A gastrointestinal stromal tumor (GIST) is a soft tissue sarcoma that can occur anywhere along the gastrointestinal (GI) tract and is the most common noncarcinomatous malignancy of the GI tract. This article will review the pathology of GISTs, the molecular pathology related to c-kit, and disease management and will discuss a new drug approved in the management of GISTs, sunitinib malate. In addition, pharmacologic properties along with nursing considerations related to sunitinib malate will be reviewed.

**Pathology**

Cancer results from a disruption of the normal regulation of the cell cycle. When the cycle proceeds without control, cells divide without order and accumulate genetic defects that can lead to cancerous tumors (U.S. Library of Medicine, 2007). In GISTs, a specific mutation causes the proto-oncogene c-kit to be expressed constitutively. The c-kit proto-oncogene is a receptor protein tyrosine kinase whose ligand is the stem cell factor responsible for sending growth and survival signals within the cell. The mutant KIT enzyme triggers runaway growth of GIST cells. Mutated KIT has been found in approximately 90% of metastatic GISTs, but mutations have been reported in all stages, even those believed to be benign (Griffin et al., 2005). KIT expression in GISTs can be identified by antibodies to the CD117 antigen, which is a diagnostic marker (Griffin et al.). Positive CD117 staining, in conjunction with tissue that exhibits characteristic GIST histologic features (e.g., spindle cell or epithelioid morphology), confirms a GIST diagnosis (Corless, Fletcher, & Heinrich, 2004).

**At a Glance**

- Sunitinib malate is an oral multikinase inhibitor that targets several receptor tyrosine kinases.
- Oncology nurses are caring for more patients on oral targeted therapies.
- Patient education for targeted therapies should include their side effects and common interactions.
Management of Gastrointestinal Stromal Tumors

Surgery is the mainstay of therapy for patients with GISTs whose primary lesion is deemed resectable by an experienced surgical oncologist (D’Amato et al., 2005). Surgery should be approached with the intention of performing a complete en bloc removal of the tumor (R0 resection) and surrounding normal tissue, including adjacent organs if they are involved (see Figure 1). Unlike intestinal adenocarcinoma, GISTs rarely metastasize to the lymph nodes; thus, lymphadenectomy seldom is warranted (El-Zohairy, Khalil, Fakhri, El-Shahawy, & Gouda, 2005). However, surgery is not curative in many cases. Historically, the five-year survival rate ranges from 35%–65% among patients who undergo complete resection (Benjamin, Blanke, Blay, Bonvalot, & Eisenberg, 2006). Tumors recur in 40%–90% of patients despite histopathologically complete resection, and 50% of the recurrences involve the liver (El-Zohairy et al.). In one study, at a median follow-up of 24 months, 32 of 80 patients (40%) who presented with primary disease and underwent complete resection developed recurrent disease (DeMatteo, Heinrich, El-Rifai, & Demetri, 2002).

Chemotherapy and radiotherapy have shown limited activity in the treatment of GISTs. In fact, GISTs are relatively resistant to radiotherapy; however, radiotherapy occasionally has a role in the management of metastatic GISTs, particularly in controlling a hemorrhaging tumor and pain (D’Amato et al., 2005). Because radiotherapy has not been efficacious, GISTs were treated as sarcomas with cytotoxic agents such as doxorubicin and ifosfamide, even though the agents had limited activity.

Understanding that the molecular pathogenesis of GISTs is linked to deregulated KIT tyrosine kinase activity has resulted in the successful application of a novel systemic tyrosine kinase inhibitor (Benjamin et al., 2006). Unlike traditional chemotherapy, which usually is nonspecifically cytotoxic, imatinib mesylate specifically targets the underlying molecular cause of certain types of cancer (Stull, 2003). Imatinib mesylate was approved by the U.S. Food and Drug Administration (2002) in February 2002 for the treatment of unresectable or metastatic malignant GISTs that are c-kit positive and for use in patients with newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia, in blast crisis, in accelerated phase, or in a chronic phase after failing interferon alfa. Imatinib mesylate is a selective inhibitor of the kinase function of KIT, which has been proven to be highly efficacious in the treatment of GISTs (Grimpen et al., 2005).

