Practical Management of Imatinib in Gastrointestinal Stromal Tumors

Tamara Barnes, RN, MSN, CNS, AOCNS®, and Denise Reinke, APRN, BC, AOCN®

Gastrointestinal stromal tumors (GISTs) have an incidence of 7–15 occurrences per million people. Tyrosine kinase inhibitors (TKIs) have significantly improved clinical outcomes as part of multidisciplinary disease management. The authors will review developments in the management of GISTs, including diagnosis, risk stratification, prognosis, and treatment with imatinib. Imatinib is recommended for postsurgical adjuvant therapy and, where appropriate, neoadjuvant therapy. Clinical practice guidelines recommend first-line imatinib for metastatic and unresectable GISTs based on trials showing efficacy at the standard dose (400 mg per day) and at higher doses of 600–800 mg per day. Oncology nurses play a key role in patient management through (a) patient education about GISTs and their treatment including the use of imatinib, (b) timely scheduling of radiologic follow-up to assess treatment response, (c) monitoring treatment adherence, (d) helping to sustain imatinib dose intensity by monitoring toxicities and drug interactions and by counseling patients to prevent treatment interruptions, and (e) collaborating with the multidisciplinary medical team to pursue imatinib dose escalation or other treatment options if patients have primary or acquired mutation-based resistance to imatinib.

At a Glance

- Gastrointestinal stromal tumors (GISTs) are characterized by mutations in the KIT proto-oncogene that lead to abnormal expression of a protein, KIT receptor tyrosine kinase.
- Multidisciplinary management of GISTs currently includes targeted therapy with the oral tyrosine kinase inhibitor imatinib.
- Oncology nurses can help sustain the effectiveness of imatinib therapy by delivering individualized patient education that promotes understanding of the disease and its treatment.

Most GISTs (85%–95%) are driven by oncogenic mutations in either KIT or platelet-derived growth factor alpha protein (PDGFRα). These gain-of-function mutations lead to the constitutive activation of the KIT and PDGFR receptors, which result in subsequent cell proliferation and the prevention of apoptosis (programmed cell death) (Fletcher et al., 2002). The observation that most GISTs express KIT or PDGFRα led to the development of the targeted oral therapy imatinib, a tyrosine kinase inhibitor (TKI) (Joensuu et al., 2002). Imatinib inhibits the constitutive activation of KIT and PDGFRα tyrosine kinase, which inhibits tumor growth and induces tumor regression (Hirota et al., 1998; Rubin et al., 2001).
Before the development of imatinib, no effective systemic treatment existed. Localized GIST was treated with surgery, and at least 40%–50% of those patients experienced recurrence (DeMatteo et al., 2000). GISTs are not sensitive to traditional chemotherapeutic agents, and radiation therapy would cause collateral damage to surrounding tissues and organs in the area, leading to significant morbidity. The addition of targeted pharmacotherapy to the GIST treatment paradigm has resulted in many patients surviving longer. In light of the complex process of diagnosis and treatment, which has resulted in improved outcomes, nurses have an important role in the multidisciplinary care of patients with GISTs (Griffin, Amand, & Demetri, 2005).

In this article, the authors will review developments in the diagnosis, risk stratification, treatment, and ongoing multidisciplinary management of patients with GIST, including the use of imatinib therapy and the nursing implications of these developments. Some of these implications are related to the long-term, daily use of oral imatinib, the need for adherence, and the possibilities of dose modification, disease recurrence, adverse events, and psychosocial and financial issues.

### Clinical Assessment and Diagnosis of Gastrointestinal Stromal Tumors

Evaluation of a patient with suspected GIST involves a multidisciplinary team that includes oncologists, surgeons, pathologists, radiologists, radiation oncologists, and oncology nurses. A GIST diagnosis is based on history, physical findings, immunopathology, histopathology, and radiographic imaging. The oncology nurse provides support to the multidisciplinary team in several ways, including obtaining physical assessment, subjective symptom data, past medical history, allergies, and a current medication list, including over-the-counter medicines, vitamins, herbs, and supplements. The oncology nurse also educates the patient about GISTs and the diagnostic testing and the treatment plan, including explanation of the role of tumor genotyping in diagnosis and treatment.

Symptomatically, patients may present with abdominal discomfort, palpable abdominal mass, abdominal fullness, anemia, and secondary symptoms of tumor bleeding, altered bowel function, bowel obstruction or perforation, dysphagia, and fever (Joensuu et al., 2002). The tumors may be discovered during emergency surgery for GI perforation or on computed tomography (CT) imaging obtained for other suspected diagnoses (Ghanem et al., 2003; Joensuu et al., 2002).

#### Histopathology and Immunopathology of Biopsied Samples

GISTs are highly cellular tumors with a range of histologic features (Miettinen, Sarlomo-Rikala, & Lasota, 1999). Histology contributes to the differential diagnosis of GISTs, as summarized in Table 1 (Joensuu et al., 2002). When reviewing the pathology report, the most common characteristics of GISTs include spindle cell or epithelioid-shaped cells with fibrillary or syncytial cytoplasm. Almost all are KIT positive, 30%–40% are smooth muscle actin positive, and about 70% are CD34 positive. Characteristically, on the pathology report, immunohistochemistry staining for GIST is positive for desmin and negative for S100.

