Gastrointestinal Stromal Tumors

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Opinion statement

Gastrointestinal stromal tumors (GISTs) are mesenchymal gut tumors that differ dramatically from other histologically similar neoplasms, such as leimomyomas, leiomyosarcomas (LMS), and neural tumors. Complete surgical removal remains the best current therapy for GISTs, but even major resections are associated with recurrence in approximately 90% of cases. GISTs are remarkably resistant to irradiation and standard chemotherapy; there is no role for treatment with those modalities. Treatment of advanced GIST patients with STI571, a novel selective tyrosine kinase inhibitor, results in remission rates that approach 60% and overall tumor control rates of 85%. Selected groups of patients, as based on tumor mutational status, have response rates as high as 80%. To date, STI571 therapy remains the only systemic treatment for GISTs to have meaningful clinical activity. Though other molecularly targeted therapies exist in oncology (eg, trastuzumab), STI571 is one of the first that applies a drug specifically designed to inhibit the product of a constitutively-activating mutation that drives pathogenesis of a solid tumor. Its use can serve as a paradigm for designing molecularly targeted therapies for other malignancies.

Introduction

Gastrointestinal stromal tumors (GISTs) are connective tissue neoplasms of the gut that may arise from any hollow GI viscera, or from mesentery and omentum [1•]. GISTs may show muscular, neural, or mixed differentiation features, and they represent a distinct pathophysiologic entity. Estimating their previous and current true annual incidence rates is difficult, because most GI tumors formerly classified as sarcomas (*eg*, gastric leimomyosarcomas) are now recognized as GISTs. However, between 5000 and 10,000 new cases of GIST are diagnosed each year in the United States. Many are small, benign appearing tumors, but predicting biologic behavior (specifically the risk of recurrence and/or metastasis) also is difficult. Factors said to be prognostic for aggressive behavior are non-gastric location, size greater than 5 cm, mitotic rate greater than 1 to 5 per 10 high power fields, mucosal infiltration, tumor necrosis, and high nuclear to cytoplasmic ratio [2]. GISTs most commonly arise from the stomach (approximately 60% to 70% of cases), and they occur in middle-age patients (median 55 to 65 years of age). They are probably more prevalent in males, though some series have suggested equal distribution between the sexes. Patients most commonly present with gastrointestinal bleeding, though symptoms of pain and nausea may be present. Many (approximately 30) of these tumors are asymptomatic and are found at screening or during investigation of other GI complaints. Median survival is 66 months for fully resected patients, but is only 9 to 20 months for those with locally advanced or metastatic disease.

GISTs differ from true LMS in many ways [3••]. GISTs tend to spread to the liver and throughout the abdomen (versus the pulmonary metastases seen commonly with true muscle tumors), and they are more likely to express multidrug resistance proteins. GISTs are markedly more chemoresistant than LMS (see Pharmacologic section below), and they have a significantly worse 5-year survival. Though GISTs often express muscle markers (*eg*, actins), they also express markers not associated with LMS, such as the hematopoietic progenitor cell antigen CD34, (approximately 70% of GISTs), as well as the KIT receptor tyrosine kinase (CD117 antigen in up to 100% of cases).

c-Kit is the normal cellular homologue of a viral oncogene. Its product, KIT, is a transmembrane receptor tyrosine kinase. c-Kit mutation allows activation without ligand binding [4•], leading to potential constitutive cell proliferation, and enhanced survival, migration, and differentiation. Mutations that drive potentially malignant behavior have been described in 15% to 80% of GISTs and formerly were thought to be associated with an increased risk of disease recurrence after curative surgery. They were also thought to predict worse overall survival. This thinking has been challenged recently (see Pharmacologic section below).

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Treatment

Procedures

- Interventional procedures for both locally advanced and recurrent/metastatic GIST should be performed for palliation of gastrointestinal bleeding.
- Bleeding complications of GIST (up to 50% in some series) [5,6], can occur either intraluminally or intraperitoneally.

