

Educational Review

The GIST of Targeted Cancer Therapy: A Tumor (Gastrointestinal Stromal Tumor), a Mutated Gene (*c-kit*), and a Molecular Inhibitor (STI571)

Ronald P. DeMatteo, MD

Abstract: Although gastrointestinal stromal tumor (GIST) is the most frequent mesenchymal neoplasm of the gastrointestinal tract, until recently it has been an obscure disease. Now, there is widespread scientific and clinical interest in GIST because its principal pathogenetic defect has been identified and a specific molecular inhibitor of GIST has been developed. Most GISTs contain a gain-of-function mutation in the *c-kit* proto-oncogene. Mutation results in constitutive activation of the Kit receptor tyrosine kinase, which induces cellular proliferation. STI571 is an oral agent that selectively inhibits Kit. It is a landmark development in cancer treatment and marks a new era of targeted molecular therapy. Its efficacy proves that a specific inhibitor can counteract the effects of a genetic defect responsible for neoplasia. Although STI571 was first applied to GIST only 2 years ago, it has already revolutionized the treatment of patients with metastatic disease and is also currently being tested as an adjuvant therapy after the resection of primary GIST.

Key Words: Gastrointestinal stromal tumor—GIST—*c-kit* Proto-oncogene—STI571.

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Currently, it is believed to originate from an intestinal pacemaker cell called the interstitial cell of Cajal.¹ GIST may develop anywhere along the gastrointestinal tract, but most often it arises in the stomach and, less commonly, in the intestine. Occasionally, GIST develops outside the gastrointestinal tract in the mesentery, omentum, or retroperitoneum. Only within the last 5 to 10 years has GIST been distinguished from visceral leiomyosarcoma, which has a similar appearance by light microscopy. GIST had also been designated variably as leiomyoblastoma,² plexosarcoma,³ gastrointestinal autonomic tumor,⁴ or gastrointestinal pacemaker cell tumor.¹

Because of prior diagnostic inconsistencies, the precise incidence of GIST is unknown. In the United States, there are probably between 500 and 1000 new cases per year, excluding the small (<1 cm), benign tumors that are discovered incidentally. The diagnosis of GIST has been facilitated considerably by the widespread application of Kit (CD117) immunohistochemistry (Fig. 1), which is nearly always positive in GIST.⁵ There is also a greater general awareness of this distinct pathologic entity because there is now an effective treatment for it.

The median age at the time of initial diagnosis of GIST is 58 years, and most patients are between 40 and 80 years old.⁶ Overall, men are affected somewhat more often than women. There is a rare entity, called Carney's triad, that occurs predominantly in young women; it is associated with gastric GIST, paraganglioma, and pulmonary chondroma.⁷ However, only one fourth of patients manifest the complete syndrome. There is a broad range of clinical presentation of patients with GIST. Those with small tumors are usually asymptomatic, and their tumor may be discovered incidentally, either at laparotomy performed for other reasons or on radiolog-

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From the Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York.

Address correspondence and reprint requests to: Ronald P. DeMatteo, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; Fax: 212-639-4031; E-mail: dematter@mskcc.org.

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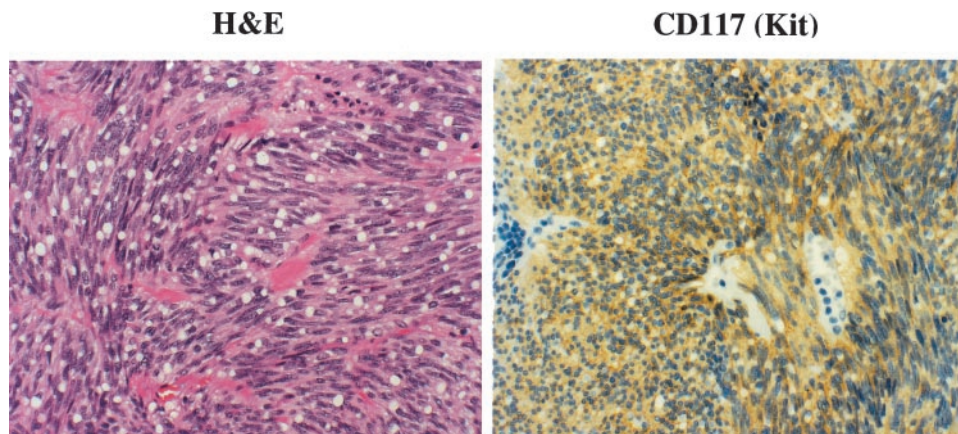


FIG. 1. Kit (CD117) staining in gastrointestinal stromal tumor. The left panel shows hematoxylin and eosin staining, and the right panel demonstrates Kit immunohistochemistry of the same tumor. Diffuse, high-level Kit staining is typical. Magnification $\times 40$ (courtesy of Dr. Cristina Antonescu, Department of Pathology, Memorial Sloan-Kettering Cancer Center).

ical examination. Patients with larger tumors may experience abdominal discomfort or develop a palpable mass. Nevertheless, even massive tumors may not be recognized for quite some time. Hemorrhage into the gastrointestinal tract or peritoneum from tumor rupture may herald the disease in up to one fourth of patients.