#### Imaging Studies

Radiographic, endoscopic, and ultrasonographic studies show GISTs as tumors with clearly demarcated borders, usually protruding into the bowel wall and often contiguous with the muscularis propria of the normal gut wall (Joensuu et al., 2002). The CT scan (with or without positron-emission tomography [PET]) usually is the initial imaging modality for evaluation of GISTs. PET is used for detecting distant metastasis, measuring response to therapy, and planning therapy.

#### Table 1. Differential Diagnosis of Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>HISTOLOGY</th>
<th>KIT</th>
<th>SMA</th>
<th>DESMIN</th>
<th>S100</th>
<th>CD34</th>
<th>CYTOGENETICS AND MOLECULAR GENETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>Spindle cell or epithelioid, fibrillar or syncytial cytoplasm; most are monomorphic.</td>
<td>+ (30%–40%)</td>
<td>+ (1%–2%)</td>
<td>+ about 5%</td>
<td>+</td>
<td>(60%–70%)</td>
<td>Monosomies 14 and 22, deletion of 1 p, KIT mutations as many as 90%</td>
</tr>
<tr>
<td>Smooth-muscle neoplasm</td>
<td>Most are spindle cell, variable atypia, well-formed fascicles, brightly eosinophilic cytoplasm.</td>
<td>–</td>
<td>+ (most)</td>
<td>–</td>
<td>–</td>
<td>+ (10%–15%)</td>
<td>Variable karyotype, no consistent pattern of gene involvement</td>
</tr>
<tr>
<td>Gastrointestinal tract schwannoma</td>
<td>Spindle cell, short intersecting fascicles; lymphocytic infiltrate; variable palisading</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Deletion of 22 q, NFE2 in-activation in about 50%</td>
</tr>
<tr>
<td>Desmoid fibromatosis</td>
<td>Spindle cell; long fascicles, collagenous stroma; palely eosinophilic cytoplasm (rare cells)</td>
<td>–</td>
<td>+ (rare cells)</td>
<td>+ (rare cells)</td>
<td>+</td>
<td>(few)</td>
<td>Deletion of 5 q, trisomies 8 and 20, APC mutation in about 50%</td>
</tr>
</tbody>
</table>

*Most, but not all, investigators report that the vast majority of fibromatoses are KIT-negative.

SMA—smooth-muscle actin

Note. S100 is a neural (schwann) cell marker.

Table 2. Stratification of Primary Gastrointestinal Stromal Tumor Risk by Mitotic Index, Size, and Site

<table>
<thead>
<tr>
<th>RISK CATEGORY</th>
<th>TUMOR SIZE (cm)</th>
<th>MITOTIC INDEX (PER 50 HPF)</th>
<th>PRIMARY TUMOR SITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt; 2</td>
<td>≤ 5</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1–5</td>
<td>≤ 5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.1–5</td>
<td>&gt; 5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>&lt; 5</td>
<td>6–10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>5.1–10</td>
<td>≤ 5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>Any</td>
<td>Any</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt; 10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>2.1–5</td>
<td>&gt; 5</td>
<td>Nongastric</td>
</tr>
<tr>
<td></td>
<td>5.1–10</td>
<td>≤ 5</td>
<td>Nongastric</td>
</tr>
</tbody>
</table>

HPFs—high-power fields


Risk Stratification

Mitotic rate and initial tumor size are reliable prognostic factors in GIST. Tumor site also impacts prognosis, with nongastric locations increasing risk for recurrence and mortality. Tumor rupture also is a strong adverse prognostic factor because it increases the risk of intra-abdominal implant tumors (Joensuu, 2008) (see Table 2). Patients who are symptomatic at presentation may have a worse outcome than asymptomatic patients.

KIT Mutation Status and Prognosis

KIT mutations—present in as many as 90% of GISTs—are a diagnostic marker for GISTs and may predict response to imatinib (Corless & Heinrich, 2008; Corless et al., 2005; Demetri et al., 2007; Fletcher et al., 2002; Heinrich et al., 2003; Hirota et al., 1998; Joensuu et al., 2002; Miettinen et al., 1999; Miettinen & Lasota, 2001; Tornillo & Terraciano, 2006).

In several studies, the presence of a KIT exon 11 mutation (the most common mutation) was the single best predictor of favorable response to imatinib (Blanke, Demetri, et al., 2008; Debiec-Rychter et al., 2006; Heinrich et al., 2003) (see Table 3). In contrast, rare KIT exon 9 and wild-type (no KIT mutation) genotypes are associated with poor prognosis and may respond less favorably to imatinib (Blanke, Demetri, et al., 2008; Debiec-Rychter et al., 2006; Heinrich et al., 2003; Lasota & Miettinen, 2008).

