



Dorothy Fox. *The Weaver*. Watercolor, 30" × 36".

*The biology and treatment of gastrointestinal sarcomas are reviewed, as well as the status of targeted therapy for these tumors.*

## Update on the Biology and Therapy of Gastrointestinal Stromal Tumors

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**Background:** *Gastrointestinal stromal tumors (GISTs), the most common mesenchymal tumors of the gastrointestinal tract, are an example of a disease with an effective, molecularly targeted therapy.*

**Methods:** *Published articles and author experience were used to comprehensively define the clinical features, biology, and state-of-the-art therapy of GISTs.*

**Results:** *GISTs are thought to originate from the neoplastic transformation of the interstitial cells of Cajal, the intestinal pacemaker cells. GISTs commonly have mutations in the kit gene, resulting in a gain-of-function mutation and ligand-independent constitutive activation of the KIT receptor tyrosine kinase. Successful tyrosine kinase inhibitors target the aberrant pathways that are critical for tumor cell viability. The development of imatinib mesylate (formerly STI 571) in the treatment of metastatic GISTs represents a therapeutic breakthrough.*

**Conclusions:** *Progress in the clinical diagnosis has led to an increased recognition of this disease as a distinct clinical entity. Treatment of metastatic GIST with imatinib has led to unprecedented improvements in progression-free and overall survival. The use of imatinib in the preoperative and postoperative treatment of GISTs is an area of intense investigation.*

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**Abbreviations used in the paper:** GIST = gastrointestinal stromal tumor, ICC = interstitial cells of Cajal, CT = computed tomography, PDGFR = platelet-derived growth factor receptor.

### Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Over 85% of GISTs express the KIT receptor (stem cell factor receptor, CD117), as shown by immunohistochemical analysis.<sup>1</sup> Approximately 60% of GISTs occur in the stomach, 25% in the small intestine, and 10% in the colon and rectum. The remainder arise from other sites in the GI tract or rare locations such as the gall bladder, appendix, omentum, or mesentery. However, GISTs account for approximately 2% of all stomach tumors, 14% of all small intestine tumors, and 0.1% of colon tumors. In the United States, the incidence is approximately 5,000 new cases

annually.<sup>2</sup> The median age at diagnosis is approximately 58 years.<sup>1</sup> As early as the 1940s, GISTs were often diagnosed as smooth muscle tumors of the GI tract (GI leiomyosarcoma, leiomyoblastoma, and leiomyoma), but advances in histopathology later provided evidence that GISTs were distinct from the smooth muscle tumors.

## Clinical Features of GISTs

### Clinical Presentation

The symptoms that patients can experience are most often representative of the site of origin of the tumor. Esophageal GISTs are rare and usually present with dysphagia, odynophagia, weight loss, dyspepsia, retrosternal chest pain, or hematemesis. The tumor may be initially localized by computed tomography (CT) radiography, modified barium swallow, or endoscopic evaluation.

Gastric GISTs typically present with vague symptoms including abdominal pain, anorexia, weight loss, or GI hemorrhage. These GISTs may be discovered and biopsied during esophagogastroduodenoscopy. Primary esophageal and gastric tumors have characteristic patterns of echogenicity, and endoscopic ultrasound may aid in the diagnosis and surgical planning.

Small intestine GISTs often present with nonspecific abdominal complaints such as pain or hemorrhage and may be misdiagnosed as peptic ulcer disease, gastroesophageal reflux, or cholelithiasis. GISTs of the small bowel are the second most common GIST and comprise more than 10% of neoplasms in this location. GISTs arising in this location are often detected by CT radiography but may be discovered by barium swallow with small bowel follow-through, or angiography.

Patients with colorectal GISTs may experience abdominal discomfort, hemorrhage, change in pattern or character of bowel movements, bowel obstruction, or perforation. Colorectal GISTs arise predominantly in the cecum and the rectum and contribute to less than 0.1% of the total number of colorectal tumors and are generally localized by CT radiography. Irrespective of anatomic location, diagnosis requires tissue biopsy evaluated by a pathologist experienced in the field.

GISTs arising from any of these locations may present with a life-threatening hemorrhage. If discovered by palpation, these tumors are generally large and often already metastatic to the liver. Patients with liver metastases may have lower-extremity edema, ascites, and even jaundice in the later stages of disease. Patients with retroperitoneal disease may experience lower-extremity edema.

GISTs that have been discovered incidentally during evaluation for other medical conditions or as part of a screening program are generally smaller in size. These incidental GISTs may be found during physical examination, laparoscopic procedures, surgery, radiographic testing, or endoscopy.

### Familial Syndromes Including GISTs

One of the early clues that GIST was a sarcoma driven by a specific genetic event was the existence of several familial syndromes that included GIST as a heritable tumor. These investigators had the additional insight to recognize GIST as a distinct histopathologic entity.<sup>3,4</sup> The Carney triad is an association of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma, and pulmonary chondroma. It was first described in 7 unrelated young women.<sup>5</sup> Although the precise germ-line abnormality remains elusive, this triad is thought to be hereditary due to the young age of the patients and the multifocal nature of the tumors. Later reports described an apparent autosomal dominant syndrome with incomplete penetrance combining paraganglioma and GIST that is distinct from the Carney triad.<sup>6</sup>

Other reports of syndromes associated with multiple GISTs involve germline mutations in the *kit* gene (discussed below). Hirota et al<sup>7</sup> reported a familial syndrome of dysphagia with multiple GISTs, and a mutation of the tyrosine kinase II domain of the *kit* oncogene was found. Two siblings with cutaneous hyperpigmentation and multiple GISTs were found have a *kit* mutation at codon 559 in exon 11.<sup>8</sup> In addition, a mother and daughter with hyperplasia of the interstitial cells of Cajal (ICCs) and multiple GISTs were found to have a *kit* point mutation at codon 557.<sup>9</sup> The genetic abnormality of a mother and son with multiple GISTs and diffuse hyperplasia of the myenteric plexus layer was found to be a single base mutation that resulted in the substitution of Glu for Lys at codon 642 in the kinase I domain.<sup>10</sup> Furthermore, Nishida et al<sup>11</sup> studied a family with overexpression of KIT protein by immunohistochemistry and an activating deletion of valine 559.

### Histopathology of GISTs

Upon gross examination, an untreated GIST is in most cases a friable, unencapsulated mass that appears to arise in the muscle rather than the epithelium of the gastrointestinal tract. Larger lesions frequently have central necrosis and may rupture at the time of surgical resection. Although data are not available from any prospective study, our experience indicates that patients who have been treated with preoperative imatinib are less likely to experience excessive blood loss or tumor rupture, possibly due to tumor cell death and a decrease in tumor vascularity.

