding study conducted at three centers of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. High objective response rates were achieved in phase I trials (see Table 2) (van Oosterom et al., 2001, 2002).

Imatinib demonstrated efficacy for GIST in a phase II, open-label, randomized trial that enrolled 147 patients with advanced GIST at four centers—one in Finland and three in the United States (Blanke et al., 2004; Demetri et al., 2002).

Based on these clinical data, imatinib now is approved for treatment of KIT-positive, unresectable and metastatic malignant GIST. Imatinib is the first-line therapeutic option for advanced disease (DeMatteo et al., 2002; Novartis Pharmaceuticals, 2004), and its use as a neoadjuvant or adjuvant therapy along with surgery is under active investigation in several clinical research studies. The drug also has shown efficacy in other investigative trials for neoplastic and myeloproliferative diseases (Cools et al., 2003; Rubin et al., 2002).

Pharmacokinetics

Imatinib is a well-absorbed, oral, bioavailable agent that exerts its optimal therapeutic effects at serum concentrations greater than 1 mcmol (Buchdunger et al., 2000). Therapeutic concentrations generally are achieved with doses of at least 400 mg daily (Druker et al., 2001). The half-life of imatinib is approximately 18–20 hours, allowing for once-daily administration at the approved dose of 400–600 mg (Dagher et al., 2002; Demetri et al., 2002). Imatinib is metabolized by cytochrome P450 (CYP) isoenzymes, primarily CYP3A4 in the liver (Dagher et al.; Novartis Pharmaceuticals, 2004). Imatinib is eliminated as metabolites in feces; approximately 81% of the drug is eliminated within seven days (Novartis Pharmaceuticals).

Tolerability

As with most treatments for cancer, the benefits of imatinib are accompanied by occasional adverse effects that must be managed to improve patients’ quality of life and promote adherence to therapy. Adverse effects in patients receiving imatinib typically have been mild to moderate in severity (grade 1 or 2), are dose-related, and often diminish over time with continued use (Demetri et al., 2002; Joensuu et al., 2002). Side effects usually can be managed without dosage reduction or permanent discontinuation of therapy (Joensuu et al., 2002). The most frequently occurring adverse effects include GI reactions (e.g., nausea, vomiting, diarrhea), edema, abdominal pain, muscle cramps, and rash (Dagher et al., 2002; Demetri et al.; Hensley & Ford, 2003). Hematologic abnormalities have been uncommon in patients treated with imatinib for GIST (van Oosterom et al., 2001).

In the phase II study in the United States and Finland, most patients experienced some mild or moderate adverse effects that might have been related to imatinib therapy, but as in the other trials of imatinib, the drug was well tolerated overall (Demetri et al., 2002). In the study, the most serious adverse event was GI or intra-abdominal hemorrhage, which occurred in seven patients (5%) with large, bulky tumors (Demetri et al.). This bleeding probably was caused by imatinib-induced tumor degeneration and was not related directly to irritation of the GI tract, nor did these patients exhibit thrombocytopenia. Adverse events were similar among patients receiving 400 mg or 600 mg daily, men and women, and patients younger or older than age 65 (Demetri et al.).
TABLE 2. IMATINIB MESYLATE FOR TREATMENT OF ADVANCED MALIGNANT GASTROINTESTINAL STROMAL TUMORS: EFFICACY IN CLINICAL STUDIES

<table>
<thead>
<tr>
<th>Phase I (EORTC Study)</th>
<th>Phase II (U.S.-Finland Study)</th>
<th>Medium 34-Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>300–600 mg per day</td>
<td>400 mg per day</td>
<td>600 mg per day</td>
</tr>
<tr>
<td>(N = 35)</td>
<td>(N = 73)</td>
<td>(N = 74)</td>
</tr>
</tbody>
</table>

**Patient Response**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>19</td>
<td>54*</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>NR</td>
<td>–</td>
</tr>
</tbody>
</table>

*Confirmed partial response

**Note.** Based on information from Blanke et al., 2004; van Oosterom et al., 2002.

**Nursing Implications**

**Dosing and Administration**

The most prominent nursing issue concerning imatinib dosing for GIST is that the therapy is long term. Over the course of several months to years of therapy, patients may need to increase dosage because of disease progression, briefly interrupt administration to resolve side effects, or decrease dosage. Encouraging patients to continue medication as long as clinical improvement or disease control occurs is critical.

