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# Imatinib mesylate acts in metastatic or unresectable gastrointestinal stromal tumor by targeting KIT receptors—a review

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**Abstract** Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy of the gastrointestinal tract. This tumor is resistant to conventional chemotherapy and radiotherapy. Although surgery has been the only effective treatment for GIST to date, it is not enough to manage metastatic GIST. Imatinib mesylate, a KIT tyrosine kinase inhibitor, is an oral agent that has been found to have a dramatic antitumor effect on metastatic GIST with either wild-type or mutant KIT. Although imatinib mesylate has been used in GIST treatment for several years, its use marks a new era of molecular targeting therapy. While several issues remain, they should be clarified by the current clinical trials and associated laboratory studies.

**Keywords** Gastrointestinal stromal tumor · Imatinib mesylate · KIT

## Introduction

Gastrointestinal stromal tumors (GISTs) are soft-tissue sarcomas primarily arising from mesenchymal tissue in the gastrointestinal tract and abdomen. They are rare neoplasms, estimated to represent approximately 1% of all tumors of the gastrointestinal tract. However, GISTs are the most common mesenchymal malignancy of the gastrointestinal tract [17]. The precise incidence of GIST is unknown. Approximately 5000 GISTs occur annually in the USA, with men and women being equally affected. The median age at the time of initial diagnosis of GIST is 58 years, and most patients are between 40 and 80 years old [3]. The definition of GIST has evolved over the years, and the actual incidence of GIST is probably underestimated, because until recently, many GISTs were classified as benign tumors or leiomyosarcomas [4]. GISTs are thought to arise from or share a common ancestor with the intestinal cells of Cajal, which collectively serve as a pacemaker for the control of contractile activity in the intestine [11]. Currently, GIST is defined as a mesenchymal tumor positive for KIT (CD117) (Fig. 1); many GISTs also express CD34 [4]. Surgery has been the only effective treatment, because GIST is resistant to radiation therapy and insensitive to chemotherapy [3]. The 5-year survival rate following surgical resection ranges from 28% to 43% [17]. However, surgery alone is often inadequate, with up to 90% of patients eventually relapsing after resection.

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## Clinical presentation

In general, small GISTs ( ≤ 2 cm) are usually asymptomatic, incidentally detected during investigations or surgical procedures for unrelated disease, and benign. Clinical signs and symptoms (nausea, vomiting, abdominal pain, gastrointestinal obstruction, abdominal mass often not initially identifiable as related to the gastrointestinal tract, anemia, and melena) are nonspecific. GISTs are endoscopically recognized as submucosal tumors (SMTs), a category composed of myogenic tumors, neurogenic tumors, lipomas, cysts, aberrant pancreatic tumors, carcinoids, and carcinomas. Endoscopic ultrasonography (EUS) is an effective examination for distinguishing GISTs from other tumors. This technique reveals the tumor's relationship to the layers of the intestinal tract and its internal echo pattern more precisely than computed tomography (CT) or magnetic resonance imaging (MRI). EUS may contribute to the differential diagnosis of SMTs, especially in the stomach

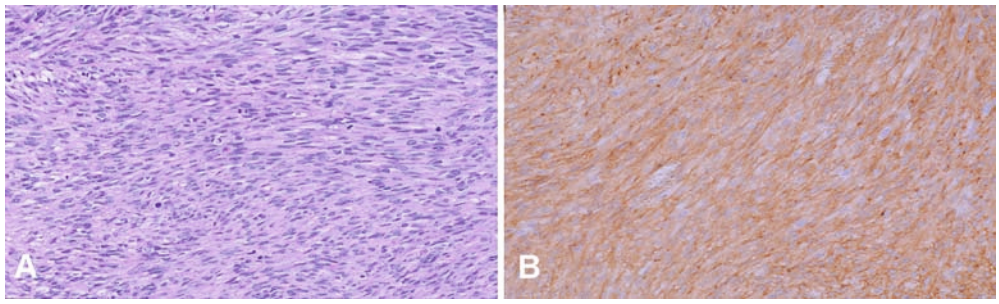


**Fig. 1A, B** Photomicrographs of spindle-cell type of GIST from the duodenum. **A** Hematoxylin and eosin staining; **B** KIT-positive immunostaining of the same tumor. High-level KIT staining is typical of GIST (×66)

[2, 16, 21]. The usefulness of EUS-guided fine-needle aspiration biopsy (EUS-FNAB) for diagnosing upper gastrointestinal SMTs has been described. Matsui et al. suggested that histological rather than cytological analysis is important for the diagnosis of myogenic tumors because the histological criteria of malignant myogenic tumors are strongly based on mitotic figures [12]. We studied tumors that showed positive immunohistochemical staining for either KIT or CD34 and the results from specimens obtained by EUS-FNAB were compared with those from resected specimens. In addition to applying the MIB-1 labeling index, we were able to make a precise distinction between low-grade and high-grade malignancies according to mitotic activity (unpublished data, 2003).