Although extraluminal in origin, GISTs may ulcerate through the overlying mucosa.<sup>12</sup> Hematoxylin and eosin staining usually reveals a spindle cell tumor with a fascicular pattern. There is generally less cellular cytoplasmic eosinophilia than in smooth muscle tumors. GISTs may show perinuclear vacuolization and nuclear palisading, which are features of smooth muscle tumors and nerve sheath tumors, respectively. Mixed spindle and epithelioid

tumors are common. Prominent nuclear pleomorphism is more common in smooth muscle tumors than in GISTs.<sup>12,13</sup> GISTs may also rarely arise in the mesentery or omentum.<sup>14,15</sup>

### Immunohistochemistry

Approximately 85% to 95% of GISTs express KIT, regardless of the site of origin, histologic appearance, or biologic behavior. Therefore, KIT is regarded as a key confirmatory marker in the diagnosis of this tumor.<sup>13</sup> KIT is not specific for GIST and is expressed in hematopoietic stem cells, mast cells, germ cells, melanocytic cells, and the ICCs.<sup>16,17</sup> GISTs and ICCs are detected with antibodies to both CD34 and KIT, suggesting that GISTs originate from the ICCs.<sup>4</sup> Most often KIT expression is pancytoplasmic, but it may also display membranous staining.<sup>13</sup> There are rare cases that are KIT-negative in small biopsies but positive in subsequent excision biopsies. This may be due to the fact that the majority of GISTs show KIT positivity in at least 90% of the tumor cells, but a small subset of this tumor type shows focal staining in as little as 5% to 20% of the tumor cells. A small proportion of GISTs (approximately 5%) show either a faint expression of KIT or negative staining.<sup>12,13</sup> It is also important to understand that not all KIT-positive tumors are GISTs. KIT is also expressed by many other tumor types, such as synovial sarcoma, rhabdomyosarcoma, angiosarcoma, Ewing's sarcoma, anaplastic large-cell lymphoma, glioma, germinoma, melanoma, fibromatosis, granulocytic sarcomas, and mastocytosis.<sup>13,18</sup> The diagnosis of GIST should be based on tumor cell morphology, radiographic findings, and clinical context. The positive staining of a tumor sample for KIT supports the diagnosis of GIST.

In addition to expression of KIT, approximately 60% to 70% of GISTs show expression of CD34<sup>19,20</sup> and 20% to 40% show immunopositivity for smooth-muscle actin. Although GISTs rarely express desmin (<2%) or S100 (<5%), the presence of these does not exclude benefit from imatinib mesylate.<sup>21</sup>

### Differential Diagnosis

The proper diagnosis of GIST is often reached only after discussion of the case between the pathologist and clinician. In general, all gastrointestinal sarcomas and certain epithelial tumors are included in the differential diagnosis of GIST. GISTs must be distinguished from smooth muscle tumors, nerve sheath tumors, and fibromatosis. Although not always the case, smooth muscle tumors consistently express desmin and smooth-muscle actin, whereas KIT expression is undetectable by immunohistochemistry. Approximately 10% to 15% of smooth muscle tumors express CD34.<sup>13,19</sup> Schwannomas are immunohistochemically positive for S100 and negative for KIT but may have focal CD34 expression. Although desmoid tumors may express KIT, the spindle cells express nuclear  $\beta$ -catenin but not CD34.<sup>22</sup>

### Prognostic Factors

The most useful clinicopathologic prognostic parameters are tumor stage, size, histologic type, degree of necrosis, cellularity, nuclear pleomorphism, and mitotic activity. The most consistent histopathologic features used to predict aggressiveness are tumor size and mitotic index.<sup>13</sup> There is reluctance to use the term "benign" to describe GISTs since this tumor may be unpredictably malignant. A recent consensus statement has suggested that patients with GISTs may be categorized into very low, low, intermediate, and high-risk tumors on the basis of an estimation of their potential for recurrence and metastasis. Very-low-risk tumors are defined as tumors less than 2 cm with less than 5 mitoses per 50 high-power fields (HPF). Low-risk tumors are defined as tumors between 2 and 5 cm with less than 5 mitoses per 50 HPF. Intermediate-risk tumors are defined as tumors less than 5 cm with 6 to 10 mitoses per 50 HPF or tumors between 5 and 10 cm with less than 5 mitoses per 50 HPF. High-risk tumors are defined as tumors greater than 5 cm with greater than 5 mitoses per 50 HPF, tumors greater than 10 cm with any mitotic rate or any size tumors with greater than 10 mitoses per 50 HPF.<sup>13</sup>

Studies at the M.D. Anderson Cancer Center (MDACC) have shown that patients with tumors <5 cm in size had a longer median disease-free survival time of 36 months longer than the 19 months in patients with tumors 5 to 10 cm and the 17 months in patients with tumors >10 cm in size.<sup>23</sup>

A high Ki-67 index and high expression of Bcl-2, p53, vascular endothelial growth factor, p16<sup>INK</sup>, and c-Myc proteins are frequently associated with poor prognosis.<sup>24-27</sup> The prognostic significance of *kit* mutations is controversial. In a series of 124 patients described by Taniguchi and colleagues,<sup>28</sup> exon 11 mutations were identified in 57% of the GISTs and seemed to correlate with a poor prognosis. Several other studies have also shown a correlation between exon 11 *kit* mutations and poor prognosis and suggested that exon 11 mutations may be one of the strongest prognostic factors.<sup>29</sup> Contrary to these reports, *kit* mutations are not restricted to high-grade large tumors but are also observed in smaller, less mitotically active GISTs.<sup>30,31</sup>

### Biology of GISTs

#### KIT Receptor Tyrosine Kinase

Cancers grow as a consequence of an imbalance between the rate of cell-cycle progression (cell division) and cell growth (cell mass) on one hand, and programmed cell death (apoptosis) on the other. It is now recognized that aberrant cellular signal transduction pathways play a vital role in driving both sides of this imbalance and hence malignant transformation.<sup>32</sup>

Tyrosine kinases are perhaps one of the most critical groups of signaling molecules involved in cellular regula-

tion.<sup>33</sup> *KIT* encodes a type III receptor tyrosine kinase that shares structural homology with platelet-derived growth factor receptors  $\alpha$  and  $\beta$  (PDGFR- $\alpha$  and - $\beta$ ), colony-stimulating factor-1 receptor, and the *fms*-related receptor FLT3. Members of this family contain 5 extracellular immunoglobulin-like domains and an intracellular kinase domain separated by a kinase insert (Fig 1).<sup>34,35</sup> *KIT* activation normally occurs when two adjacent receptors are brought together by a homodimer ligand.<sup>36</sup> A series of events occurs to activate cell-signaling cascades that are important in the regulation of proliferation, apoptosis, adhesion, and differentiation in several cell types, including ICCs. Disruption of *KIT* (eg, in mouse models) results in the absence of a functional ICC compartment, manifested by aperistalsis of the gut,<sup>17,37</sup> whereas mutations that constitutively activate *KIT* are associated with the pathogenesis of mastocytosis<sup>38</sup> and GISTs.