The U.S. Food and Drug Administration approved dosages of imatinib for patients with GIST at either 400 mg or 600 mg daily, but doses lower than 400 mg per day are not recommended (Druker et al., 2001). Imatinib should not be discontinued permanently because of side effects without first attempting to manage them with optimal supportive treatments or, as a last resort, to lower the dosage to mitigate the rare case of intolerable symptoms. An initial imatinib dosage of 400 mg per day can be increased to 600 mg per day if disease progression occurs. In the U.S.-Finland study, three of nine patients with evidence of disease progression who had crossed over from the 400 mg to the 600 mg arm achieved either a sustained partial response or stable disease at the higher dosage (Demetri et al., 2002).

When first approved, imatinib was available as a 100 mg hard gel capsule, which required patients to take a minimum of four large capsules per day to attain therapeutic concentrations. In early 2003, the U.S. Food and Drug Administration approved two new dosage forms—400 mg film-coated tablets and 100 mg scored film-coated tablets. Concerns about patient convenience, the risk of underdosing, and potential problems with long-term compliance using multiple daily capsules prompted the development of the 400 mg tablet. Although the two dosage forms of imatinib are the same color, the 400 mg tablet is oblong, whereas the 100 mg tablet is round. Patients should be alerted to this shape difference to avoid accidental overdosing. The scored 100 mg tablet allows for greater flexibility in achieving optimal therapeutic dosing, particularly in pediatric patients. These new dose forms became available in the United States in July 2003. Approval in Europe and Japan is expected. Imatinib should be stored at room temperature.

**Contraindications and Interactions**

The potential interactions of imatinib with other therapeutic drugs are another important aspect of nursing management of GIST. Imatinib is contraindicated in patients with hypersensitivity to the drug or any of its components (Novartis Pharmaceuticals, 2004). Caution is recommended when initiating imatinib therapy in patients with myelosuppression, infection, hepatic or renal function impairment, GI disorders, or risk factors for fluid retention or edema.

Consideration must be given to potential drug interactions during therapy with imatinib (Novartis Pharmaceuticals, 2004) (see Figure 1). Inhibitors, inducers, or substrates of CYP3A4 and other CYP isoenzymes may alter plasma imatinib concentrations or have their plasma concentrations altered by imatinib. For example, patients treated for yeast infections may require higher doses of itraconazole or ketoconazole to achieve efficacy, and dosing with these agents also may change the biologically active levels of imatinib. Therefore, other side effects potentially could occur with coadministration, such as worsening edema. Concomitant use of imatinib and rifampicin or other potent inducers of CYP4503A may lead to subtherapeutic plasma concentrations of imatinib (Bolton et al., 2004). Conversely, administration of imatinib with simvastatin (Zocor® [Merck & Co., Inc., Whitehouse Station, NJ]), a lipid-lowering agent, can lead to a severalfold increase in exposure to simvastatin (O’Brien, Meinhardt, et al., 2003). Caution is necessary when administering imatinib with drugs that have a narrow therapeutic window and are substrates for CYP3A4 and CYP2C9. Patients requiring anticoagulants should receive low molecular weight or unfractionated heparin rather than warfarin, which is metabolized by CYP3A4 and CYP2C9 (Novartis Pharmaceuticals, 2004). Nurses should be aware of concurrent medications taken by patients treated...
with imatinib, including over-the-counter medications and herbal remedies. Also, caution regarding potential hepatotoxins (e.g., acetaminophen, ethanol) is advisable, particularly if serum transaminase levels elevate. Patients taking imatinib should not exceed the recommended daily dose of acetaminophen.

Because imatinib has been demonstrated to be teratogenic in animal models (pregnancy category D), both female and male patients taking imatinib must understand the importance of contraceptive measures (Hensley & Ford, 2003; Novartis Pharmaceuticals, 2004). Although the reproductive risk in males is not clearly defined, men should not father a child while undergoing imatinib therapy as a precautionary measure. Before imatinib therapy is initiated, consideration should be given to sperm banking if time allows and if the patient wishes. Patients also should continue to use a reliable birth control method for at least three months after discontinuing the drug for any reason. The possibility that oral contraceptive drug interactions might occur with imatinib should be considered. Women should not breast-feed while taking imatinib.