Table 3. Relationship Between Kinase Genotype, Response, and Outcome on Imatinib Therapy by Study

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>B2222 PHASE II (N = 127)</th>
<th>EORTC-AUSTRALASIAN PHASE III (N = 363)</th>
<th>NORTH AMERICA SWOG S0033 PHASE III (N = 324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective responsea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT exon 11</td>
<td>83%b</td>
<td>70%c</td>
<td>67%b</td>
</tr>
<tr>
<td>KIT exon 9</td>
<td>48%</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>No mutation</td>
<td>–</td>
<td>25%</td>
<td>39%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT exon 11</td>
<td>5%</td>
<td>3%</td>
<td>NR</td>
</tr>
<tr>
<td>KIT exon 9</td>
<td>17%</td>
<td>17%</td>
<td>NR</td>
</tr>
<tr>
<td>No mutation</td>
<td>56%</td>
<td>19%</td>
<td>NR</td>
</tr>
</tbody>
</table>

a Defined as complete or partial response by Response Evaluation Criteria in Solid Tumors; excludes nonevaluable patients.
b Statistically significant difference versus KIT exon 9 and no mutation groups. EORTC—European Organisation for Research and Treatment of Cancer; NR—not reported; SWOG—Southwest Oncology Group


Treatment of Gastrointestinal Stromal Tumors

Multidisciplinary management of GISTs can help achieve fundamental treatment goals, including reducing recurrent disease after primary GIST, optimizing timing of surgery and organ preservation, extending survival times, enabling more cases to be surgically resected by debulking with preoperative delivery of pharmacologic agents, and sustaining response to imatinib in metastatic disease (Demetri et al., 2007). Current recommendations for GIST management have been developed by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (Casali, Jost, Reichardt, Schlemmer, & Blay, 2008; Demetri et al., 2007). Key recommendations for treatment planning are summarized in Figure 1.

Primary Resectable Gastrointestinal Stromal Tumors

If GISTs can be resected, surgery is the primary treatment of choice with the goal being clear surgical margins with no microscopic disease. However, at least 40%~50% of patients will experience disease recurrence or develop metastases even after complete surgical resection (clean margins and no evidence of disease) with a median time to recurrence of two years (Dematteo et al., 2000, 2008; Eisenberg & Judson, 2004). Survival rates parallel recurrence rates: surgical cohorts from the pre-imatinib years had five-year mortality rates of 22%~68% and 10-year mortality rates of 37%~81% (Dematteo et al., 2008). Patients with higher risk of disease recurrence may be considered for adjuvant therapy. In cases where complete surgical resection is not feasible, or where it could be later achieved by less extensive...
surgery, the team may first consider a neoadjuvant strategy (Casali et al., 2008; NCCN, 2011).

**Imatinib**

By the late 1990s, the discovery that *KIT* expression is a hallmark of GISTs provided the rationale for the use of the first TKI-targeted therapy to treat GISTs—imatinib (Blanke, Demetri, et al., 2008; Joensuu et al., 2002; Maki, 2007; Manley et al., 2002). **Adjuvant therapy:** The Z9001 trial, a multicenter, double-blind, placebo-controlled, randomized study conducted by the American College of Surgeons Oncology Group, evaluated adjuvant imatinib at 400 mg daily in 713 patients who had complete surgical resection of GISTs (DeMatteo et al., 2009). After complete gross resection of their primary *KIT*-positive GIST (tumor size of 3 cm or greater), patients were randomized to either imatinib 400 mg per day or matching placebo for one year. Imatinib significantly improved recurrence-free survival, the primary endpoint, compared with placebo at one year (98% versus 83%; hazard ratio [HR] 0.35 [0.22–0.53]; p < 0.0001). At a median follow-up of 19.7 months, 30 (8%) patients in the imatinib group and 70 (20%) in the placebo group had tumor recurrence or death (see Figure 2). Although the duration of imatinib in this study was for one year only, the optimal duration of adjuvant therapy is not known and ongoing clinical trials are examining imatinib 400 mg per day as adjuvant therapy to help define the optimal duration of adjuvant imatinib therapy.

In addition, data have been presented from the Scandinavian Sarcoma Group on SSGXVIII comparing survival of patients with GIST who received one year of adjuvant imatinib (400 mg daily) to patients receiving the same dose for three years (Joensuu et al., 2011). At the three-year follow-up, recurrence-free survival (RFS) was 60% in patients who received imatinib for a year compared to 87% for patients who received treatment for three years. At the five-year follow-up, RFS was 48% in the one-year treatment group compared to 66% in the three-year treatment group.

**Neoadjuvant therapy:** Imatinib currently is under investigation as neoadjuvant therapy to determine the potential to shrink unresectable tumors, allowing for organ-sparing surgery, decreased seeding of tumor cells, and decreased bleeding during resection (Demetri et al., 2007; Maki, 2007). Neoadjuvant imatinib may be considered in patients with marginally resectable or resectable GIST lesions with potential surgical-related significant morbidity; however, close monitoring is essential as some patients may progress and become unresectable (Demetri et al., 2007; Maki, 2007; NCCN, 2011).

Two published trials (Eisenberg et al., 2009; McAuliffe et al., 2009) reported efficacy and safety of neoadjuvant imatinib. A phase II study randomized 19 *KIT*-positive, treatment-naïve patients with GISTs of 1 cm or greater to receive three, five, or seven days of preoperative imatinib (600 mg per day) (McAuliffe et al., 2009). Imatinib 600 mg per day was continued postoperatively for two years. The primary end point of disease-free survival was 94% at one year and 87% at two years. Radiographic response occurred in the first week of therapy, and imatinib administered even hours before surgery appeared to be safe and did not compromise surgical outcome.