## Pathology

Gross pathology shows that GISTs vary greatly in size, ranging from less than 1 cm to more than 20 cm in diameter. Large tumors may show cystic degeneration, necrosis, hemorrhage and calcification. Although the tumors often have pseudocapsules, some appear to have an infiltrative growth pattern. These tumors occur in the muscularis propria and occasionally in the submucosa or serosa. Large tumors cause ulceration of the overlying mucosa. Of all GISTs, 70% are composed of spindle cells, 20% are composed of epithelioid cells, and 10% are composed of mixed cells [6]. Some tumors show a variable prominent myxoid stroma, while other tumors in the small intestine show a nested paraganglioma-like or carcinoid-like growth pattern. GISTs of the spindle cell type are composed typically of eosinophilic cells arranged in short fascicles. The tumor cells have paler eosinophilic cytoplasm than myogenic tumors. GISTs of the epithelioid cell type are composed of round cells with variably eosinophilic or clear cytoplasm. Aside from consistent positivity for KIT, 60–100% of GISTs show positive immunostaining for CD34, 30–70% show positive immunostaining for smooth muscle actin, and about 5% show positive immunostaining for S-100 protein. None of the latter antigens are specific for GIST. Positive desmin immunostaining in true KIT-positive GISTs is rare and is invariably focal, with positive staining in only a small number of tumor cells. The immunophenotype of true KIT-positive GISTs varies to some degree by location, with CD34-positive immunostaining seen most consistently in colorectal and esophageal lesions and positive smooth muscle actin immunostaining seen most often in small-bowel tumors [9]. Malignancy has been associated with nuclear atypia, high cellularity, mixed spindle-epithelioid morphology, a mitotic rate above 5 or 10 in 50 high-power fields, MIB-1 index, mucosal invasion and necrosis [13, 19]. However, GISTs are not always clearly identifiable as benign or malignant pathologically, and they are thought to have malignant potential, even when the tumor diameter is $< 5$ cm and the cells show low mitotic activity.

## Definition

Presently, GISTs are generally thought as KIT-positive mesenchymal tumors of the gastrointestinal tract [18, 19, 20]. The protein KIT is encoded by the c-kit protooncogene and is immunologically identified by the CD117 antigenic epitope. The KIT receptor is a member of the receptor tyrosine kinase family, and closely related to the receptors for platelet-derived growth factor, macrophage colony-stimulating factor, and FMS-like receptor tyrosine kinase (FLT3) ligand [8]. The juxtamembrane and kinase domains of all these receptors are strongly conserved. The protein KIT is expressed by hematopoietic progenitor cells, mast cells, germ cells, and the interstitial cells of Cajal. The extracellular portion of the KIT receptor binds a ligand (stem-cell factor) and the intracellular domain contains the kinase enzymatic domain (ATP binding site).

## Prediction of tumor behavior

Many attempts have been made to distinguish between benign and malignant GISTs, but there are no clear criteria. Many parameters have been proposed and the morphological features that have been widely accepted as predictive parameters are tumor size and mitotic activity. Although metastatic tumors are generally $> 5$ cm, up to 20% of GISTs $< 5$ cm exhibit metastatic behavior [17]. However, even small lesions ($< 2$ cm) and those with low mitotic activity can metastasize [6], and all GISTs should be viewed as having some metastatic potential. Increasingly, GISTs are no longer considered to be benign.

Predicting the potential biological behavior of these tumors remains unresolved and an analysis of the literature to resolve this issue provides many conflicting reports. Mitotic activity, tumor size, tumor necrosis, histological type and pattern, immunohistochemical profile and staining for proliferating antigens have all been evaluated extensively in this context although no consensus has been established. Tumors from the small and large intestines often behave more aggressively than tumors from the stomach. Suggested definitions of the different risk categories have been proposed by Fletcher et al. [6] and are outlined in Table 1. Thus, instead of referring to a particular GIST as benign or malignant, the risk of metastasis and recurrence would be more recognized. Because it is impossible to describe every GIST as benign or malignant with reasonable confidence, the authors advocate an indefinite period of patient follow-up.

## Metastatic GIST

Before the development of imatinib mesylate, the outlook for patients with metastatic GIST was bleak. A large number of patients with initial resection of GIST eventually experience recurrence, for which there has been no effective treatment [15]. The primary sites of recurrence in GIST are mainly localized in the liver and the peritoneum [4]. Mudan et al. conducted a retrospective study of 60 patients with recurrent GIST [14]. The median survival after resection was 15 months, but was longest in patients with metastases localized in the liver. Only approximately one-third of the patients had recurrent disease that was thought to be completely resectable.