### **KIT Signaling Pathways**

Normally, *KIT* activation by stem cell factor induces rapid autophosphorylation of tyrosine residues at positions 567, 569, 702, 719, 728, and 934. These phosphorylated tyrosines bind SH2 signaling proteins. SH2 proteins serve as a docking station for a number of signaling proteins, including phosphatidylinositol 3' kinase (PI-3 kinase, codon 719),<sup>39</sup> Shc,<sup>40</sup> PLC $\gamma$  (728),<sup>41</sup> Vav,<sup>42</sup> Grb2 (702),<sup>43</sup> Shp-1 and Shp-2,<sup>44</sup> and Src family kinases (567, 569).<sup>45</sup> Thus,

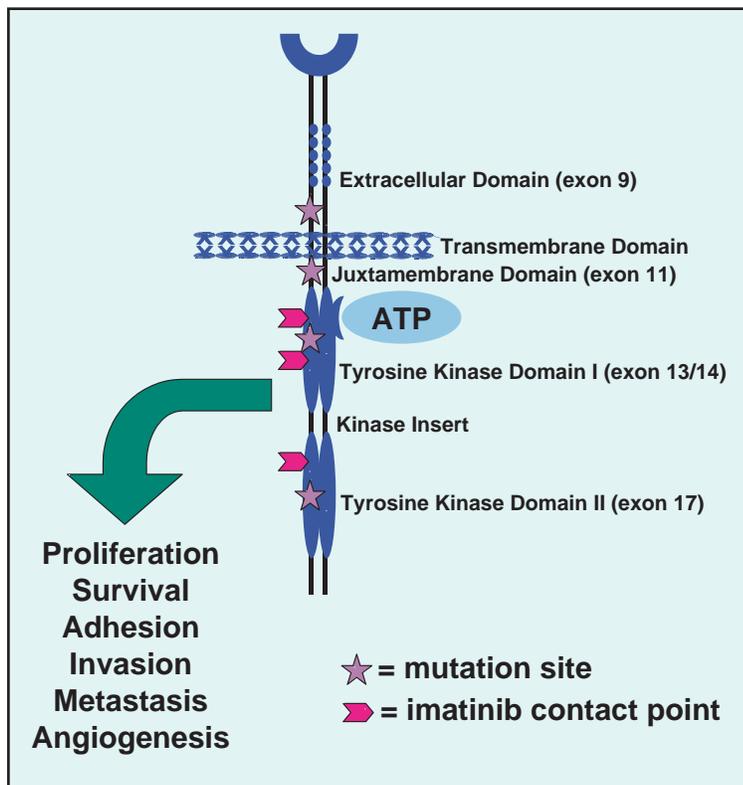


Fig 1. — *KIT* receptor tyrosine kinase structure and function. Activation by mutation or ligand leads to transphosphorylation, binding of ATP, and phosphorylation of downstream substrates. These downstream molecules drive the transcription of genes involved in supporting the tumor phenotype. Binding of imatinib interrupts the signaling pathway.

activated *KIT* can potentially serve as a signaling center from which a variety of intracellular signaling cascades are initiated, thereby implicating *KIT* in regulation of cell proliferation, adhesion, and apoptosis.<sup>46</sup> Elucidation of the oncogenic *KIT* signaling pathways is clinically important. Patients with GIST may ultimately become resistant to *KIT*-inhibitor therapies. Thus, essential downstream signaling proteins must be identified that can serve as alternative therapeutic targets to more effectively silence *KIT* signaling in GISTs.<sup>46</sup>

### **KIT Gene Mutations**

The majority GIST tumors contain a gain-of-function mutation in the *kit* protooncogene, leading to ligand-independent constitutive activation of the *KIT* receptor.<sup>4,47</sup> Somatic mutations that result in constitutive activation of *KIT* kinase have been reported in a number of studies of GIST. However, the frequencies reported have varied widely (30% to 92%), possibly because only one segment of exon 11 was evaluated and the study populations in each series were genetically heterogeneous.<sup>31,46</sup> Systematic sequencing of the juxtamembrane coding region, coupled with evaluation of the entire *kit* coding sequence in GISTs that lack juxtamembrane coding region mutations, reveals oncogenic *kit* mutations in most GISTs.<sup>31,46</sup> Mutations are most frequent in exon 11 and are less common in exons 9, 13, 14, and 17.<sup>4,30,31</sup> In a single institution study, Singer et al<sup>48</sup> reported 71% of patients had exon 11 mutations, 13% had exon 9 mutations, 4% had exon 13 mutations, and 4% had exon 17 mutations. The precise frequency of exon 14 mutations is not apparent.

Patients with GISTs expressing exon 11 *kit* mutants who received imatinib had a substantially higher partial response rate, longer median survival, and less likelihood of progressing than those with GISTs expressing wild-type or exon 9 mutant *kit*.<sup>49,50</sup> In contrast, patients whose tumor encodes the kinase mutant D816V, known to be associated with mastocytosis, were resistant to imatinib treatment.<sup>51</sup> Taken together, these results illustrate the importance of understanding the role of *kit* mutations in mediating GIST response to imatinib.

Despite the success of imatinib in targeting *KIT* in GISTs, cases of drug resistance have started to emerge. Mutations at or near sites of the drug-protein interaction or mutations inducing conformational changes that reduce the affinity of *KIT* for imatinib mesylate could reduce the efficacy of the drug. Chen et al<sup>52</sup> described an acquired-resistant V654A mutation in 5 patients with GISTs having prior imatinib-sensitive *kit* mutations in exons 9 or 11. Resistance of the V654A mutant for imatinib can most likely be attributed to a conformational change in *KIT*,

changing the affinity of the protein for imatinib.<sup>52</sup> These results further suggest the importance of *kit* mutational status in GIST response to imatinib.

Heinrich et al<sup>49</sup> recently discovered a small subset of GISTs that are *kit* wild-type and have highly activated PDGFR- $\alpha$  detected by immunoprecipitation with polyclonal antisera (panRTK antisera) against peptides from regions of strong sequence conservation across the family of RTKs. These GISTs showed mutually exclusive phospho-Kit and phospho-PDGFR- $\alpha$  expression. The authors also evaluated PDGFR- $\alpha$  genomic mutations in exons 10, 12, 14, and 18 that corresponded to the *kit* exons containing oncogenic mutations in many GISTs and found PDGFR- $\alpha$  mutations in 11 of 37 (29.7%) *kit*-wild-type GISTs but not in 36 *kit*-mutant GISTs.