**Patient Monitoring and Intervention**

Adverse events associated with imatinib generally are moderate and most often are tolerable in light of the significant improvement of the disease for most patients with GIST. Large GISTs can be uncomfortable or painful, significantly decreasing patients’ quality of life, and the authors have seen tremendous patient benefit from disease control and dramatic improvements in patient function and quality of life.

Nausea, vomiting, dyspepsia, and diarrhea occasionally occur with imatinib treatment but can be minimized if the drug is taken with food and at least eight ounces of water. Acidic citrus products, such as grapefruit and grapefruit-containing foods, can exacerbate GI side effects; therefore, they should be avoided for one hour before and after taking imatinib (Novartis Pharmaceuticals, 2004). Grapefruit juice also is not recommended because it is a CYP3A4 inhibitor and may increase plasma imatinib concentrations. If nausea and vomiting persist, patients can try altering the time of day they take imatinib. Patients with a history of esophagitis or hiatal hernia should take imatinib at least two hours before bedtime (Deininger, O’Brien, Ford, & Drucker, 2003). The total daily dosage also can be divided into two equal doses taken with separate meals. For example, two 100 mg tablets may be taken twice daily. If patients have difficulty swallowing the tablet, imatinib can be drunk immediately after being dissolved into an eight-ounce glass of water. Finally, antiemetics, such as compazine (10 mg as needed every four to six hours), can be taken. If vomiting occurs, patients should not repeat the dose of imatinib. Loperamide is recommended for patients who experience diarrhea. An effective regimen is 4 mg initially, then 2 mg after each loose stool to a total daily maximum of 16 mg. In rare cases, proprylactic loperamide is given before imatinib. In severe cases of diarrhea, Metamucil® (Proctor & Gamble, Cincinnati, OH) taken two to three times daily can provide relief by adding bulk to chronically liquid stool.

Edema is the most commonly reported side effect of imatinib in patients with GIST and occurred in 74% of patients in the U.S.-Finland study (Demetri et al., 2002). Generally, edema is mild to moderate and superficial and occurs most often in the periorbital area or lower limbs. Ascites or pleural effusion may develop in a small percentage of patients. Rapid weight gain, with or without superficial edema, has been reported in patients taking imatinib and should be investigated, although edema associated with imatinib usually is self-limiting. Patients should weigh themselves periodically and report any weight gain of five pounds (about 2 kg) or more to their nurses and physicians. If fluid retention becomes a concern, prompt initiation of diuretic therapy or an increase in diuretic dosage should be considered. Counseling patients to limit their salt intake also is a very important part of the nursing and medical management of patients. If necessary, imatinib can be withheld for two or three days in cases of severe edema. In most cases, such a brief interruption in therapy successfully ameliorates edema, although interrupting dosing for any reason is not preferable. However, dosage reduction rarely is necessary because of edema alone.

Most cutaneous reactions related to imatinib treatment consist of a mild focal or generalized rash or dermatitis that usually is self-limiting and manageable (Deininger et al., 2003). Even if no rash occurs, skin tends to be dry and bruise easily in patients on imatinib therapy. Therefore, skin should be well moisturized to prevent further damage. Thirty-one percent of patients in the U.S.-Finland study had some degree of rash or dermatitis, but it usually was quite mild and tolerable (Demetri et al., 2002). The most common rash is characterized by maculopapular lesions, which are most prominent on the forearms, trunk, and, occasionally, the face. Pruritus is frequent (Deininger et al.). Rash is more likely to develop at higher imatinib doses and in female patients (Valeyrie et al., 2003). Severe (grade 3 or 4) exfoliative rashes are rare and were reported in about 1 of 500 patients treated with imatinib in all studies. They generally occurred early in the course of therapy (Hensley & Ford, 2003).

In patients with mild to moderate skin reactions during imatinib therapy, symptomatic management with antihistamines and topical preparations has proved effective (Deininger et al.). Topical or short-course oral glucocorticoid treatment can be used if the patient has an inadequate response to more conservative measures. Interruption of imatinib therapy as well as all other potentially causative agents is mandatory in rare cases of a very severe reaction (e.g., Stevens-Johnson syndrome) (Deininger et al.; Roujeau, 1999). In patients with no alternative treatments for GIST, reinstating imatinib by gradual dosage escalation after the resolution of severe, desquamative rashes has been possible (Deininger et al.; Rule, O’Brien, & Crossman, 2002). In general, cutaneous side effects of imatinib have been manageable across the spectrum of severity.