The second study, RTOG 0132, a phase II study of neoadjuvant and adjuvant imatinib for advanced primary (n = 30) and

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**Figure 1. Key ESMO and NCCN Recommendations for Gastrointestinal Stromal Tumors**

*Note. Based on information from Casali et al., 2008; Demetri et al., 2007.*

**Figure 2. One-, Two-, and Three-Year Recurrence-Free Survival and Overall Survival Rates With Adjuvant Imatinib in the Z9001 Trial**

*Note. Based on information from DeMatteo et al., 2008, 2009.*
metastatic operable (n = 22) GISTs, examined the use of imatinib 600 mg per day for 8–12 weeks preoperatively and postoperatively for two years. Two-year progression-free survival occurred in 85% of patients with primary GISTs and 77% of patients with metastatic or recurrent GISTs (Eisenberg et al., 2009). The two-year estimated OS was 93% and 91%, respectively, for patients with primary GIST and for metastatic or recurrent patients.

An update on the long-term follow-up of the RTOG 0132 trial (Wang et al., 2011) revealed a five-year progression-free survival of 57% in patients with primary GIST and 30% for patients with metastatic or recurrent GIST. OS for the primary GIST group was 77%, and 68% for the metastatic or recurrent group. Wang et al. (2011) noted that many patients progressed once the two years of therapy were completed, suggesting high-risk patients may benefit from longer therapy.

**Metastatic or unresectable gastrointestinal stromal tumors:** Phase II and III trials also have demonstrated the efficacy of imatinib in advanced, unresectable, or metastatic GISTs (Blanke, Rankin, et al., 2008; Demetri et al., 2002; Verweij et al., 2004). Prior to the use of imatinib, median OS for a patient with metastatic or unresectable GISTs was 19 months, and median time to progression was as short as 1.5 months (DeMatteo et al., 2000). Figure 3 summarizes the survival rates from these trials (Blanke, Rankin, et al., 2008; Demetri et al., 2002; Verweij et al., 2004).

The median survival of patients with GISTs continues to improve with ongoing analysis. New information, from the long-term follow up of patients on the B2222 trial (Von Mehren et al., 2011) revealed an overall GIST survival rate of 35% at nine years. The nine-year survival rate for patients with complete response or partial response is 38%, and, for those with stable disease, 49%.

Two abstracts (Domont et al., 2011; Le Cesne et al., 2011) were presented on the BFRI14 trial, which was designed to answer the question whether imatinib could be stopped in patients with GISTs who had achieved complete or partial response or had stable disease. Patients (N = 135) who had received either one, three, or five years of imatinib for metastatic or unresectable GISTs were randomized to interrupt or continue imatinib. Median progression-free survival (months) for the one-year group was 7 months for interrupted versus 29 months for continued, the three-year group was 9 months for interrupted versus not reached for continued, and the five-year group was 12 months for interrupted versus not reached for continued. Patients who had imatinib therapy interrupted experienced rapid progression. Resuming imatinib resulted in tumor control in 94% of patients; however, the tumor response after interruption was not as good as the first response (based on Response Evaluation Criteria in Solid Tumors [RECIST]). The conclusion reached was that imatinib should not be stopped or interrupted in nonprogressive patients with advanced GIST. They also suggested that these findings can be applied to high-risk patients with GIST in the adjuvant setting regarding whether imatinib should be given for life and, when patients relapse, whether imatinib should be reintroduced (Domont et al., 2011; Le Cesne et al., 2011).

**Dosing considerations:** For adult patients, the recommended dose of imatinib is 400–600 mg per day (Blanke, Rankin, et al., 2008; Demetri et al., 2002; Novartis Pharmaceuticals, 2009; Verweij et al., 2004). However, increasing the dose

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**Figure 3. Survival Rates in Advanced, Metastatic, or Unresectable GIST From the B2222, EORTC 62005, and SWOG S0033 Trials**

- **A. Study: B2222 (N = 147)**
  - Year 1: 100%
  - Year 2: 89%
  - Year 5: 67%

- **B. Study: EORTC 62005 (N = 946)**
  - Year 1: 100%
  - Year 2: 87%
  - Year 1: 100%
  - Year 2: 79%

- **C. Study: SWOG S0033 (N = 746)**
  - Year 1: 100%
  - Year 2: 90%
  - Year 1: 100%
  - Year 2: 80%

EORTC—European Organisation for Research and Treatment of Cancer; GIST—gastrointestinal stromal tumor; SWOG—Southwest Oncology Group
of imatinib up to 800 mg per day may be beneficial in patients who show signs of disease progression (Blanke, Rankin, et al., 2008; Casali et al., 2008; Verweij et al., 2004; Zalcberg et al., 2005). Patients with a KIT exon 9 mutation also may respond better to the 800 mg per day dose (Casali et al., 2008; Debiec-Rychter et al., 2006; Van Glabbeke et al., 2007). If a lower than therapeutically effective dose of imatinib is given, a possible KIT mutation-based drug resistance may occur during therapy (secondary resistance) as a consequence of selecting for resistant mutations (Heinrich et al., 2006, 2007).

Preliminary evidence suggests that adequate plasma levels of imatinib may be necessary for patients to achieve optimal clinical responses (Von Mehren et al., 2008). Inadequate plasma levels of imatinib may be the result of individual pharmacokinetic variations, inadequate dosing, poor adherence, or drug-drug interactions (Widmer et al., 2008). Although the optimal duration of imatinib therapy in patients with responding tumors is unknown, evidence supports long-term continuation of imatinib.