## Therapy of GISTs

Surgery is the mainstay of therapy for patients with GISTs whose primary lesion is deemed resectable by an experienced surgical oncologist. Before the introduction of imatinib mesylate (Gleevec, formerly STI 571), patients with an inoperable GIST had limited therapeutic options. Gottlieb et al<sup>53</sup> observed that leiomyosarcomas originating from the GI tract did not respond as well to doxorubicin as did those arising from other organ systems. More regimens were tried, but patients with GISTs had response rates of less than 10%. A recent trial of temozolomide in patients with confirmed GISTs showed no response in 17 of 17 patients, many of whom had tumors that had failed to respond to other chemotherapeutic agents.<sup>54</sup> Imatinib is now the standard of care for patients who are not surgical candidates. At the present time, radiation therapy has little role in the management of this disease.

### Surgical Resection

Ongoing studies are evaluating the impact of imatinib mesylate on long-term survival as well as its curative effect. Thus, complete surgical resection remains the mainstay of treatment. Wedge resection of the stomach or segmental resection of the intestine provides adequate local therapy.<sup>23</sup> Metastases occur in usually only occur in two patterns: liver and intra-abdominal dissemination. One exception is rectal GISTs, which frequently metastasize to the lungs. GISTs rarely metastasize to lymph nodes, and thus lymph node dissection or biopsy is not routinely performed. DeMatteo and colleagues<sup>55</sup> reported that in a series of 200 GISTs, the median survival for patients with primary disease who underwent complete resection was 66 months compared with 22 months for those who underwent incomplete resection or whose tumor was unresectable.

In a prospective analysis of 200 patients with GIST at the Memorial Sloan-Kettering Cancer Center, 80 patients with primary tumor without metastasis underwent complete surgical resection. The overall survival rate was 55%

at a median follow-up of 24 months; two thirds of these tumors were over 5 cm in size, and most arose from the stomach. After a median follow-up of only 24 months, 27% of patients had recurred (11% local and 16% metastatic). On multivariate analysis of this patient subset, tumor size was an independent prognostic factor in survival. Patients with tumors larger than 10 cm had a disease-specific 5-year survival rate of only 20% after resection.

Studies at the MDACC have shown that tumor rupture before or during resection is a predictor of poor outcome. Surgical dissection by a skilled sarcoma surgeon is imperative to avoid tumor rupture and intraperitoneal dissemination during the resection of these tumors.<sup>56</sup>

As discussed above, GISTs of the esophagus are rare, and data regarding the efficacy of surgical resection are limited. However, extrapolating from other sarcoma histologies, 75% of esophageal sarcomas are amenable to complete resection, but the 5-year overall survival rate is only 30%.

Long-term follow-up reveals that the majority of patients with GIST tend to recur. An MDACC series has reported that 90% (119 of 132 patients) of patients that underwent an initial complete resection had intra-abdominal, local, or metastatic recurrence after a median follow-up of 68 months.<sup>23</sup> The median time to relapse was 18 months, and most recurrences occurred within 2 years of initial resection. Poor prognostic factors for recurrence included tumor size >5 cm, high grade, tumor rupture, and small bowel primary site.

### Surgical Resection of Metastases

The most common site for GIST tumors to metastasize is the liver. Most patients with metastatic GISTs have multiple, bilobar intrahepatic metastases, large metastases, or intraperitoneal sarcomatosis. Prior to the use of imatinib, a study reported that of 131 patients with GIST or intra-abdominal leiomyosarcoma, 34 patients underwent hepatic resection of all surgically visible disease. The 1- and 3-year survival rates were 90% and 58%, respectively.<sup>57</sup> Surgical consolidation should be considered for patients who have a long disease-free interval, who do not tolerate administration of imatinib and those whose tumors are resistant to imatinib.

### Hepatic Artery Embolization of Liver Metastases

Hepatic artery embolization or chemoembolization appears to be an effective palliative option for patients with liver metastases from GIST. Embolization of the same lesion or alternate lesions is often repeated. Chemoembolization mechanically occludes the arterial blood supply to the tumor, increases intratumoral concentration of drug in the tumor, and minimizes systemic toxicity because of systemic dilution and metabolism. Mavligit et al<sup>58,59</sup> described 14 patients treated with intra-arterial chemoembolization of liver metastases using polyvinyl alcohol sponge particles mixed with cisplatin powder (150

mg) followed by intrahepatic arterial vinblastine (10 mg/m<sup>2</sup>). A partial or complete response lasting from 8 to 31 months (median 12 months) occurred in 70% after an average of two embolizations. Toxicity was limited to mild myelosuppression, right upper quadrant pain, minimally elevated hepatic enzyme levels, and transient ileus. Although this was a small series, these results are superior to systemic chemotherapy. Patients with ascites or hyperbilirubinemia are considered "high risk" and should not undergo this therapy. It is interesting that we have seen disease stabilization in patients receiving "bland" embolization (polyvinyl alcohol sponge particles without chemotherapy). Thus, it is not clear whether the results of chemoembolization are due to an increased tumor exposure to chemotherapy or to blockage of the tumor blood supply. Hepatic arterial embolization or chemoembolization therapy should be considered for patients with liver metastasis who are resistant to imatinib mesylate.

### **Radiation Therapy**

Radiation therapy has a limited role in the treatment of patients with GIST. These tumors are relatively radioresistant. There is difficulty in delivering adequate cytotoxic doses of radiation due to the proximity of vital organs such as the kidney, spleen, liver and bowel. These same organs make delivery of meaningful adjuvant radiotherapy impossible. Although there are no studies showing the efficacy of radiation, it has an occasional role in the management of metastatic GIST. Radiation therapy has the potential to control a hemorrhaging tumor. Otherwise, the pattern of metastasis in the liver and peritoneum involves too large of a field to be amenable to radiation therapy. In the era of imatinib mesylate, the role of radiation therapy in esophageal and rectal GIST is currently being explored.

### **Intraperitoneal Chemotherapy**

There are patients who present with intra-abdominal sarcomatosis and minimal other organ involvement. Bilimoria et al<sup>56</sup> found that tumor volume was a prognostic factor. Patients with tumors <5 cm in diameter or <10 peritoneal nodules had a superior 2-year overall survival rate of 75%. On the other hand, only 14% of patients were alive at 2 years when their tumors were >5 cm or they had >50 peritoneal nodules.