GIST represents a spectrum of tumors that range from benign to highly malignant. Predicting the clinical behavior of a particular GIST is imprecise. In general, the malignant potential of GIST depends primarily on tumor size, mitotic activity, and anatomical origin. However, there are no widely accepted criteria for what constitutes a malignant GIST. Consequently, many pathologists will classify GIST only as low risk or high risk of being malignant. It is generally agreed that almost all tumors <1 cm in size are benign. Conversely, tumors >5 to 10 cm are usually malignant, as are tumors with >2 to 5 mitoses per 10 high-power microscopic fields.⁸ Tumors from the small intestine often behave more aggressively than tumors from the stomach. However, most GISTs fall into a “gray zone,” and, therefore, the ultimate determination of malignancy depends on the development of tumor recurrence or metastasis.

TREATMENT OF PRIMARY GIST

Surgical Resection

The principal treatment of a patient with a primary GIST is complete surgical resection. The tumor is often fragile, especially if it is large or there is extensive intratumoral hemorrhage or necrosis. Therefore, preoperative biopsy is used selectively to avoid the risk of rupture, bleeding, or tumor extravasation. Meticulous

surgical technique is necessary to avoid intraoperative tumor rupture, which is associated with a poor prognosis.⁹ Usually, only a wedge or segmental resection of the underlying organ is required because GISTs tend to protrude from the tissue of origin and displace surrounding structures, unlike other intra-abdominal malignancies, which are often invasive. Consequently, negative surgical margins are usually attained. However, the importance of negative microscopic margins on the resected organ is dubious when there is a massive (e.g., 15-cm) GIST that is free to shed cells throughout the abdomen. Lymphadenectomy is not performed routinely in patients with GIST because lymph node metastases are rare.

Many of the published results of surgical resection in patients with primary GIST have several limitations. First, most of the series contain few patients because the disease is uncommon, and the experience at a single institution is therefore limited. To compensate for the small numbers, investigators often collectively analyze patients with primary disease and those with recurrent or metastatic disease. Most of the published results are also confounded by the inclusion of patients with other intra-abdominal sarcomas (leiomyosarcoma in particular) because of the previous difficulties in the diagnosis and classification of GIST.

Recently, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) reported a series of 200 patients who were treated and followed up prospectively.⁶ Of 93 patients who presented with a primary tumor and lacked metastasis, 80 (86%) were able to undergo complete surgical resection of their disease. These 80 patients were analyzed further. Their 5-year disease-specific survival rate was 54%. Tumor size was an independent

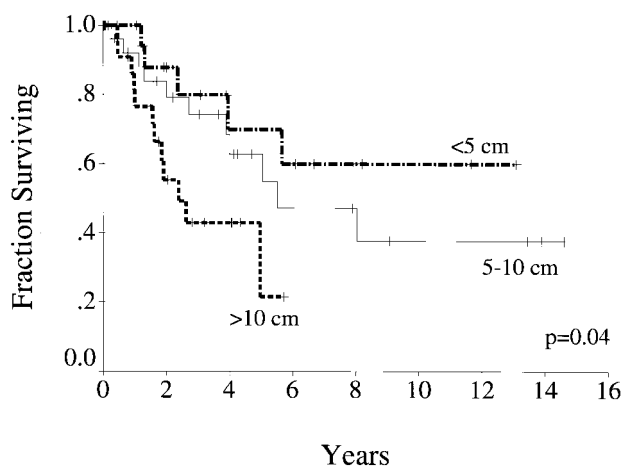


FIG. 2. Disease-specific survival after complete resection of primary gastrointestinal stromal tumor (GIST) in relation to tumor size. Eighty patients underwent complete resection of a primary GIST. Patients with tumors >10 cm (n = 27) had a lower survival rate than those with 5- to 10-cm tumors (n = 30) or <5-cm tumors (n = 23). (Reproduced with permission from DeMatteo et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000;231:51-8; Copyrighted 2000, Lippincott Williams & Wilkins).