Safety and tolerability: In general, imatinib was well tolerated in GIST trials, with only 5% of patients discontinuing because of adverse reactions; severe grade (3 or 4) toxicities were observed in only 2% of patients. The most frequently reported adverse reactions to imatinib in clinical trials for GISTs were edema, fatigue, nausea, abdominal pain, diarrhea, rash, vomiting, myalgia, anemia, and anorexia (Deininger, O’Brien, Ford, & Druker, 2005; Guilhot, 2004; Novartis Pharmaceuticals, 2009).

Liver function should be assessed before initiation of treatment and monthly thereafter or as clinically indicated because long-term imatinib use can cause hepatotoxicity (Novartis Pharmaceuticals, 2009). Severe congestive heart failure and left ventricular dysfunction are rare, but have been reported in about 1% of patients. Patients with cardiac disease or risk factors for cardiac failure should be monitored (Novartis Pharmaceuticals, 2009). Grade 3 and 4 hemorrhages have been reported in clinical studies of patients with newly diagnosed GISTs, possibly from GI tumor sites. GI perforations, some fatal, also have been reported. Bullous dermatologic reactions, such as erythema multiforme and Stevens-Johnson syndrome, also have been reported with the use of imatinib (estimated incidence 0.01%–1%) (Novartis Pharmaceuticals, 2009). Stevens-Johnson syndrome is a rare but potentially life-threatening condition characterized by widespread cutaneous and mucosal lesions and is predominantly medication-induced (Papa, 1990).

Drug interactions: Interactions via the cytochrome P450 hepatic enzyme system (CYP) can increase or decrease imatinib plasma concentrations, sometimes necessitating dose adjustments (Demetri et al., 2007). In particular, the concomitant use of dexethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, and phenobarbital should be avoided if possible, as these strong CYP3A4 inducers can markedly reduce the plasma concentration of imatinib and, therefore, its clinical efficacy. If patients must be given a strong CYP3A4 inducer concomitantly with imatinib, a dose increase by 50% should be considered and clinical response should be monitored carefully (Novartis Pharmaceuticals, 2009). In addition, strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin, voriconazole) should be used with caution as they increase imatinib plasma concentrations, which can result in increased toxicity (Novartis Pharmaceuticals, 2009). Patients taking imatinib who require anticoagulation should receive low molecular weight heparin rather than warfarin, which may interact with imatinib. Acetaminophen hepatotoxicity can increase when acetaminophen is concomitantly administered with imatinib. Table 4 summarizes potential drug interactions with imatinib (Demetri et al., 2007).

Second- and Third-Line Therapeutic Options in Metastatic or Unresectable Gastrointestinal Stromal Tumors

Second-line treatment with another therapeutic option may be necessary because of the development of either imatinib resistance or intolerance. Once resistance is suspected, treatment modification may include imatinib dose escalation (e.g., from 400 mg once daily to 400 mg twice daily [800 mg per day]); second-line therapy with sunitinib, another TKI; surgical management or radiation for appropriate patients; or, possibly, experimental therapies that include newer-generation TKIs (e.g., nilotinib, sorafenib, dasatinib) or the monoclonal antibody bevacizumab (Nimeiri et al., 2008; Von Mehren, 2006a, 2006b;
Von Mehren et al., 2007). These latter therapies all have biologic rationales for their use in GISTs and are being evaluated for use alone or concomitantly with imatinib in clinical trials (Von Mehren, 2006b).

Sunitinib has the largest evidence base as an effective second-line treatment (Demetri et al., 2006). Sunitinib has different KIT-receptor interactions than imatinib, resulting in a more favorable response than imatinib in patients with KIT exon 9 mutations or

Table 4. Potential Drug Interactions With Imatinib

<table>
<thead>
<tr>
<th>DRUG</th>
<th>BRAND NAME</th>
<th>INTERACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Tylenol®</td>
<td>Imatinib can cause liver function test abnormalities.Liver failure and death may occur when taking large doses of both acetaminophen and imatinib.Use of acetaminophen should be limited in patients taking imatinib.</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>Emend®</td>
<td>Aprepitant inhibits CYP450 3A4, increasing the imatinib plasma concentration.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegero®</td>
<td>Carbamazepine induces CYP450 3A4 and decreases plasma concentration of imatinib. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin®</td>
<td>Clarithromycin inhibits CYP450 3A4, increasing imatinib plasma concentration.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Sandimmune®</td>
<td>Imatinib inhibits CYP450 3A4, increasing the cyclosporine plasma concentration; this is a concern because of cyclosporine’s narrow therapeutic window.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Decadron®</td>
<td>Dexamethasone induces CYP450 3A4, decreasing imatinib plasma concentration. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Dihydropyridine calcium channel blockers (e.g., amlodipine, nitrendipine, nifedipine)</td>
<td>Procardin®, others</td>
<td>Imatinib may increase plasma levels of dihydropyridine Ca++ channel blockers.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>–</td>
<td>Erythromycin inhibits CYP450 3A4, increasing imatinib plasma concentration.</td>
</tr>
<tr>
<td>Hypericum perforatum (St. John’s wort)</td>
<td>–</td>
<td>St. John’s wort induces CYP450 1A2 and may decrease the imatinib plasma concentration. An increase in imatinib dose may be necessary.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Sporano®</td>
<td>Itraconazole inhibits CYP450 3A4, increasing imatinib plasma concentration.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nizoral®</td>
<td>Ketoconazole inhibits CYP450 3A4, increasing imatinib plasma concentration.</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Synthroid®</td>
<td>Hypothyroid patients receiving imatinib need increased levothyroxine doses. A twofold increase in levothyroxine substitution therapy is recommended before initiation of imatinib.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>–</td>
<td>Phenobarbital induces CYP450 3A4, decreasing imatinib plasma concentration. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dilantin®</td>
<td>Phenytoin induces CYP450 3A4, decreasing imatinib plasma concentration. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap®</td>
<td>Imatinib inhibits CYP450 3A4, increasing pimozide plasma concentration. This is a concern because of pimozide’s narrow therapeutic window.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Mycobutin®</td>
<td>Rifabutin induces CYP450 3A4, decreasing imatinib plasma concentration. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifadin®, Rimactane®</td>
<td>Rifampin induces CYP450 3A4, decreasing imatinib plasma concentration. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Prifitin®</td>
<td>Rifapentine induces CYP450 3A4, decreasing imatinib plasma concentration. An increase in imatinib dose usually is necessary.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Zocor®</td>
<td>Imatinib inhibits CYP450 3A4, increasing the simvastatin plasma concentration. A dose adjustment of simvastatin may be necessary.</td>
</tr>
<tr>
<td>Triazolobenzodiazepines (e.g., alprazolam)</td>
<td>Xanax®</td>
<td>Imatinib may increase drug levels of alprazolam.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin®</td>
<td>Warfarin is metabolized by the CYP450 2C9 isoenzymes CYP 2C9 and CYP 3A4. Patients requiring anticoagulation should use heparin or low molecular weight heparin instead of warfarin.</td>
</tr>
</tbody>
</table>