Eilber et al<sup>60</sup> used intraperitoneal mitoxantrone to treat 54 patients with intra-abdominal sarcomatosis, 33 of whom had GISTs. Fifty-four patients were surgically debulked and then treated with intraperitoneal mitoxantrone. This approach was shown to be safe and technically feasible. The 5-year overall survival rate was 46% for patients with peritoneal only disease, while only 5% of those with liver metastases survived. In the 27 patients with peritoneum-only disease, the median time to recurrence was increased from 8 months to 21 months by the addition of postoperative intraperitoneal mitoxantrone.

Therefore, intraperitoneal chemotherapy may provide benefit for patients with peritoneum only disease. Additional studies with intraperitoneal chemotherapy for recurrent GIST are also being evaluated at MDACC for patients with imatinib-resistant tumors.

### **Systemic Chemotherapy**

The availability of KIT immunohistochemistry and the unprecedented activity of imatinib have allowed GIST to be routinely distinguished from intra-abdominal leiomyosarcoma. Thus, interpretation of most chemotherapy trials of intra-abdominal soft tissue sarcoma is impossible. Presumptively, many if not most tumors classified in the past as gastrointestinal leiomyosarcoma were actually GISTs.

Until the development of imatinib, there has been no standard therapy for GIST. Doxorubicin and ifosfamide are the two most active agents in sarcoma. However, these two agents have limited activity in patients with GISTs. Investigators at the MDACC reported their experience with patients treated for GI leiomyosarcomas (stomach and small bowel, presumably GISTs) between 1948 and 1989.<sup>61</sup> Of 120 patients with measurable disease and treated with a doxorubicin-based regimen, 4 objective responses were observed (1 complete and 3 partial) for an objective response rate of 3.3. Patel et al<sup>62</sup> also reported their experience with ifosfamide in patients treated for GI leiomyosarcomas between 1985 and 1989. Of the 30 patients with evaluable disease, 4 objective responses occurred for a response rate of 13.3%. Investigators at Mayo Clinic have confirmed these observations.<sup>63</sup> Only 1 objective response (4.8% of patients) was observed in 21 patients with GISTs who were treated with the combination of doxorubicin, dacarbazine, mitomycin, and cisplatin.

Until recent trials with imatinib, several phase II trials evaluating new agents for activity against GIST were completed with only an occasional partial response. These data reflect the refractory nature of GISTs to systemic treatment with standard cytotoxic chemotherapy drugs.

Based on the disappointing results with conventional agents, it has been difficult to recommend any particular agent or combination of drugs as standard care for metastatic GIST. The resistance of GIST to chemotherapy is currently unknown. However, it may be related to elevated multidrug resistance protein compared to those found with leiomyosarcoma. It is interesting to speculate that oncogenic activation of KIT in GIST may contribute to chemoresistance through upregulation of antiapoptotic signaling or activation of other drug resistance mechanisms.

### **Imatinib Mesylate**

The development and use of imatinib mesylate have demonstrated that tyrosine kinase inhibitors could have a wide therapeutic window.<sup>64,65</sup> Even though tyrosine kinases share catalytic domains, there are enough structural differences to allow specificity. The adenosine triphosphate

**Table 1. — Summary Data From Selected Trials of Imatinib Mesylate in Patients With GISTs**

Study	Phase	No. of Patients	Objective Response*	Complete Response	Partial Response	Stable Disease	Progressive Disease	Overall Survival	Time to Progression	Progression-Free Survival
van Oosterom et al <sup>65</sup>	I	36	53%	0%	53%	36%	11%	NA	NA	NA
von Mehren et al <sup>76</sup>	II	147	63%	0%	63%	19%	12%	NA	72 wks (median)	NA
Verweij et al <sup>95</sup>	II	27	71%	4%	67%	18%	11%	NA	NA	73% (1 yr)
Rankin et al <sup>87</sup>	III	746								
400 mg daily			48%	3%	45%	NA	NA	78% (2 yr)	NA	50% (2 yr)
800 mg daily			48%	3%	45%	NA	NA	73% (2 yr)	NA	53% (2 yr)
Verweij et al <sup>95</sup>	III	946								
400 mg daily			50%	5%	45%	32%	13%	69% (2 yr)	NA	44% (2 yr)
800 mg daily			54%	6%	48%	32%	9%	74% (2 yr)	NA	52% (2 yr)

\* objective response by RECIST or WHO  
NA = no data available

(ATP)-binding pocket lies within the kinase fold. The ATP-binding site has been the focus of inhibitor design that exploits differences in kinase structure in order to achieve selectivity. Imatinib mesylate occupies the nucleotide-binding cleft of the tyrosine kinase, preventing access of ATP to the substrate and, thus, competitively inhibiting phosphorylation of downstream effector molecules.<sup>66</sup>

In a pioneering work, Druker et al<sup>67</sup> demonstrated that imatinib mesylate suppressed proliferation of Bcr-Abl-positive chronic myelogenous leukemia cells in vitro. Normal hematopoietic progenitors were largely unaffected. This compound was discovered to be an effective inhibitor of the PDGF receptor and KIT (CD117, stem cell factor receptor) tyrosine kinases.<sup>68,69</sup> Imatinib mesylate is specific with 50% inhibiting concentrations (IC<sub>50</sub>) of 188nM for c-Abl, 413nM for KIT, and 386nM for PDGFR-β. In contrast, the IC<sub>50</sub> of most of the other cellular tyrosine kinases<sup>67,70,71</sup> was found to be >10 μmol/L. These observations laid the groundwork for the use of imatinib mesylate in the clinical setting, with potential for killing tumor cells harboring the target kinases and without harm to normal host tissue. The antitumor effects of imatinib mesylate in GIST with activating *kit* mutations is remarkable.<sup>72-77</sup>

### Pharmacokinetics and Metabolism of Imatinib Mesylate

The pharmacokinetics of imatinib mesylate are similar in patients with chronic myelogenous leukemia and GIST.<sup>75</sup> Imatinib mesylate has an oral bioavailability of >97% in oral solution or capsule form.<sup>78</sup> Once absorbed, it binds avidly to serum proteins and reaches peak concentrations in the serum 4 hours after administration (4–5 μg/mL for a 600-mg dose and 2–3 μg/mL for a 400-mg dose).<sup>79</sup> Imatinib mesylate crosses the blood-brain barrier and results in a 38-ng/mL concentration in the cerebral spinal fluid after a dose of 400 to 600 mg per day.<sup>79</sup> Drug accumulation of 1.5–3-fold occurs after daily dosing, with a steady state reached

within 1 week.<sup>80</sup> Approximately 13% of the drug is excreted in the urine, while most is metabolized in the liver by the cytochrome P450 isoenzyme CYP3A4. The major metabolite of imatinib mesylate is N-desmethyl-imatinib (CGP74588), and its concentration is approximately 17% of imatinib mesylate's at steady-state conditions. This metabolite has been shown to have comparable activity to imatinib in vivo. The half-life of imatinib mesylate is approximately 25 hours, whereas that of its metabolite is 89 hours.