Percutaneous transarterial embolization

Standard procedure	Arterial embolization can be useful in clinical situations, such as when a patient with large primary or metastatic/recurrent GIST presents with bleeding complications requiring transfusion. The gastrointestinal bleeding generally emanates from tumor erosion into a major vessel, or from friable neovascularity associated with a rapidly expanding tumor mass. Successful application of this technique requires angiographic demonstration of ongoing bleeding and a feeder vessel or vessels that can be selectively embolized. This technique may require repeated applications to be effective. Rebleeding after a successful embolization is not an uncommon occurrence.
Contraindications	The patient must be hemodynamically stable and must have normal or mildly elevated renal function. The procedure cannot be successful without active bleeding and the demonstration of an identifiable source vessel.
Complications	Selective vessel embolization and thrombosis can result in tissue necrosis and abscess or visceral perforation. In addition, the standard potential complications of arterial manipulation (intimal flap dissection and thrombosis of the major entry peripheral artery) can rarely be seen.
Special points	This method should only be considered as a palliative procedure for those patients who have GI bleeding that requires multiple or frequent transfusions, who otherwise have no other significant sequelae of advanced disease (*eg*, multiple sites of obstruction). Embolization is more effective in the management of intratumoral or intraluminal bleeding, rather than free intraperitoneal bleeding and hemoperitoneum.
Cost effectiveness	The procedure is cost effective relative to the alternative of multiple or prolonged hospitalizations and transfusions.

Surgery

- The primary treatment for gastrointestinal stromal tumor is surgical resection. Thus far, this is the only therapy that offers the possibility of long-term disease control and potential for cure.
- Approximately one half of the patients who present with the initial diagnosis of GIST will have primary localized non-metastatic disease. Of these, approximately two-thirds will undergo complete surgical resection of all disease [7••].
- The outcome (freedom from disease and overall survival) of surgical resection of a primary GIST depends on many variables, including the ability to resect all gross disease, and the size and grade of the tumor.
- Despite adequate surgical resection (even in those with favorable prognostic features), recurrence rates remain high in single institutional series. Five-year disease-specific survival rates approximate 50% [8••, 9, 10]. Patients also may have late relapses. Long-term follow-up in some series indicate only 10% of patients are cured of disease [11].
- Locally recurrent or metastatic GISTs are associated with extremely poor outcomes, with median survivals of 6 to12 months.

Complete resection of the primary tumor

Standard procedure The standard surgical resection for primary non-metastatic GIST should include a complete resection of all gross tumor. Depending on the organ of involvement (stomach, small intestine, colon) and the size of the tumor, a subtotal or segmental resection is adequate, provided that all gross disease is removed. It is unusual for GISTs to involve regional lymph nodes; therefore a standard lymphadenectomy is not required. Additionally, because microscopic margin status after removal of all gross disease is not an important prognostic feature, a conservative resection without wide margins is adequate for disease clearance. If tumor spillage is encountered or if gross disease is left behind, survival is significantly altered. The surgical resection technique should follow standard guidelines of organ resection/preservation and reanastomosis. Palliative surgery (leaving gross residual disease) can be justified in those patients with good performance status, for whom surgery may ameliorate symptoms associated with obstruction or bleeding.

Contraindications Patients with contraindications for major abdominal surgery, and those patients who are asymptomatic with clear preoperative staging evidence of unresectable disease.

Complications Complications may be those of any major abdominal GI procedure, including risks of anastomotic leak, bleeding, and postoperative infectious complications.

Special points There has been no effective adjuvant therapy to offer to patients who undergo complete GIST resection. These patients are profiled as high risk for recurrence (*eg*, >10 cm, high grade). A trial sponsored by the American College of Surgeons Oncology Group (ACOSOG) will address the potential benefit of STI571 (see Pharmacologic section below) in this population.

Surgical resection for recurrent or metastatic GIST

Standard procedure Recurrence involves peritoneal surfaces or the liver. Hepatic metastases are reported in approximately two thirds of patients with recurrence after primary resection. The liver is the only site of recurrence in 44% of patients. Preoperative staging involves complete diagnostic scanning to detect presence and overall extent of this potential disease recurrence. Selected patients who have either single site disease (liver) or low volume multiple site disease (peritoneal surfaces) should have an attempt made at complete surgical resection. The surgical technique depends on the recurrence site. Resection of multiple intra-abdominal

organs and debulking is not warranted and will not result in substantial benefit. The possible unusual exceptions to this are the patients with localized bleeding or obstruction and otherwise excellent performance status.