wild-type genotype (Hopkins, Marples, & Stark, 2008), although sunitinib also may be subject to acquired resistance (Heinrich et al., 2007). Regular monitoring of blood counts, thyroid function, blood pressure, and signs and symptoms of congestive heart failure are required with sunitinib (Hopkins et al., 2008; Pfizer Inc., 2009; Rock et al., 2007).

Follow-Up in Patients With Gastrointestinal Stromal Tumors

Disease Monitoring

For primary GISTs that have been surgically resected, imaging studies to monitor for recurrence should be conducted every three to six months after resection. For recurrent, metastatic, or unresectable GISTs, treatment response should be monitored by imaging starting within three months after the initiation of imatinib (NCCN, 2011).

Initial treatment responses to imatinib are not always accompanied by reductions in tumor size; in fact, conventional size-based response criteria, such as RECIST, may lead to underestimation of responses to imatinib and, therefore, may have poor predictive value for outcome. Responding tumors may in fact increase in size and still be responding to therapy because responding tumors become less solid. The responding tumor, therefore, can become fluid filled and expand (the tumor becomes cyst-like in consistency). Consequently, other parameters should be considered in the response assessment. Tumors responding to imatinib demonstrate decreased metabolic activity on PET scan within the first weeks of treatment and often show reduced density and greater homogeneity on CT scans regardless of initial changes in tumor size. Choi criteria, developed to assess reductions in tumor size or tumor density on CT and PET scans, appear to be a more sensitive and specific indicator of GIST response to imatinib than traditional RECIST criteria (Choi et al., 2007; Demetri et al., 2007; Eisenhauer et al., 2009) (see Table 5). The Choi criteria may detect early responses to imatinib. Figure 4 depicts sequential PET and corresponding CT scans for a patient at baseline and after 1 and 16 months of imatinib treatment, respectively. CT scans prior to treatment initiation provide a baseline characterization of the tumor and are useful to monitor tumor response to imatinib.

Patients on imatinib should be monitored for side effects. Imatinib therapy may need to be adjusted for hematologic toxicities such as anemia, thrombocytopenia, and neutropenia, as well as nonhematologic toxicities such as hepatotoxicity. Commonly, complete blood counts are obtained and reviewed weekly for the first month, biweekly for the second month, and periodically at the discretion of the clinician thereafter. Liver function tests are generally obtained before initiation of treatment and monthly thereafter or as clinically indicated.

Implications for Oncology Nursing

The oncology nurse has an important role in the management of patients with GISTs, particularly those who are receiving therapy with imatinib. Priorities include assisting patients in understanding their diagnosis, treatment plan, and the meaning of diagnostic and disease-monitoring test results; monitoring and supporting patient adherence with the prescribed dose; assessing, monitoring, and managing adverse events associated with therapy and drug interactions; ensuring that follow-up evaluations are scheduled; providing counseling, education, and comfort for the patient; and assisting the patient with financial or reimbursement problems associated with obtaining medication. Best practices to optimize therapy are summarized in Figure 5 (Blay et al., 2005; Casali et al., 2008).

### Table 5. Modified CT Response Evaluation Criteria

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>DEFINITION OF CT RESPONSE</th>
<th>COMPARISON TO RECIST DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>• Disappearance of all lesions</td>
<td>• Disappearance of all target lesions (confirmed at week 4)</td>
</tr>
<tr>
<td></td>
<td>• No new lesions</td>
<td>• No new lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduction in short axis of lymph nodes to less than 10 mm</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>• A decrease in size of 10% or greater or a decrease in tumor density (HU) of 15% or more on CT</td>
<td>• 30% or greater decrease in tumor size (confirmed at week 4)</td>
</tr>
<tr>
<td></td>
<td>• No new lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No obvious progression of nonmeasurable disease</td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>• Does not meet the criteria for CR, PR, or PD</td>
<td>• Neither PR or PD criteria met</td>
</tr>
<tr>
<td></td>
<td>• No symptomatic deterioration attributed to tumor progression</td>
<td></td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>• An increase in tumor size of 10% or greater and does not meet criteria of PR by tumor density (HU) on CT</td>
<td>• 20% or greater increase in tumor size</td>
</tr>
<tr>
<td></td>
<td>• New lesions</td>
<td>• New lesions</td>
</tr>
<tr>
<td></td>
<td>• New intratumoral nodules or increase in the size of existing intratumoral nodules</td>
<td></td>
</tr>
</tbody>
</table>