A few dark-skinned patients have experienced a uniform lightening of their skin tone during imatinib therapy. Counseling should prepare patients for this possible effect. Because the KIT enzyme target also is critical for development of the pigmented cells in the skin (melanocytes), skin lightening would be expected with imatinib therapy. Patients also should be counseled that they may experience some uneven tanning and should use a powerful sunblock to prevent solar damage to skin.

Myelosuppression requiring therapy is rare in patients with GIST who are treated with imatinib and is more common among those treated for CML, which suggests that the myelosuppression is related to the pathology of the disease itself. Myeloid growth factors (e.g., granulocyte–colony-stimulating factor, granulocyte macrophage–colony-stimulating factor) or erythropoietin can be given, if needed, to patients with GIST taking imatinib. Neutropenia usually can be managed with an interruption of treatment or a dosage reduction. If the absolute neutrophil count (ANC) is lower than 1 x 10^9/L, imatinib administration should be stopped temporarily until it rises to 1.5 x 10^9/L or higher. Treatment can be resumed at the original starting dosage of 400 or 600 mg per day. If the ANC again drops lower than 1 x 10^9/L, imatinib should be withdrawn until the ANC recovers, as previously, and then be reinstated at a reduced dosage (i.e., 300 mg if the starting dosage was 400 mg, or 400 mg if the starting dosage was 600
Imatinib mesylate is an oral anticancer drug that has demonstrated efficacy in the treatment of advanced GIST and works differently than traditional chemotherapy. 

Imatinib is indicated for the treatment of KIT-positive (CD117) unresectable and/or metastatic malignancy. Approved dosages of imatinib for patients with GIST are 400 mg or 600 mg daily by mouth, and use of aspirin, or activities that increase the risk of bleeding and infection (Ault, Kaled, & Rios, 2003; Campbell, 2003; Capriotti, 2002). These management strategies are based on the authors’ experience with patients with CML.

Male and female patients taking imatinib should be counseled to use reliable birth control and contraception for three months after cessation of imatinib therapy. Women taking imatinib should continue contraception for three months after cessation of imatinib therapy. Nurses should give a message of hopefulness because imatinib therapy clearly helps the majority of patients with GIST to live longer lives that offer high levels of functionality and quality time.

Nurses can assist patients encountering financial or reimbursement obstacles with obtaining an initial prescription for imatinib. The manufacturer has a comprehensive patient assistance program that ensures that underinsured, uninsured, and indigent patients are not denied imatinib therapy for economic reasons. This program helps patients to assess their own financial resources and determine their eligibility for reimbursement. For more information, patients or family members may call the U.S. information line at 877-453-3832.

Summary and Conclusion

Since the discovery of the molecular basis of GIST, much progress has been made in the diagnosis and treatment of the disease. Inhibiting KIT kinase activity with imatinib has proven, in clinical trials such as the U.S.-Finland study, to benefit patients with GIST and offer excellent tolerability. Ongoing investigations of imatinib treatment for GIST are expected to clarify key issues, such as optimal dosage and duration of treatment and the potential for neoadjuvant and adjuvant use to improve outcomes of surgery.

In essence, GIST has become a new disease entity as a result of these discoveries. More accurate diagnosis has increased the number of GIST cases identified, and GIST has become more treatable because both pharmacotherapy and surgery currently are used to combat the disease. These developments require that oncology nurses become familiar with the indications, administration, and side effects of imatinib, as well as interventions that can help optimize this therapy in patients with GIST (see Figure 2).

Author Contact: George D. Demetri, MD, can be reached at gdemetri@partners.org, with copy to editor at CJONeditor@jsobel.com.

Education

Counseling and patient education for patients with GIST are dictated because patients have metastatic or recurrent disease and are confronted with all of the psychosocial issues common to most patients with advanced cancer. Nurses are in a position to work with patients with GIST to attain maximum symptom relief, manage side effects, and provide education about medication precautions to improve patients’ quality of life.
Case Study: Imatinib Mesylate for an Advanced Gastrointestinal Stromal Tumor

A 65-year-old Caucasian woman was enrolled at the Dana-Farber Cancer Institute in Boston, MA, for the U.S.-Finland study of imatinib mesylate (then called STI571) of gastrointestinal stromal tumor (GIST). She initially had presented in June 1998 with bloating, incomplete bladder emptying, and occasional right lower-quadrant abdominal pain. She also reported rectal and vaginal bleeding and increased abdominal size and had a past medical history of diverticulitis and gastritis. Her medications were oral ranitidine and calcium. The patient’s family history included a brother with melanoma and a paternal aunt with breast cancer. The patient’s performance status score was zero, according to Eastern Cooperative Oncology Group criteria.