Contraindications Contraindications include poor performance status and significant comorbid conditions.

Complications These are associated with the site and extent of surgical resection, including but not limited to bleeding, infections, bile leak, and abscess. The morbidity of a major hepatic resection should not exceed 20%.

Special points

Despite the poor prognosis of this patient group, complete surgical resection of local recurrence or metastatic disease (including peritoneal implants), can provide selective patients with median survival of 16 (metastatic disease) to 54 months (local recurrence only). Overall, however, previous data regarding surgical management and outcome in patients with recurrent, unresectable, or metastatic GIST all suggest minimal benefit, with short duration of disease-free survival; only a few patients derive meaningful results. However, STI571, the specific molecular targeted inhibitor of KIT (see Pharmacologic section below), has the potential to change the surgical paradigm. The neoadjuvant/adjuvant use of STI571 may increase the number of patients eligible for surgical management of locally advanced, recurrent, or metastatic disease, by downstaging the tumor size and extent, and improving the long term prospects for survival even in the face of residual gross disease. Additionally, knowledge of the specific mutational profile of a GIST relative to the c-Kit oncogene may enhance selection factors of patients considered for extensive surgery. As they are clarified, the presence of other molecular downstream mediators of response also may become important in determining surgical options. A Radiation Therapy Oncology Group (RTOG) clinical study supported by the Cancer Therapy Evaluation Program (CTEP) will address some of these issues.

Pharmacologic treatment

- Deriving the true response rate of GISTs to standard chemotherapy is difficult. Older trials included many patients with non-GIST muscle and/or neural tumors, which may be more chemosensitive than GISTs.
- A phase II trial contrasted the response rate of patients with proven advanced GIST with those who had other incurable LMS [12••]. Thirty-nine patients were treated with outpatient doxorubicin-based combination chemotherapy. The response rate for the LMS patients was 67% (95% CI = 44–90), including a 33% response rate in those with somatic tumors. Only a single response was seen in the 21 GIST patients (colon primary), for an overall response rate of 4.8% (95% CI = 0–14.5).
- A phase II trial of STI571 (see below) allowed patients to have previous treatment with chemotherapy (n = 81) or irradiation (n = 24)[13••]. The investigators reported fewer than 1% of patients responded to these modalities.
- STI571 (Imatinib mesylate) is a 2-phenylaminopyrimidine derivative that selectively inhibits several tyrosine kinases, such as platelet derived growth factor receptor (PDGFR), bcr-abl (the causative molecular defect in chronic myelogenous leukemia-CML), and both wild-type and mutated KIT. Pre-clinically, treatment with STI571 leads to apoptosis in cells dependent on the kinase activity of the KIT receptor [14•]. Treatment of chronic phase CML patients at a dose of 300 mg daily, for greater than 4 weeks, leads to durable complete hematologic remissions in 98% of cases [15]. A recent case report described the treatment of a patient with advanced GIST who was heavily pretreated with STI571, at a dose of 400 mg per day [16•].

The patient had a dramatic metabolic response as evidenced by decreased uptake on positron emission scan within one month of starting drug, histologic changes suggesting necrosing and fibrosing of tumor, and true radiographic evidence of tumor regression. The response was reported as durable, lasting at least 11 months after the start of treatment.