Because imatinib mesylate is hepatically metabolized by CYP3A4, drugs that are administered with it may undergo changes in their pharmacokinetics and vice versa. For example, ketoconazole, a broad-spectrum antifungal agent, was shown to increase patients' exposure to imatinib mesylate when coadministered.<sup>78</sup> Additionally, rifampicin increased blood levels of imatinib mesylate. Conversely, imatinib mesylate increased the exposure of patients to simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.<sup>81</sup> Moreover, several other drugs for cancer patients, such as alprazolam, caffeine, clindamycin, clonazepam, cortisol, ethinyl estradiol, and verapamil, may cause toxic effects when administered with imatinib mesylate.<sup>81</sup> Frye et al<sup>82</sup> recently reported that the popular over-the-counter product, St John's wort, increased imatinib clearance by 43%. Acetaminophen is also metabolized by CYP3A4, and patients should be advised to avoid daily use or excessive amounts of this agent. Recent studies have also shown in vitro synergism between imatinib mesylate, other tyrosine kinase inhibitors, and cytotoxic chemotherapeutics.<sup>83</sup>

### Phase I Studies of Imatinib Mesylate in GISTs

A single-patient pilot study confirmed the efficacy of imatinib mesylate in GISTs. This first patient to be treated with imatinib mesylate was a 50-year-old woman with chemotherapy-resistant metastatic GIST who received once-daily doses of 400 mg of imatinib mesylate starting in

March 2000. Response was evaluated objectively, using 18 fluorodeoxyglucose positron-emission tomography (FDG-PET) and CT radiography. The patient's tumor remained stable after 1 year of therapy, and she had only mild GI side effects. Serial tumor biopsies revealed myxoid degeneration after only 4 weeks of treatment.<sup>84</sup>

A phase I study of imatinib mesylate in GIST was done in three centers of the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group.<sup>85</sup> Between August 3 and December 21, 2000, 40 patients (36 patients with advanced GIST) received imatinib mesylate at doses of 400 mg once daily, 300 mg twice daily, 400 mg twice daily, or 500 mg twice daily. The maximum tolerated dose of imatinib mesylate was judged to be 400 mg twice daily due to unacceptable toxicity at the 500-mg twice-daily dose, which included grade 3 nausea/vomiting, edema, and dyspnea. Myelosuppression was an infrequent side effect and did not seem to be dose-dependent. However, mild anemia and neutropenia grade 2 or 3 were reported. Although not the primary endpoint, a partial response rate of 53% was reported (Table 1).

### Phase II Studies of Imatinib Mesylate in GISTs

These encouraging results, as well as the experience of using imatinib mesylate in patients with chronic myelogenous leukemia, led to the rapid deployment of several phase II and phase III studies of imatinib mesylate in GIST. The initial trial, designated as the US-Finland trial,<sup>76</sup> was a multicenter, open-label, randomized phase II clinical trial of imatinib mesylate in patients with unresectable or metastatic KIT-expressing GIST. Between July

2000 and April 2001, 147 patients were randomly assigned to receive 400 or 600 mg of imatinib mesylate orally daily. At a median follow-up of 24 months, 63% of patients had a partial response, 19% of patients had stable disease, and 12% had confirmed tumor progression (Table 1, by WHO criteria). The median time to progression was 72 weeks, and the median survival had yet to be reached. The response rates did not differ significantly between the two doses.<sup>76</sup>

The above results were confirmed with another phase II trial performed by the EORTC Soft Tissue and Bone Sarcoma Group (Table 1). A total of 27 patients with advanced and/or metastatic GIST received imatinib at the highest feasible dose of 400 mg twice daily. Side effects were mild to moderate, and the most common effects included anemia, periorbital edema, skin rash, fatigue, nausea, granulocytopenia, and diarrhea. Response rates were similar to those in the US-Finland phase II trial: 4% complete response rate, 67% partial response rate, 18% stable disease, and 11% disease progression. At 1 year, 73% of patients were free of disease progression.<sup>86</sup>

### Phase III Studies of Imatinib Mesylate in GISTs

Two large consortia conducted two phase III studies nearly simultaneously. One was the North American Sarcoma Intergroup study S0033, consisting of the US cooperative oncology groups (Southwest Oncology Group, Cancer and Leukemia Group B, and the Eastern Cooperative Group) and the National Cancer Institute of Canada Sarcoma Group. The primary aim of this study was to assess the impact of imatinib mesylate dose (400 mg vs 800 mg daily) on survival. Secondary aims were to evaluate response rates and confirm the tolerability of imatinib mesylate therapy in patients with GIST. Between December 15, 2000, and September 1, 2001, 746 patients from 57 institutions were enrolled. Patients randomized to receive the 400-mg daily dose were allowed to cross over to the 800-mg daily dose if they had progressive disease. Early results of this trial were presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2003.<sup>73</sup> At a median follow-up of 14 months, overall response rates were similar in both arms: 43% at the 400-mg dose and 41% at the 800-mg dose. There was no difference in progression-free or overall survival between dose levels. The most recent update of this trial was presented at the 2004 ASCO meeting.<sup>87</sup> Median overall survival had not been reached in either arm after a median follow-up of 25.6 months, and there were no significant differences between the two arms in progression-free and overall survival. Progression-free survival rate estimates at 2 years are 50% for the 400-mg arm and 53% for the 800-mg arm. Survival estimates at 2 years are 78% vs 73% for the 400-mg vs 800-mg arms, respectively. However, of the 106 patients who crossed over to the higher dose after having progressive disease on the 400-mg daily dose, 7% had a partial response and 32% had stable disease, indicating that

**Table 2. — Toxicity Associated With Imatinib Mesylate Therapy in the US-Finland Phase II Trial of 147 Patients With Advanced GIST**

Symptom	Any Grade (%)	Grade 3 or 4 (%)
Fluid retention	74.1	1.4
Nausea	52.4	1.4
Diarrhea	44.9	2.0
Myalgia or arthralgia	43.6	0
Fatigue	34.7	0
Rash	30.6	2.7
Headache	25.9	0
Abdominal pain	25.9	0.7
Vomiting	12.9	0.7
Hemorrhage	12.2	4.8
Dyspepsia	10.9	0
Lacrimation	9.5	0
Anemia	8.8	2.0
Taste disturbance	8.2	0
Neutropenia	6.8	4.8
Abnormal liver-function results	5.4	2.7
Blurred vision	3.4	0
Photosensitivity	2.7	0

From Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347:472-480. Copyright © 2002 Massachusetts Medical Society. All rights reserved. Adapted with permission.

patients can benefit from a higher dose after their disease progresses on 400 mg daily.

The EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastro-Intestinal Trials Group conducted the second phase III trial of imatinib mesylate (Table 1). Between February 2001 and February 2002, 946 patients with GIST were randomized to receive imatinib mesylate at a dose of either 400 mg daily or 400 mg twice daily. This trial was powered to detect a 10% difference in progression-free survival rates, with objective response to treatment as a secondary endpoint. The objective response rates were 50% and 54% for the 400-mg and 800-mg arms, respectively. The 2-year overall survival estimate was 69% for patients treated at an initial daily dose of 400 mg and 74% for those patients started at 400 mg twice daily ( $P=NS$ ). Progression-free survival rates were 44% and 52% ( $P=.026$ ) for patients allocated to imatinib once a day compared to twice a day, respectively.<sup>88</sup> As reported earlier, the North American trial did not show a difference in survival or progression-free survival, and the reason for this discrepancy is unknown. It is possible that different results in the two studies are due to the greater number of patients enrolled in the EORTC study, thus allowing more power to detect statistical differences. Another possible explanation would be different genetic composition of patients enrolled in the two trials. Moreover, the patients enrolled in these two trials have not been analyzed by location of *kit* mutation. It is possible that exon 11 mutation was more common in tumors from patients enrolled in the EORTC study compared to those in the US Intergroup trial.

### Safety and Tolerability of Imatinib in GISTs

The US-Finland phase II trial demonstrated that imatinib mesylate was generally well tolerated. However, virtually every patient had at least some mild or moderate adverse events (grade 1 or 2) that were attributable to therapy.<sup>75</sup> The most common adverse events were edema (which was most frequently periorbital), nausea, diarrhea, myalgia or musculoskeletal pain, fatigue, rash, headache, and abdominal pain (Table 2). Although most of these adverse events were mild or moderate, 21% of patients had serious adverse events (grade 3–4). Five percent of patients experienced intra-abdominal hemorrhages,<sup>75</sup> which were postulated to be associated with massive tumor necrosis induced by this active agent.

Early toxicity results of the large phase III trial conducted by the EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastro-Intestinal Trials Group were reported at the ASCO 2002 annual meeting.<sup>89</sup> The most frequent side effects were anemia (88%), edema (67%), fatigue (60%), nausea (44%), neutropenia (32%), and skin rash (24%). Most side effects were mild to moderate. However, 1 patient died of drug-related neutropenic sepsis. In summary, imatinib mesylate is safe and generally well tolerated at doses up to 800 mg daily.

### Preoperative and Postoperative Imatinib in GISTs

The high response rates with imatinib in the advanced and metastatic setting have fostered interest in its role in the adjuvant setting. There may be an improvement in surgical outcome in patients treated with imatinib pre-

Table 3. — Surgery and Imatinib for GIST: Clinical Trials

Trial	Description	Objectives
MDACC ID03-0023	Study of preoperative plus postoperative imatinib in patients with GIST with laboratory correlates	Determine the preoperative safety of imatinib, the progression-free survival, overall survival, and the early molecular events that lead to response in patients with GIST treated with imatinib
RTOG-S0132	Neoadjuvant and adjuvant imatinib in patients with resectable GIST	Determine progression-free survival, objective response rate, and safety; 8 weeks of imatinib therapy, then surgical debulking of all gross tumor and reinstitution of imatinib for 2 years
ACOSOG-Z9000	Phase II study of adjuvant imatinib mesylate in patients with completely resected high-risk primary GIST	Determine 2- and 5-year recurrence rates and toxicity; imatinib initiated within 84 days of surgical resection and continued for 1 year; enrollment complete
ACOSOG-Z9001	Phase III randomized study of 1 year of adjuvant imatinib vs placebo	Compare overall and recurrence-free survival, adjuvant imatinib vs placebo for 1 year, with crossover to imatinib if recurrence; projected enrollment = 380
EORTC Soft Tissue and Bone Sarcoma Group	An adjuvant trial of 2 years of imatinib vs placebo	Compare adjuvant imatinib vs no treatment with respect to progression-free and overall survival; risk stratification/randomization after complete GIST resection; projected enrollment = 400
Scandinavian Sarcoma Group Trial SSGXVIII	An adjuvant trial of imatinib administered for 1, 2, or 3 years after resection	Determine recurrence-free survival, safety, overall survival; projected enrollment = 80

ACOSOG = American College of Surgeons Oncology Group  
GIST = gastrointestinal stromal tumor  
EORTC = European Organization for Research and Treatment of Cancer  
RTOG = Radiation Therapy Oncology Group

operatively. Currently, there are several ongoing phase II and III trials to address combining surgery and imatinib (Table 3).

Patients with resectable or potentially resectable GISTs may be eligible for one of two clinical trials in which patients receive preoperative imatinib: MDACC ID03-0023<sup>90</sup> or Radiation Therapy Oncology Group S0132.<sup>91</sup> These trials provide innovative approaches with important biologic correlates that may provide insight into the mechanism of action of imatinib in GIST. In ID03-0023, patients with resectable GIST undergo standard surgery followed by adjuvant imatinib mesylate for 2 years (Fig 2). In order to understand the early molecular and pathologic changes in GIST tumors treated with imatinib mesylate with respect to PET response, patients will undergo baseline studies including a tumor biopsy followed by therapy with imatinib mesylate and surgical resection. Genomic changes, KIT signaling, tumor vascularity, and apoptosis are evaluated before and after imatinib.<sup>92</sup>

Patients whose GIST has been resected may be eligible for a clinical trial of adjuvant imatinib through the American College of Surgeons Oncology Group (ACOSOG Z9001).<sup>93</sup> On this trial, patients with completely resected high-risk GIST are randomized to receive either 1 year of adjuvant therapy with imatinib vs placebo. Patients must have a KIT-expressing GIST and be registered within 70 days of their surgical resection. This study will determine whether postoperative imatinib will improve disease-free survival.