prognostic factor of survival on multivariate analysis. Patients with tumors larger than 10 cm had a relative risk of 2.5 (95% confidence interval, 1.2-5.5) and only a 20% actuarial 5-year survival (Fig. 2). An older series from the M. D. Anderson Cancer Center with much longer follow-up showed similar findings.⁹ In addition to tumor size, mitotic rate, location, and tumor rupture, a variety of other prognostic factors have been identified, including aneuploidy, proliferative index, and percentage S-phase fraction.⁸

Adjuvant Therapy

Although many patients with GIST have a high likelihood of recurrence after surgical resection, adjuvant therapy with conventional chemotherapeutic agents is not indicated because of their lack of activity (vide infra). Radiotherapy also has limited value because of the radiosensitivity of surrounding structures, such as the intestine. There are only anecdotal reports of adjuvant radiation in GIST.^{10,11} It may be useful after the resection of rectal GIST in which there are close or positive microscopic margins.

TREATMENT OF METASTATIC GIST

After resection of the primary tumor, most patients still subsequently develop recurrent GIST. In some

cases, tumor rupture can account for the recurrence, particularly if it occurs in the peritoneum. However, in most patients, recurrence develops after what seemed to be a curative resection. Strikingly, only 13 (10%) of 132 patients who underwent complete resection of the primary tumor were disease free after a median follow-up of 68 months in the M. D. Anderson Cancer Center series.⁹ The median time to recurrence is approximately 1.5 to 2 years.^{6,12} The first site of recurrence in GIST is typically within the abdomen and involves the peritoneum, the liver, or both. In the MSKCC report, there were 27 patients who had complete resection of their primary tumor at MSKCC, were followed up prospectively, and had an assessable first recurrence.⁶ The first recurrence involved the peritoneum in half of the patients and the liver in nearly two thirds of the patients. Unfortunately, once patients develop recurrent disease, their chance of cure with conventional therapy is extremely low (i.e., <10%).

Conventional Chemotherapy

Conventional chemotherapeutic agents, including doxorubicin and ifosfamide, have only minimal activity in patients with metastatic GIST. As is the case with the surgical literature, most published studies of chemotherapy contain an admixture of GIST and other intra-abdominal sarcomas and are therefore difficult to interpret. There are only a few reports in which GIST was studied specifically. In a phase II study, only 1 (5%) of 21 patients with metastatic GIST treated with doxorubicin, dacarbazine, mitomycin, cisplatin, and granulocyte-macrophage colony-stimulating factor had a therapeutic response.¹³ In contrast, the response rate for intra-abdominal or retroperitoneal leiomyosarcoma was 33% (two of six patients). Meanwhile, other investigators have tested a variety of other agents without success.¹⁴ Multidrug resistance in GIST was suggested in one report to result from the increased expression of P-glycoprotein (17 of 25 patient specimens tested) and multidrug resistance protein (17 of 25 specimens tested).¹⁵ Overall, then, there is no obvious or standard drug regimen to use for patients with metastatic GIST.

Surgical Resection

Surgical resection may be beneficial in some patients with GIST who develop peritoneal recurrence. Unfortunately, what may appear as limited intraperitoneal disease on preoperative radiological imaging often turns out to be numerous nodules, if not frank sarcomatosis, at laparotomy. The recurrent tumors may be limited to the region of the primary tumor or located diffusely throughout the abdomen. As with primary GIST, recurrent peri-

toneal nodules tend to rest on the surface of the intestine, omentum, mesentery, or abdominal wall and not significantly invade the surrounding structures. Therefore, they can often be removed with limited resections. Lymph node metastases are uncommon as with primary GIST.