- Two trials that tested STI571 in treatment of GIST patients were presented at the Plenary Session of the 2001 meeting of the American Society of Clinical Oncologists [13••,17••]. The EORTC Soft Tissue and Sarcoma Group performed a phase I study of STI571 in patients with advanced soft tissue sarcomas, including GISTs [17••]. KIT positivity was required for patients with the stromal cancers. Forty patients, of whom 36 had GISTs, were treated with dose levels from 400 mg to 1000 mg daily, with therapy continuing until progression, unacceptable toxicity, or patient refusal to proceed. A dose of 500 mg twice a day resulted in dose-limiting toxicities (mostly nausea and vomiting) in 5 of 8 patients. Substantial activity was seen only in the GIST patients, with 36% having confirmed responses, and 33% unconfirmed or minor responses. Eleven percent frankly progressed. Non-GIST patients did dramatically worse, with no documented responses in that treatment population. The investigators recommended a dose of 400 mg twice a day be pursued for phase II testing.
- The second reported ASCO trial was a randomized phase II study of STI571 in patients with unresectable or metastatic KIT-positive GISTs [13••]. The primary goal of the study was to determine objective response rates in patients treated with a 400 mg or 600 mg total daily dose of STI. One hundred forty-eight patients were randomized, with 145 evaluable for toxicity and 86 (with 3 months' minimal follow-up) evaluable for efficacy. Eighty-nine percent of symptomatic patients derived clinical benefit, as evidenced by improvement in performance status and/or decreased need for narcotics. Overall objective response rates were 50% for patients who received 400 mg daily, and 68% for those who received 600 mg, for an overall partial response rate of 59%. An additional 26% had prolonged stable disease, and 13% frankly progressed. Analysis of tumor mutational status demonstrated 86% of patients had c-kit mutations. Those patients whose tumors had an activating mutation of c-kit had a significantly higher chance of response to STI571 (78% for those with exon 11 mutations versus 29% for those with wild-type c-kit). This trial established STI571 as an active treatment for advanced GIST, but it could not define the most appropriate dose. That question should be answered by the recently completed U.S. Intergroup Trial, or the phase III EORTC study, both of which test 400 mg versus 800 mg daily.

STI571 (Imatinab mesylate)

Standard dosage	The best standard dosage is currently unknown. The EORTC Soft Tissue and Bone Phase I Study Group has suggested 400 mg orally twice a day might be optimal. The current EORTC and U.S. Intergroup trials compare 400 mg daily with 800 mg each day.
Contraindications	Acute or chronic liver disease.
Drug interactions	Medications that interact with the CYP450 enzymes (2D6 and 3A4) may reduce activity or enhance toxicity of STI571 or may themselves have a change in level of activity. Warfarin use with STI571 is discouraged or at least should be monitored closely.
Side effects	Severe or life threatening toxicities were seen in 21% of patients on the GIST Working Group study. These included gastrointestinal bleeding (tumor related, and not mucosal injury), hepatotoxicity, neutropenia, and infection. Other toxicities

seen were abdominal pain, rash, and diarrhea. Fatigue, thrombocytopenia, and arthralgias/myalgias have been described in the chronic phase CML population treated with STI571.

Special points On the American trial, no patient progressing on the lower dose of STI (400 mg daily) then responded to the higher (600 mg per day). On the European study, one patient progressing on 400 mg stabilized when escalated to 400 twice a day, and one progressing on 400 daily actually responded to the higher dose.

Cost effectiveness No data exist.

Radiation therapy

- Irradiation is clearly effective in therapy of other soft tissue sarcomas. However, data are sparse on its use in GIST. One case report discussed adjuvant irradiation (5040 cGy) after resection of a high-risk GIST), with no recurrence 2 years after treatment [18]. Shioyama discussed treatment of a retroperitoneal GIST with primary radiotherapy (5100 cGy), accompanied by arterial chemotherapy (carboplatin and epirubicin) and immunotherapy (OK432) [19]. Serum lactate dehydrogenase normalized by the end of irradiation, with no change on computerized tomographic scan at that time. Computed tomography performed 6 years after completion of therapy showed a marked decrease in tumor size. Patients on the GIST Working Group Study frequently had been treated with irradiation before enrollment. Few if any patients responded. Overall, GISTs do not appear to be particularly radiosensitive.

Emerging therapies

- With the exception of STI571, there is no effective systemic therapy for GISTs. However, many questions still remain regarding the best use of that drug. Its precise mechanism of action (KIT inhibition alone versus inhibition of other targets such as PDGFR) is not completely characterized, and the optimal dose is not known. It is unclear whether patients who achieve remission can safely stop the drug, or even whether how long responses (or stability) will last in patients who do not progress but continue therapy.
- Other KIT tyrosine kinase inhibitors exist, such as PTK787 and SU6668. These could be effective in treatment of GISTs. They are slightly less potent than STI571 for KIT inhibition in vitro, but unlike STU571 offer the possible advantage of directly inhibiting angiogenesis. With the exception of STI571, most other KIT tyrosine kinase inhibitors are in preclinical studies or are currently being tested only in non-GIST malignancies.

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