CR—complete response; CT—computed tomography; HU—Hounsfield unit; PR—partial response; PD—progressive disease; RECIST—Response Evaluation Criteria in Solid Tumors; SD—stable disease

*Note. For RECIST, all definitions are based on the size of the tumor as measured by the sum of the longest diameters of target lesions. Measures by Choi et al. (2007) decrease in size on CT scan using the same method.


*Note. Based on information from Eisenhauer et al., 2009.
Clinical Assessment, Diagnosis, and Disease Monitoring

The complexity of diagnostic criteria, including radiographic imaging, histopathology, and immunopathology, may seem daunting and confusing to patients, particularly given that they are likely to be experiencing stress and anxiety over their diagnosis at the same time they are initiating treatment. Patients may need assistance in understanding the meaning and implications of test results, their diagnosis, their prognosis, and the treatment plan appropriate for their type and stage of disease. Patient and caregiver education, as well as reassurance and support, can enhance patient understanding of the need for diagnostic and monitoring procedures, increase their cooperation with these procedures, and reduce anxious feelings. At regular follow-up visits to monitor tumor response to therapy, nurses should ensure that patients understand any changes that may be recommended in the treatment plan.

Imatinib in the Management of Gastrointestinal Stromal Tumors

This review of current treatment strategies for GISTs outlines key roles for nurses as they help patients with GISTs manage their imatinib treatment.

- Ensure that follow-up imaging is appropriately scheduled.
- Help maintain the necessary dose intensity of imatinib, keeping in mind that interruption of imatinib may result in rapid progression. Interruption is not advisable except when toxicity is intolerable (Blay et al., 2007). This requires nurses to attend carefully to both prescribed dosing and patient adherence.
- Assess for and manage adverse events and drug interactions.
- Update patient medication list continually.
- Educate patients about treatment-associated adverse events, potential drug interactions, and emphasize the rationale and the importance of following the treatment plan.
- Be familiar with second-line therapy for patients refractory to or intolerant of imatinib. This familiarity should include an understanding of sunitinib, along with newer TKIs currently being studied, such as nilotinib, sorafenib, and dasatinib.

**Patient adherence:** Because imatinib is a self-administered oral medication, patients preparing to start therapy should receive detailed instructions in their dosing schedule. Nurses should emphasize the need for patients to adhere to the treatment, avoid skipping days, and refrain from discontinuing or adjusting the imatinib dose on their own. Older adult patients and those with cognitive impairments or language barriers may require more intensive educational interventions plus the involvement of caregivers and bilingual relatives as appropriate. Nurses also should assess patients to determine whether they exhibit any common risk factors for nonadherence, such as cost concerns, adverse reactions, lack of understanding, or a perception that the drug has worked and they are cured (Osterberg & Blaschke, 2005; Partridge, Avorn, Wang, & Winer, 2002; Tsang, Rudychev, & Pescatore, 2006).

Nurses have a role in assessing and promoting patient adherence and avoiding interruptions of the imatinib regimen. Going beyond a simple “yes” or “no” response question and inquiring how and when patients are taking their imatinib is essential. Some patients may forget from time to time or decide to stop taking their medication for various reasons. Asking patients to report any times they have forgotten to take their medication and seeking strategies to increase adherence are valuable. Suggest that the patient keep a symptom and treatment diary for imatinib so they can show their doctors and nurses to look for events and trends and can be advised how to better manage side effects. Given that imatinib therapy may continue for prolonged periods, nurses should proactively assist patients who may experience treatment fatigue, particularly if the symptoms of their disease subside.

**Monitoring and the management of adverse events and drug interactions:** Adverse events that noticeably affect quality of life, such as rash, fatigue, edema, and nausea, require proactive management to help patients adhere to therapy. Superficial edema, usually of the face (periorbital) or legs, can be managed with diuretics or decreased salt intake (Deininger et al., 2003; Guilhot, 2004); severe fluid retention may require imatinib dose adjustment (Novartis Pharmaceuticals, 2009). Nurses should weigh patients regularly, observe for edema, and advise at-home weight measurement to screen for fluid retention. Nausea and vomiting, muscle cramps, diarrhea, and rash can be managed with appropriate medication and supportive care. Because imatinib therapy may be affected by drug interactions, nurses should regularly review the medications taken...
by patients and request a list of all over-the-counter medicines; vitamin, mineral, and herbal supplements; and prescription medications taken by patients before initiating imatinib and periodically during treatment. Some concomitant medications may need to be changed or discontinued based on this review (e.g., warfarin can be changed to low molecular weight heparin, acetaminophen for minor pain control may be stopped).