Unfortunately, resection of recurrent peritoneal GIST is seldom curative, even when all gross tumor is removed. To improve the results of surgery, Berthet et al.¹⁶ championed the strategy of cytoreduction and intraperitoneal chemotherapy for peritoneal recurrence of GIST and other intra-abdominal malignancies. The approach is rational for GIST because of the superficial growth pattern of the peritoneal tumors. It also provides justification to treat patients with sarcomatosis in whom all gross disease cannot be removed but can be debulked, and minimal residual disease (<1-cm nodules) can be treated with topical chemotherapy. Eilber et al.^{17,18} at the University of California–Los Angeles studied adjuvant intraperitoneal mitoxantrone after the resection or debulking of recurrent peritoneal GIST. Mitoxantrone, a derivative of doxorubicin, had been used previously in a similar manner for the treatment of ovarian carcinomatosis.¹⁹ It is an attractive agent because it binds rapidly to tissue and therefore achieves high local drug concentrations with minimal systemic absorption and toxicity. There were 33 patients with peritoneal recurrence treated with four to six treatments of mitoxantrone every 2 to 3 weeks at a dose of 20 mg/m² starting 1 to 2 weeks after surgery. There was minimal toxicity. The treatment did not influence survival in patients who also had hepatic metastases. In patients with disease isolated to the peritoneum, the median time to subsequent recurrence after therapy was increased from 8 months in 8 patients who had surgery alone to 21 months in 19 patients who had surgery and intraperitoneal mitoxantrone. The 2-year actuarial survival in these groups was 0% and 33%, respectively. Intraperitoneal mitoxantrone for recurrent GIST is currently being examined at MSKCC, although the first dose is being administered during surgery to promote broader peritoneal distribution of the drug. However, it is now indicated only for patients whose tumor is resistant to STI571.

Most patients with liver metastases from GIST have multiple, diffuse tumors and are therefore inoperable. In a recent analysis of 131 patients with liver metastases from GIST or intestinal leiomyosarcoma (not all archival specimens could be tested for Kit) treated at MSKCC, hepatic resection of all gross disease was possible in 34 (26%) patients.²⁰ There were no perioperative deaths after resection. The 1- and 3-year survival rates were 90% and 58%, respectively (Fig. 3). On multivariate

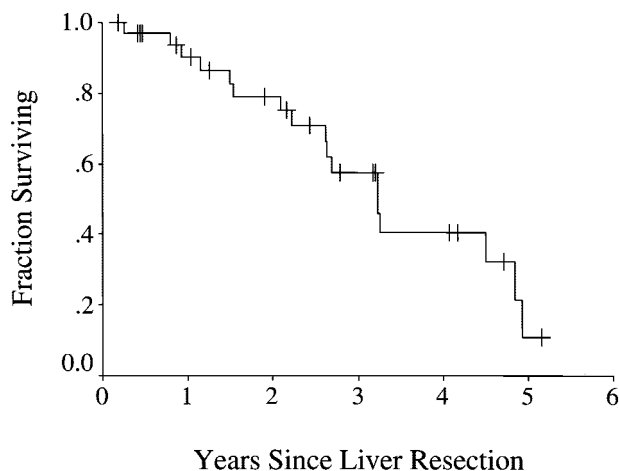


FIG. 3. Disease-specific survival after hepatectomy for liver metastases from gastrointestinal stromal tumor (n = 34). The median survival after hepatectomy was 3.2 years.²⁰

analysis, survival was predicted by the time interval between the resection of the primary tumor and the development of a liver metastasis. In fact, all five patients who took at least 2 years to develop liver metastases survived more than 4 years after hepatic resection. Others have had similar results.²¹ Nevertheless, as is the case after resection of peritoneal recurrence, nearly all patients' disease subsequently recurs after hepatectomy, with the liver being the most common site of relapse.

Hepatic Artery Embolization

Hepatic artery embolization (HAE) is an effective palliative therapy for patients with liver metastases from GIST because the tumors tend to be hypervascular and derive most of their blood supply from the hepatic artery. The principle is to selectively occlude the major arterial branches supplying the tumors by injecting them with particles such as polyvinyl chloride. If there are diffuse metastases, then generally half of the liver is treated at one time to minimize the associated postembolization syndrome (abdominal pain, fever, and nausea) and avoid the development of an intrahepatic abscess. The procedure may be repeated several times. The value of adding a chemotherapeutic agent to the injection of particles is controversial. The chemotherapy may enable prolonged drug delivery and enhance the effects of arterial occlusion.^{22,23} However, because chemotherapeutic agents are ineffective against GIST when given systemically, they may only increase the toxicity of HAE. Indeed, comparable results can be achieved with particles alone. HAE may be used to treat patients with liver metastases who have pain or discomfort. It is also the first line of therapy in patients with acute hemorrhage from a liver metastasis.

sis. However, in most patients, HAE is used to reduce the size of the liver metastases. Although it may produce a dramatic reduction in tumor burden, there is no conclusive evidence that it actually prolongs survival. Nevertheless, it seems to be a valuable modality for the treatment of patients with GIST metastatic to the liver.

Radiotherapy

External beam radiation is generally not indicated in patients with metastatic GIST because of the diffuse distribution of recurrent disease that typically occurs within the liver or peritoneum. When radiation is used, it is strictly for palliation. It can reduce pain or discomfort associated with a liver metastasis or pelvic recurrence. Occasionally, it may also be used to control bleeding from a peritoneal recurrence that is causing gastrointestinal bleeding.