The efficacy of imatinib mesylate has been demonstrated in several clinical trials. Demetri et al.’s (2002) open-label, randomized, multicenter, phase II study was pivotal in the approval of imatinib mesylate for GISTs. In the study, 147 patients with advanced GISTs were treated with imatinib mesylate 400 mg or 600 mg daily. At the median follow-up of 4.4 years, the combined complete and partial response rate was 68% and an additional 16% had long-term disease stability. Furthermore, von Mehren (2006) noted a 50%–96% reduction in tumor bulk—an important aspect of modern GIST therapy. The dramatic results of imatinib therapy in patients with metastatic or unresectable GISTs suggest a possible benefit in patients with GISTs who are or may become candidates for surgery (Benjamin et al., 2006). However, 5% of the patients in Demetri et al.’s study showed primary resistance to imatinib mesylate within the first two months of therapy. Longer follow-up of patients with GISTs treated with imatinib mesylate showed development of resistance to the selective kinase inhibitor, resulting in disease progression in most patients after durable initial objective response or disease stabilization. After two years of therapy, disease progression occurred in approximately 75% of patients with metastatic GISTs treated with imatinib mesylate (Demetri et al.).

In their mutational analysis of resected lesions, Grimpen et al. (2005) identified additional acquired mutations in exon 17, indicating the likely pathogenetic mechanism of resistance. In addition, exon 17 encodes for the kinase domain of KIT and a mutation causing structural alteration, preventing the binding of imatinib mesylate. Grimpen et al. also described other mutations that may cause imatinib mesylate resistance in GISTs by KIT, located on exon 9, 11, and 13. As a result of the mutations, patients eventually become refractory to imatinib mesylate.

The efficacy between a 400 mg and 800 mg dose of imatinib mesylate has been evaluated. A phase III study indicated that overall response, progression-free survival, and overall survival were similar for both doses (Rankin et al., 2004). However, imatinib mesylate should not be discontinued if a patient does not respond. The National Comprehensive Cancer Network (2006) suggested that if a response is not seen in three months or the disease progresses, an increase in the imatinib mesylate dose (to 600 mg or 800 mg) should be considered for another three to six months.

Sunitinib Malate

Because of imatinib mesylate resistance in patients with GISTs and the inactivity of chemotherapy and radiotherapy, another option is available for patients—sunitinib malate. Approved by the U.S. Food and Drug Administration in January 2006, sunitinib malate is indicated for the treatment of GISTs after disease progression or when patients become refractory to imatinib
mesylate. Sunitinib malate has a broader spectrum of kinase inhibition than imatinib mesylate and also is indicated for the treatment of advanced renal cell carcinoma (Pfizer Oncology, 2006).

Sunitinib malate was approved in the management of GISTs based on a randomized, double-blind, placebo-controlled, international, phase III trial (N = 312). The trial was unblinded early by the Data Safety and Monitoring Board at the first planned interim analysis because of a significantly prolonged median time to progression of 27.3 weeks (6.3 months) in the sunitinib malate arm versus 6.4 weeks (1.5 months) in the placebo arm. In addition, the risk of progression was reduced by 67%. Median overall survival has not been reached, and overall survival has not been determined (Pfizer Oncology, 2006).

Mechanism of Action

Sunitinib malate is an oral multikinase inhibitor that targets several receptor tyrosine kinases. Some of the receptor tyrosine kinases are involved in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Inhibiting activity against more than 80 kinases was reported. Sunitinib malate is an inhibitor of platelet-derived growth factor receptors α and β; vascular endothelial growth factor receptors 1, 2, and 3; stem cell factor receptor (KIT); FMS-like tyrosine kinase 3; colony-stimulating factor receptor type 1; and glial cell line–derived neurotrophic factor receptor (Pfizer Oncology, 2006). Thus, SU011248 (sunitinib malate’s preclinical name) is not only able to exert direct antitumor activity against tumor cells that rely on receptor tyrosine kinases for proliferation and survival, but it also is able to indirectly inhibit tumor growth by inhibiting angiogenesis (i.e., the proliferation of a network of blood vessels that penetrates into cancerous growth, supplying nutrients and oxygen and removing waste products [National Cancer Institute, 2005]) (Mendel et al., 2003). The antiangiogenic activity from sunitinib malate results from the inhibition of vascular endothelial and platelet-derived growth factors (Mendel et al.).