### Imatinib Mesylate-Refractory GISTs

The appropriate management of metastatic GIST that has not responded or has become resistant to imatinib mesy-

late is not known. Patients with imatinib-resistant GIST should be given the option of participating in a clinical trial. Clinical trials for this patient population are in various stages of development, although none have been published in a peer-reviewed journal. An ongoing clinical trial for which patients with imatinib mesylate-refractory GIST are eligible is that of the topoisomerase I inhibitor irinotecan (Camptosar, CPT-11) given daily for 5 days with 2 days off for 2 weeks on an every-3-week schedule at a dose of 20 mg/m<sup>2</sup> per day. In development are clinical trials combining imatinib mesylate with oblimersen (Genasense), an inhibitor of the antiapoptotic protein bcl-2, and single-agent Amgen 706, a small-molecule multi-targeted kinase inhibitor of KIT and the vascular endothelial growth factor receptor (VEGFR).<sup>94</sup> An alternative study sponsored by Pfizer Inc is now recruiting patients with either imatinib-resistant disease or intolerance to imatinib to be randomized to receive either a placebo or SU11248, a multi-targeted receptor tyrosine kinase inhibitor of PDGFR, VEGFR, and KIT. The sarcoma community has recognized that GIST patients with progression of disease experience a rapid acceleration of progression if imatinib is discontinued. Thus, it appears that patients with an enlarging GIST continue to benefit from imatinib therapy rather than discontinuation, including randomization to the placebo arm of a study.

Physicians should be encouraged to refer patients with GIST to centers that have access to these clinical trials. For those patients whose disease becomes refractory to imatinib mesylate and who are not eligible for a clinical trial, palliative therapy, such as hepatic artery embolization, surgical debulking, radiofrequency ablation, and intraperitoneal chemotherapy, should be considered.

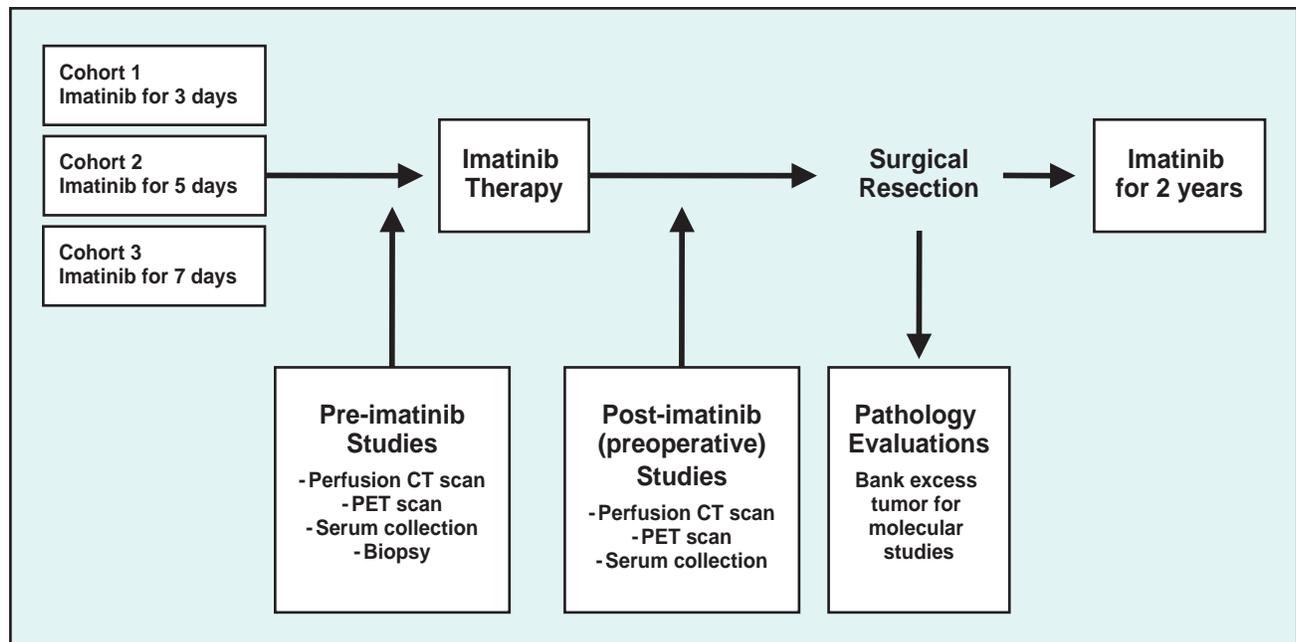


Fig 2. — The schema for an innovative trial to elucidate the mechanism of imatinib activity in GIST. Patients with operable GIST have baseline evaluations, a biopsy, repeat evaluations and surgical resection. Laboratory correlates include angiogenesis, apoptosis, and genomics.

## Conclusions

Imatinib mesylate has quickly become the most active targeted, small-molecule therapy in patients with solid tumors. Imatinib mesylate is the first-line agent for metastatic GIST and is currently being evaluated against other tumor types. Several ongoing studies of imatinib mesylate in GIST address the important issues of efficacy of neoadjuvant and adjuvant therapy, duration of therapy, safety in the perioperative period, and molecular response measured by PET imaging. The use of imatinib mesylate for treating patients with GIST will be tailored by the final results of these neoadjuvant, adjuvant, and metastatic clinical trials and their associated correlative studies.

The identification of imatinib mesylate as an agent to specifically target the critical pathogenetic mechanisms of GIST represents a major advance in the treatment of this disease. The information gained from the success of imatinib mesylate in GIST will enhance drug development for oncology in general, but many challenges lie ahead in the applications of these strategies to other human cancers.

On the basis of current studies, it appears that few patients with metastatic GIST exhibit complete responses to imatinib mesylate therapy, perhaps due to relatively slow responses or the failure of imatinib mesylate to induce cell death in some cases. The exact cause may be determined by studies in which GIST patients receive imatinib mesylate preoperatively. If in fact imatinib mesylate arrests cell growth but does not induce apoptosis, combination therapy with a proapoptotic agent would be intriguing. If imatinib mesylate has no effect on tumor vasculature, perhaps combining it with an antiangiogenic agent would enhance efficacy.

The mechanisms of primary and acquired resistance to imatinib mesylate are unknown but are being investigated. It is possible that the site of the mutation on the *kit* gene determines the kinetics of KIT inhibition by imatinib mesylate. Tumors from patients whose disease relapses after an initial response to imatinib mesylate therapy may be undergoing clonal selection for tumor cells encoding a *kit* mutation in an imatinib mesylate-resistant domain, such as the ATP binding site. Alternatively, resistance may develop through the activation of pathways located downstream or in parallel to KIT, and therefore the tumor cells are not sensitive to inhibition by imatinib mesylate. Whatever the outcome, this is an opportunity to understand the biological basis of resistance to one of the most successful therapeutic advances in oncology.

It appears that the wild-type expression of KIT is not sufficient to confer the antitumor activity of imatinib mesylate. Thus, inhibiting a normal target may not have antitumor activity if the target does not provide an essential function to the tumor cell. Therefore, identification of molecular abnormalities that are essential for tumorigenesis will lead to the development of new anticancer therapies.

Understanding diseases such as GIST may lay the foundation for understanding the more complex types of human cancer.

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