THE *c-kit* GENE

In 1987, the human *c-kit* gene was cloned.²⁴ It is an oncogene located on chromosome 4 that is the cellular homolog of *v-kit* from the Hardy-Zuckerman 4 feline sarcoma virus.²⁵ The gene encodes a transmembrane receptor tyrosine kinase called Kit, which is expressed by the interstitial cells of Cajal (from which GIST is thought to originate), hematopoietic cells, melanocytes, and mast cells. The natural ligand for Kit is known variably as Kit ligand, stem cell factor, Steel factor, or mast cell growth factor. Binding of Kit ligand induces dimerization and autophosphorylation of Kit. This, in turn, increases the interaction with and phosphorylation of signal transduction proteins. The result is activation of a cascade of intracellular proteins that promote cell survival and proliferation.

In 1998, Hirota et al.²⁶ reported that a mutation of *c-kit* was found in the tumors of five patients with GIST. The mutations were identified in exon 11 (juxtamembrane domain) of the gene and resulted in activation of the Kit receptor. Mutations in other regions of the *c-kit* gene, including exons 9, 13, and 17, have also now been reported, although they occur at a much lower frequency.^{27,28} The mutation is nearly always somatic, because only a few families with a germline mutation have been identified.²⁹ Activating mutations in *c-kit* have also exist in germ cell tumors, myelofibrosis, chronic myelogenous leukemia (CML), and mastocytosis.³⁰

The reported prevalence of *c-kit* mutations in GIST has varied considerably.^{27,28,31,32} In the largest published reports, an exon 11 mutation was found in 71 (57%) of 124 cases and 103 (52%) of 200 cases.³² Recently, the rate of exon 11 mutation was found to be even higher,

and, including a few patients with exon 9 or 13 mutations, nearly 90% of tumors were found to contain a mutation.^{27,28} The discrepancy in prevalence may relate to different methods of detection and the type of tissue analyzed (paraffin-embedded vs. frozen tissue). GIST has also been shown to contain a variety of chromosomal abnormalities.³³

The presence of *c-kit* mutation has been reported to adversely affect survival in patients with GIST.³⁴ A Japanese study showed it to be an independent predictor of poor survival.³² The 5-year disease-specific survival was 49% in 71 patients with an exon 11 mutation compared with 86% in 53 patients without one ($P = .0001$). Patients with mutations had larger tumors and were more likely to develop recurrence. However, the study has several major limitations. First, the analysis was confounded by the inclusion of 11 patients with metastatic disease. Second, only exon 11 was examined. Third, mutations were identified in only 57% of patients, which is considerably lower than recent reports. Thus, whether the presence of *c-kit* mutation alone actually influences clinical outcome remains uncertain.

STI571

The development of STI571 (Gleevec,TM imatinib mesylate; Novartis Pharmaceuticals, Basel, Switzerland) is a landmark achievement in cancer therapy. The application of STI571 to GIST was a direct result of (1) its selective inhibition of the Kit receptor tyrosine kinase, which is constitutively active in most GISTs; (2) its efficacy and minimal toxicity in patients with CML; (3) the parallels between the pathogenesis of GIST and CML; and (4) the lack of effective alternative treatments for metastatic GIST. Its use in GIST has been exceedingly rapid (Table 1). Unlike traditional chemotherapeutic agents that are relatively nonspecific, STI571 is a specific inhibitor that acts on only a few tyrosine kinases. It inhibits the Bcr-Abl fusion protein in CML that possesses constitutive tyrosine kinase activity from a balanced translocation between chromosomes 9 and 22. STI571 has shown considerable activity in CML in vitro and in clinical trials, where it induced complete responses in more than 90% of patients in the chronic phase of CML.³⁵⁻³⁷ Because of STI571's activity, the Food and Drug Administration approved its use for CML in May 2001. STI571 also inhibits the Abl and platelet-derived growth factor receptor tyrosine kinases.^{38,39}

TABLE 1. *Timeline of STI571 development for GIST*

1986	<i>v-kit</i> gene cloned from the Hardy-Zuckerman 4 feline virus
1987	Human <i>c-kit</i> gene cloned
January 1998	GIST reported to contain mutation in the <i>c-kit</i> proto-oncogene
1998	Trials of STI571 in CML begin
February 2000	STI571 tested in first patient with metastatic GIST in Finland
June 2000	First patient with metastatic GIST treated with STI571 in the United States
January 2001	SWOG opens intergroup trial of STI571 in metastatic GIST
May 2001	FDA approves STI571 for CML
May 2001	Preliminary results of STI571 in metastatic GIST reported at the American Society of Clinical Oncology meeting
October 2001	ACOSOG opens trial of adjuvant STI571 in primary GIST
February 2002	FDA approves STI571 for unresectable GIST

GIST, gastrointestinal stromal tumor; SWOG, Southwest Oncology Group; FDA, Food and Drug Administration; CML, chronic myelogenous leukemia; ACOSOG, American College of Surgeons Oncology Group.