Pharmacokinetics

The pharmacokinetics of sunitinib malate were evaluated in 135 healthy volunteers and 266 patients with solid tumors. Maximum plasma concentrations of sunitinib malate generally are observed 6–12 hours following oral administration. Food has no effect on the bioavailability of sunitinib malate, so the agent can be taken with or without food (Pfizer Oncology, 2006).

Sunitinib malate is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is metabolized further by CYP3A4. The primary active metabolite comprises 23%–37% of the total exposure. Elimination primarily occurs via the feces; however, no clinical studies were conducted in patients with impaired renal or hepatic function. Patients were excluded from the clinical trial with sunitinib malate if alanine or aspartate aminotransferase was more than 2.5 times the upper limit of normal (ULN) or if the underlying disease was more than five times the ULN. Patients also were excluded if they had a serum creatinine of more than two times the ULN (Pfizer Oncology, 2006).

Dosage and Drug Interactions

One 50 mg oral dose of sunitinib malate is recommended daily for four weeks, followed by a rest period of two weeks (Pfizer Oncology, 2006). However, a dose reduction for sunitinib malate should be considered when coadministering with a strong CYP3A4 inhibitor, such as ketoconazole, whereas a dose increase in sunitinib malate should be considered when coadministering with a CYP3A4 inducer, such as rifampin. The dose of sunitinib malate should be reduced or increased in increments of 12.5 mg (see Figure 2). The dose can be increased up to a maximum total of 87.5 mg. Capsules are available in 12.5 mg, 25 mg, and 50 mg formulations (Pfizer Oncology).

Some herbal medications are not recommended for use with sunitinib malate, particularly St. John’s wort, which may decrease the drug’s concentrations (Pfizer Oncology, 2006). Patients should be instructed to bring a list of medications for review by the healthcare provider prior to starting therapy with sunitinib malate.

Adverse Reactions

Some of the most common emergent adverse events associated with sunitinib malate treatment are fatigue, diarrhea, nausea, vomiting, and stomatitis. Dermatologic effects also are common and include skin discoloration, possibly related to the drug’s color (yellow); dryness, thickness, and cracking of the skin; blisters; and a rash on the palms of the hands and soles of the feet. Despite the mentioned adverse reactions, sunitinib malate was well tolerated. Only 7% of patients receiving sunitinib malate discontinued therapy because of treatment-emergent nonfatal adverse reactions (Pfizer Oncology, 2006).

Contraindications

The use of sunitinib malate is contraindicated in patients with hypersensitivity to sunitinib malate or any other component of sunitinib malate (Pfizer Oncology, 2006). In addition, no adequate or well-controlled studies have evaluated the use of sunitinib malate in pregnant women; however, because angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of sunitinib malate should be expected to cause adverse effects. As
a result, women should be advised to avoid becoming pregnant while receiving sunitinib.

**Precautions**

Physicians should be cautious when administering sunitinib malate. Some patients in the phase III clinical trial with sunitinib malate experienced left ventricular dysfunction, hemorrhagic events, and hypertension. Patients should be advised of the possibility of developing the events prior to starting therapy. The precautions are similar to those for the drug bevacizumab, which also is a vascular endothelial growth factor inhibitor; therefore, the adverse events may be related to the antiangiogenic component of sunitinib malate.

Epistaxis was the most common hemorrhagic event reported, but rectal, gingival, upper GI, genital, and wound bleeding also occurred. Patients should be advised to discontinue sunitinib malate for two weeks prior to any surgical procedure. Surgery can be scheduled during the two-week off period to avoid discontinuation of the drug for an extended period.