**Additional patient education:** Patients should be educated about the potential adverse events and toxicities of imatinib before the initiation of therapy and then periodically as appropriate. Part of this discussion is an overview of testing for hematologic and hepatic toxicity and the dose-adjustment process. Patients and their caregivers must have a very active role in observing and reporting side effects to the nurse or other medical professionals. As noted, self-monitoring for signs and symptoms of fluid retention and reporting of specific symptoms like rash or diarrhea are important topics for education. For some patients, rash, pigmentation changes, or other dermatologic adverse events may be embarrassing or upsetting if they are unprepared for these potential side effects. With counseling, patients can learn to adapt to these changes and continue with therapy. Another important nursing action is education on imatinib dose modification or changing therapies. Counseling and ongoing communication with patients and caregivers are essential to ensure understanding of the need for the change and any differences in the way the medication looks or is to be taken. Finally, because imatinib is classified as pregnancy category D, men and women receiving imatinib should be counseled on the importance of contraceptive use to prevent potential harm to the fetus.

Because GIST remains a serious disease that often is discovered late in its progression, patients with a poorer prognosis—such as those with large tumors, metastatic disease, or imatinib resistance—may need counseling, emotional support, and pain and symptom management, which the oncology nurse is well positioned to provide.

**Case Study: Supporting Dose Intensity in a Patient With a KIT Exon 9 Mutation**

**Patient**

K.J., a 48-year-old woman, was diagnosed with unresectable, duodenal gastrointestinal stromal tumor (GIST). Positive CD117 staining identified the tumor as GIST; *KIT* exon 9 mutation also was identified at the time of initial workup. The tumor was fairly large (10 cm) and mitotic rate was greater than 5/50 high-power field.

**Treatment**

Because K.J. had a *KIT* exon 9 mutation, which confers resistance to imatinib, she was started on a high dose of 800 mg per day (400 mg twice daily). K.J. was petite, and some concern arose that a dose that high might produce intolerable toxicities or adverse effects. She was therefore counseled to report any potential adverse events immediately to the nurse or physician and was scheduled for weekly follow-up appointments for the month after starting imatinib. In addition, the nurse counseled K.J. not to take clarithromycin for bacterial infections of comorbid chronic bronchitis because this antibiotic can increase imatinib plasma levels. The nurse also sent this information to K.J.’s primary care physician.

**Follow-up**

Within two weeks of starting therapy, K.J. experienced hematologic toxicity, with a platelet count of less than 50 × 10⁹/L. She also reported fatigue, slight ankle edema, and frequent vomiting.

**Intervention**

Imatinib was temporarily stopped. The nurse provided counseling on coping skills and fatigue management and the physician recommended reduced salt intake and prescribed an antiemetic to manage edema and vomiting. When the patient’s platelet count rose to more than 75 × 10⁹/L, the dose of 800 mg per day was immediately resumed and platelet count remained in a safe range. The physician ordered a computed tomography scan at month 2 to determine whether the elevated imatinib dose was achieving desired results. The scan showed a partial response to imatinib therapy (Choi’s criteria). This favorable result—despite a poor prognosis—motivated K.J. to stay with imatinib therapy. She remained in regular telephone contact with the nurse, who reinforced learned coping skills when K.J. experienced adverse events.

**Figure 5. Best Oncology Nursing Practices to Optimize Imatinib Therapy for GIST**

- Collaborate with a multidisciplinary medical team including oncologists, surgeons, pathologists, and radiologists.
- Ensure that patients are taking the recommended dose of imatinib (400–600 mg per day, or 800 mg per day) if patients progress on treatment or have *KIT* exon 9 mutations.
- Ensure scheduling of follow-up for laboratory tests as well as CT scans with radiology team (typically at three- to six-month intervals after resection of primary GISTs and starting at about three months after initiation of imatinib).
- Identify and manage adverse events (e.g., nausea, vomiting, edema, abdominal pain, muscle cramps, rash) and observe for drug-drug interactions.
- Follow recommended dose adjustments for toxicities.
- Assess and educate patients about the use of other medications that can affect imatinib plasma concentrations (e.g., cytochrome P450 substrates).
- Educate patients and caregivers to improve understanding of — The nature of the disease and prognosis — The meaning of diagnostic and monitoring test results — Treatment plan and the need to adhere with it — Treatment-associated adverse side effects and drug interactions.
- Urge patients to take imatinib with food and at least 8 ounces of water to minimize gastrointestinal discomfort.
- Counsel patients and caregivers and provide emotional support to keep them motivated to continue therapy.
- Counsel patients on the need for contraception use.

CT—computed tomography; GIST—gastrointestinal stromal tumor

Conclusion

The management of GIST has advanced markedly since 2001 with the development of targeted therapy with TKIs. Patients with resectable GISTs can be treated more successfully with a multimodal approach including the use of imatinib as both neoadjuvant and adjuvant therapy. With the advent of imatinib, patients with metastatic and unresectable GISTs that were once untreatable can now live longer and have their disease controlled with medication. In the adjuvant setting, the optimal duration of imatinib therapy has yet to be determined, but evidence...
supports long-term continuation of imatinib. Oncology nurses play key roles in the clinical management of patients with GISTs, including support of therapy with TKIs. Nurses can identify and manage adverse reactions and drug interactions; ensure that follow-up evaluations are scheduled; and counsel, educate, and support patients and caregivers. Nurses often are the primary source of education about disease and treatment; they can help to monitor and ensure patient adherence. In fulfilling these responsibilities, nurses collaborate with a multidisciplinary medical team to optimize therapy for patients with GISTs.

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**References**