STI571 IN METASTATIC GIST

As is the case with CML, the pathogenesis of GIST seems to depend primarily on aberrant tyrosine kinase activity. The fact that STI571 inhibits Kit made it a rational therapy to examine in GIST.^{40–42} In February 2000, the first patient with metastatic GIST was treated with STI571.⁴³ The patient had previously failed a variety of therapies. The patient's tumor contained an exon 11 mutation and stained positive for Kit by immunohistochemistry. STI571 therapy rapidly produced a partial response in tumor size and a dramatic reduction in tumor uptake of ¹⁸[18F]fluorodeoxyglucose on positron emission tomography imaging. The tumor underwent myxoid degeneration by histological analysis.

These initial observations prompted two clinical trials in the United States and Europe. A phase II trial was started in July 2000 in which 36 patients with unresectable or metastatic GISTs were treated at the University Hospital of Helsinki, Dana Farber Cancer Institute, Oregon Health Sciences University, and Fox Chase Cancer Center. STI571 demonstrated minimal toxicity and substantial activity, with a partial response rate of approximately 60%. The trial size was then expanded, and the interim results were presented at the 2001 meeting of the

American Society of Clinical Oncology.²⁸ There were 86 of 145 treated patients who were assessable. Patients had been treated with a dose of 400 or 600 mg/day. Toxicity was generally acceptable. There were a few patients who developed bleeding as a result of rapid tumor necrosis induced by the agent. The common side effects were diarrhea, periorbital edema, and fatigue. The partial response rate was 59%, confirming the initial data (Table 2). Only 13% of patients experienced progression of disease, and there were no complete responses. The preliminary results of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trial were reported concurrently.^{44,45} The maximum-tolerated dose of STI571 was determined to be 400 mg twice a day. There was a 69% response (major and minor) rate in 36 treated patients (Table 2). Again, progression was observed in only a small percentage of patients. The striking activity of STI571 led to development of the North American Sarcoma Intergroup study (S0033) sponsored by the Southwest Oncology Group, the Cancer Therapy Evaluation Program of the National Cancer Institute, and Novartis (Fig. 4). The trial is comparing a dose of 400 mg once a day to 400 mg twice a day in patients with metastatic GIST. Remarkably, the trial exceeded its accrual goal of 600 patients within 8 months of activation and is now closed to accrual; the preliminary results are pending. A typical response to STI571 is shown in Fig. 5.

TABLE 2. *Results of STI571 in patients with metastatic GIST*

Variable	US-Finland GIST Study Group ²⁸ (n = 86) ^a	EORTC Soft Tissue and Bone Sarcoma Group ⁴⁵ (n = 36) ^b
Partial response (%)	59	69 ^c
Stable disease (%)	26	19
Progression (%)	13	11

GIST, gastrointestinal stromal tumor; EORTC, European Organization for Research and Treatment of Cancer.

^a Dose ranged from 400 to 600 mg/day.

^b Dose ranged from 400 to 1000 mg/day.

^c Partial and minor responses.

STI571 IN PRIMARY GIST

STI571 is being evaluated as an adjuvant therapy after complete resection of primary GIST because (1) the risk of recurrence after surgical resection alone is high, (2) conventional chemotherapy is ineffective in preventing or treating recurrent disease, and (3) STI571 has demonstrated considerable activity in metastatic GIST. It is

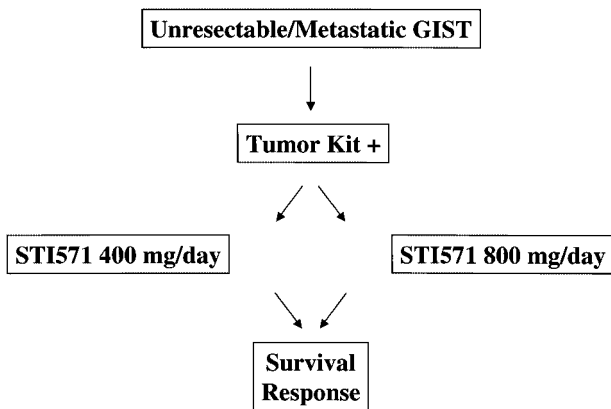


FIG. 4. Randomized phase III intergroup trial of STI571 in metastatic/unresectable gastrointestinal stromal tumor (GIST) sponsored by the Southwest Oncology Group, the Cancer Therapy Evaluation Program, and Novartis.