Abdominal ultrasonography and magnetic resonance imaging revealed a pelvic mass at the midline of the lower abdominal quadrant. A 14 × 12 × 4 cm mass was removed in September 1998. A pathology study confirmed that it was a KIT-positive GIST with negative margins. The tumor was thought to have high malignancy potential because of its size (> 10 cm) and mitotic rate (6 mitoses per 10 high-power fields).

Following surgery to remove the tumor, the patient had a lengthy postoperative course complicated by fevers and malnutrition, which required total parental nutrition. A computed tomography (CT) scan in January 1999 showed no evidence of disease. A CT scan in March 1999 showed stranding in the periceliac region, which was thought to be a postoperative change. In June 1999, a recurrent 3.5 cm mass was evident in the abdomen. The patient still felt well and was offered the option of a surgical consultation or enrollment in a clinical trial. She decided not to pursue treatment at that time.

In September 1999, the patient began to experience nausea, vomiting, and abdominal cramping, and required hospitalization. A CT scan demonstrated GIST progression. Two tumors were evident, sized 5.6 × 4.2 cm and 3 × 3.9 cm. The patient decided to receive systemic therapy. Because of evidence that conventional chemotherapy is not effective for the treatment of GIST, the patient consented to participate in a clinical trial of eceitasmidin 743 (ET743), a novel marine organism-derived cytotoxic compound with antiproliferative activity (Ryan et al., 2002). Unfortunately, her disease progressed during ET743 treatment (October–November 1999), and the masses increased to 6.1 × 4.8 cm and 5.6 × 4.2 cm. The patient was discontinued from the study.

By the end of December 1999, the masses had grown to 7.3 × 5.6 cm and 8.0 × 6.8 cm. Because of symptoms from tumor compression of the bladder, she elected to undergo standard palliative chemotherapy with gemcitabine, which appeared to slow disease progression. She was admitted to the hospital again in March 2000 with nausea, vomiting, and small-bowel obstruction. A CT scan showed progression of the tumors, which measured 8.9 × 9.9 cm and 8.2 × 8.2 cm. An exploratory laparotomy revealed disseminated unrespectable disease.

During her recovery from surgery, she became eligible to participate in the U.S.-Finland study of imatinib for the treatment of unresectable or metastatic malignant GIST expressing KIT. Her dosage of imatinib was 400 mg daily. Weekly laboratory results during the first month of therapy remained stable. A positron emission tomography (PET) scan obtained after one month of treatment showed a decrease in the size and glycolytic activity of the large pelvic mass compared with baseline levels, suggesting a therapeutic response. CT scanning showed a decrease in the large masses. The patient stated that she felt better after two weeks of treatment with imatinib, and after one month she said, “I feel like I have my life back.” Her total measurable burden of GIST lesions decreased from a cumulative total area of 346 cm² at baseline to 81.5 cm².

This patient tolerated imatinib well and remained on the 400 mg daily dosage continuously for more than two years. She experienced grade 1 adverse events related to imatinib: periorbital edema, mild alopecia, nausea, and cutaneous pruritus, which were tolerable and required no intervention except for moisturizers to relieve itchy, dry skin. This patient was treated effectively with imatinib from July 2000–January 2003, when her restaging CT and PET scans demonstrated disease progression. Despite dose escalation to 600 mg per day, her tumors continued to grow and imatinib therapy was stopped in March 2003. However, the patient entered a clinical research trial of another molecularly targeted drug and remained alive as of January 2004.

References


Rapid Recap

**Nursing Implications of Imatinib as Molecularly Targeted Therapy for Gastrointestinal Stromal Tumors**

- Oncology nurses are seeing more patients with gastrointestinal stromal tumors (GISTs) in their practices because of improved diagnostic techniques.
- A receptor tyrosine kinase, KIT, is overactivated and leads to growth and survival of GIST cells.
- A novel agent, imatinib mesylate, has demonstrated efficacy in the treatment of these tumors.