*To assess left ventricular function, ejection fraction should be measured using a multigated angiogram or echocardiogram prior to therapy with sunitinib malate. Thirty-one of 202 patients reported hypertension of all grades while on sunitinib malate. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. For severe hypertension, sunitinib malate should be suspended temporarily until hypertension is controlled.* (Pfizer Oncology, 2006)

**Nursing Considerations**

Patient education is a priority before beginning therapy with sunitinib malate. The drug is oral and self-administered, but teaching should include proper administration, expected side effects, and side-effect management.

When discussing drug administration, patients should be aware that sunitinib malate is taken once a day with or without food for four weeks followed by a two-week rest period. Patients can be instructed to maintain a calendar so that missed or improper dosing can be avoided. However, if a dose is missed, patients should be instructed not to double the dose. They should report the missed dose to their healthcare provider and resume regular administration the following day.

Healthcare providers should obtain and review patients' medication lists prior to starting therapy to avoid drug interactions. The list should include prescription drugs, over-the-counter medications, herbal remedies, and vitamins. Nurses should report any possible drug interactions to the treating physician. Doses can be reduced or increased in increments of 12.5 mg if certain medications cannot be discontinued. In addition, patients should be instructed to store sunitinib malate at room temperature.

As with any chemotherapy agent, oncology nurses must educate patients about the drug's side effects as well as their management. Dermatologic side effects of erythema and dryness or peeling of the skin may occur, usually on the hands and feet, which is better characterized as hand and foot syndrome. Patients should be instructed to apply thick moisturizing creams throughout the day to help alleviate the symptom. A dose reduction can be considered if the hand and foot syndrome is classified as grade 3 or greater (National Cancer Institute, 2005) (see Figure 3). Grade 2 reactions usually are managed during the two-week rest period. Hand and foot syndrome can be very debilitating and painful; therefore, patients may require additional time off sunitinib malate if symptoms do not improve. Patients may be given analgesics for further relief of pain associated with the syndrome. In addition, patients can apply ice packs or immerse the hands and feet in cool water. Patients should avoid pressure, friction, and direct exposure to sunlight. Patients should apply multiple layers of sunscreen to prevent further skin damage.

Patients taking sunitinib malate should be educated about changes in pigmentation of the skin. Many dark-skinned individuals' skin develops a yellow cast, and dark-colored hair loses pigmentation and may change to blonde or white (Pfizer Oncology, 2006). For many patients, the hair and skin discoloration is reversible and improves during the two-week rest period.

GI side effects of sunitinib malate are treated similarly to those experienced by patients receiving capecitabine. The main GI side effects described by Pfizer Oncology (2006) during its clinical trials were nausea, vomiting, stomatitis, and diarrhea, which were classified as grade 1 or 2 in severity. Patients can be given a 5HT, serotonin receptor antagonist for nausea and vomiting and loperamide for diarrhea.

The goal of managing stomatitis is to minimize the effects and subsequent sequelae. The cornerstone in preventing or minimizing the effects of oral mucositis is an oral care protocol. A literature review indicated that no single evidence-based protocol is used universally in caring for mucositis in patients with cancer (Cawley & Benson, 2005). As a result, patients can be taught to keep the mouth clean by brushing, flossing, and rinsing with a saline or sodium bicarbonate solution after each meal and at bedtime.

One of the major roles that nurses play when caring for patients with GISTs is in the provision of supportive care. Many times patients who have poor prognoses (unresectable or imatinib-resistant GISTs) have been through all lines of therapy. After sunitinib malate, best supportive care—hospice—or participation in a clinical trial is the treatment of choice. Education on clinical trials and symptom management (e.g., control of pain, nausea, and vomiting) should be emphasized.

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**Figure 3. National Cancer Institute Grading for Hand and Foot Syndrome**

*Note. Based on information from National Cancer Institute, 2003.*
Future Directions

Many advances have been made in the area of molecular biology of cancer cells, some of which have shown to improve the management of certain cancers. Unresectable GISTs have limited activity with radiotherapy or chemotherapy. Drugs such as imatinib mesylate and sunitinib malate offer patients a better outlook. Several clinical trials with new drugs similar to imatinib mesylate and sunitinib malate are being investigated in the management of GISTs (Gold & DeMatteo, 2006). Oncology nurses can provide better evidence-based care by studying and educating their patients about clinical trials.

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References


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Spot on Patient Support . . .

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