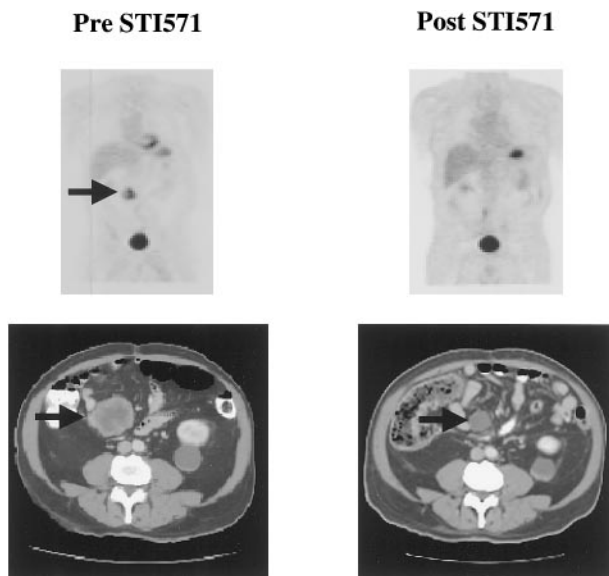


FIG. 5. Response to STI571 in a patient with recurrent gastrointestinal stromal tumor. The patient had a peritoneal mass (lower left) that demonstrated metabolic activity on [18F]fluorodeoxyglucose positron emission tomography scan (upper left). After several weeks of STI571 therapy, the patient had a partial response, with reduction of tumor size (lower right) and loss of positron emission tomography activity (courtesy of Robert Maki, Department of Medicine, Memorial Sloan-Kettering Cancer Center).

conceivable that STI571 may have its greatest effect on survival when there is minimal disease, as is the case after complete gross tumor resection when only residual microscopic disease may exist. Avoidance of recurrent disease is paramount because STI571 has not produced any complete responses and conventional agents are ineffective in recurrent (and primary) GIST. The hypothesis of the adjuvant trials is that STI571 may prevent, or

at least delay, recurrence and consequently prolong survival. The American College of Surgeons Oncology Group is leading a phase II intergroup trial sponsored by the Cancer Therapy Evaluation Program and Novartis that will test the value of adjuvant STI571 (400 mg/day) for 1 year after complete resection in patients with high-risk primary GIST⁴⁶ (Fig. 6). High risk is defined as tumor size ≥ 10 cm, tumor rupture, tumor hemorrhage, or multifocal (more than five) tumors. Survival will be compared with that of historical controls. In addition, a phase III intergroup trial led by the American College of Surgeons Oncology Group has been opened for patients with tumors ≥ 3 cm. It is a randomized, double-blinded trial in which patients will receive STI571 (400 mg/day) or placebo for 1 year after complete resection of their primary tumor (Fig. 7). Patients assigned to the placebo arm will cross over to STI571 therapy in the event of tumor recurrence. The primary end point is survival

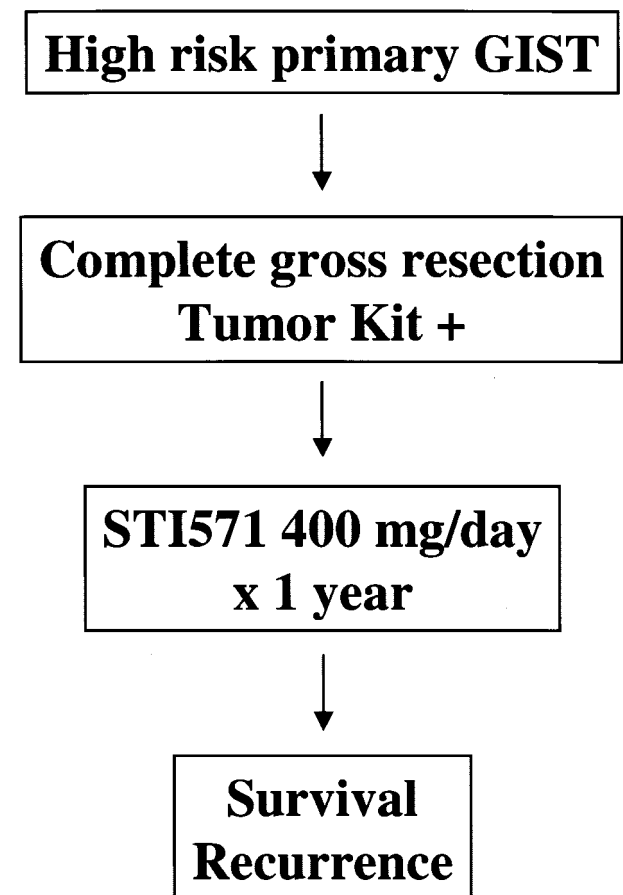


FIG. 6. Phase II intergroup trial of adjuvant STI571 after complete resection of high-risk primary gastrointestinal stromal tumor (GIST), sponsored by the American College of Surgeons Oncology Group (trial Z9000), the Cancer Therapy Evaluation Program, and Novartis.

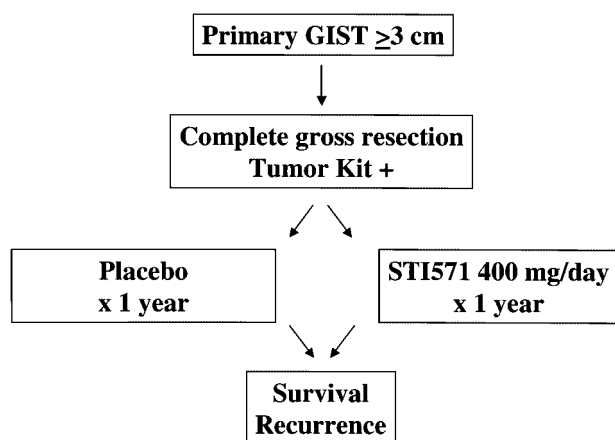


FIG. 7. Phase III intergroup trial of adjuvant STI571 after complete resection of high-risk primary gastrointestinal stromal tumor (GIST), sponsored by the American College of Surgeons Oncology Group (trial Z9001), the Cancer Therapy Evaluation Program, and Novartis. Patients who develop recurrent disease in either arm will be treated with STI571 at a dose of 400 to 800 mg/day.

between the two arms. A preoperative (neoadjuvant) phase II trial for primary GIST is also being developed by the Radiation Therapy Oncology Group.

CURRENT MANAGEMENT OF GIST

STI571 has rapidly become the first-line treatment for patients with metastatic GIST. Nevertheless, conventional therapies, and surgery in particular, may actually now become more important in the treatment of metastatic GIST. Because complete responses have not been observed with STI571 therapy, patients with stable disease or partial responses should be considered for surgical resection or cytoreduction. It is unknown when, and to what extent, resistance to STI571 will occur in STI571-responsive patients with GIST, but it is likely to emerge as it has in CML. Patients who do not respond initially to STI571 should be treated with the traditional palliative options for metastatic GIST that include chemotherapy, surgery with or without intraperitoneal chemotherapy, HAE, or radiation. For patients with primary GIST, surgery remains the principle treatment but the results may be improved by neoadjuvant or adjuvant STI571. Because of the complexities of multimodality therapy, the treatment of patients with GIST now requires a multidisciplinary team that may include medical oncologists, general surgeons, surgical oncologists, hepatobiliary surgeons, molecular pathologists, surgical pathologists, and radiologists.

FUTURE OF STI571

There are a number of unanswered questions regarding the use of STI571 in patients with GIST. The first question is whether the type of *c-kit* mutation will predict the clinical response to STI571 therapy. There is preliminary evidence that it may.²⁸ Other critical issues are to determine the duration of response in patients with STI571-sensitive tumors and the mechanisms of STI571 resistance. Gene amplification and additional mutation have already been identified in the development of resistance to STI571 in CML.^{47–50} All of these uncertainties should be answered by the current clinical trials and the correlative laboratory studies that accompany them. Perhaps the ultimate question, though, will be how the paradigm of STI571 in CML and GIST will apply to other human malignancies.⁵¹ Because the pathogenesis of many common tumors seems to be more complex and involve multiple genetic aberrations, as opposed to what seems to be a single, dominant defect in GIST (and CML), other molecularly targeted agents may not demonstrate such dramatic activity as STI571. Nevertheless, the identification of critical pathways will enable the development of specific inhibitors in the ongoing colossal effort to uncover the true essence of neoplastic diseases and develop more effective therapies against them.

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