As is the case with chronic myeloid leukemia (CML), early pathogenesis of GIST appears to depend on aberrant tyrosine kinase activity. The fact that imatinib mesylate inhibits both wild-type and mutant KIT made it a rational therapy to examine in the treatment of GIST [7, 22]. In 2001, Joensuu et al. were the first to report a patient with widely metastatic GIST who was treated with imatinib mesylate [10]. This patient had undergone surgery and chemotherapy including thalidomide for recurrent disease, with no response. Within 1 month after starting therapy with imatinib mesylate 400 mg/day taken orally, the patient had a complete metabolic response as assessed by fluorodeoxyglucose (FDG) positron emission tomography (PET) and a 52% decrease in tumor volume detected by magnetic resonance imaging (MRI). The tumor underwent myxoid degeneration, determined by histological analysis. Toxicities were mild and the response lasted through at least 11 months of imatinib. This remarkable efficacy was confirmed in larger studies in the USA and Europe. Van Oosterom et al. led a phase I study involving 36 patients with metastatic GIST treated with imatinib mesylate 400–1000 mg/day [23]. Objective responses were seen in 69% of the patients, although 5 of 8 patients at the 1000-mg/day level had dose-limiting toxicities. Other dose levels were well tolerated. Demitri and colleagues conducted a study in which imatinib mesylate 400 or 600 mg/day was administered to 147 patients with metastatic or unresectable GIST [5, 25]. A partial response was seen in 63% of the patients, and an additional 20% of the patients achieved stable disease. The median duration of response had not been reached at a median follow-up of 24 weeks, but responses had lasted for more than 46 weeks. Treatment was generally well tolerated.

**Table 1** Risk of aggressive behavior in GISTs (*HPF* high-power field)

| Risk | Size (cm) | Mitotic count |
|---|---|---|
| Very low | < 2 | < 5/50 HPF |
| Low | 2–5 | < 5/50 HPF |
| Intermediate | < 5 | 6–10/50 HPF |
| | 5–10 | < 5 HPF |
| High | > 5 | > 5 HPF |
| | 10 | Any mitotic rate |
| | Any size | > 10/50 HPF |

Imatinib mesylate represents a breakthrough in the management of metastatic GIST, producing dramatic efficacy where conventional chemotherapy and radiation therapy have failed. Even at this early stage of development, given the lack of any effective therapy other than surgery, imatinib mesylate has become the first-line treatment for metastatic or unresectable GIST [4]. The results of two previous studies have indicated that patients with metastatic or unresectable GIST can safely be given imatinib mesylate at a dose of 400–800 mg/day [5, 23, 25]. The optimal dosing schedule of imatinib mesylate in GIST is being investigated in clinical trials. The final analysis of a trial led by Verweij suggests that imatinib mesylate at 800 mg/day might yield a 6-month advantage over the 400-mg/day dose level in terms of progression-free survival. Preliminary results of a similar trial led by Benjamin do not show an efficacy advantage favoring the 800-mg/day dose level; however, 46% of patients who crossed over to the high-dose arm on progression at the time of this report continued on treatment, suggesting possible activity [1].

In Japan, studies in which patients with recurrent or unresectable GIST receive either 400 or 600 mg/day doses of imatinib mesylate have been underway since April 2002. Although these data have not been confirmed yet, we believe that these are the first large-scale studies of this subject in Japan.

## Management of adverse events

Imatinib mesylate is generally well tolerated at doses up to 800 mg/day, and no prophylactic treatment is required. The most severe adverse event has been gastrointestinal bleeding, probably as a result of rapid tumor necrosis induced by the agent [4, 5, 25]. Common

side effects are nausea, vomiting, diarrhea, periorbital edema, eruption, skin rash, myalgia, fatigue, leukocytopenia and thrombocytopenia. These side effects, reminiscent of those seen in patients with CML, are mild and easily manageable. Edema may be treated with the diuretic furosemide. For nausea and vomiting, metoclopramide or diphenhydramine may be administered. Patients experiencing diarrhea may be given loperamide. Skin rash is exacerbated by exposure to sunlight, so sun blockers and a moisturizing cream should be applied. These adverse events decrease in severity during the course of treatment [24].

## Evaluation of efficacy

A phase I study of imatinib mesylate in advanced soft-tissue sarcomas conducted by the European Organization for Research and Treatment of Cancer (Soft Tissue and Sarcoma Group) [23] showed that imatinib mesylate inhibited tumor growth in 32 patients. Tumor volume decreased by more than 50% in 19 of these 32 patients. Moreover, most patients had rapid symptomatic benefit with improvement in performance status. In these responding patients, an impressive reduction was demonstrated by FDG-PET and an objective response was predicted from CT results after 8 weeks.

A multicenter phase II trial of imatinib mesylate for the treatment of unresectable or metastatic GIST was initiated in July 2000 [5, 25]. In this trial, 53.7% of all patients had a partial response, defined by a decrease in lesion size of at least 50%, and disease stabilization was noted in an additional 27.9%. With limited follow-up, only 13.6% of patients experienced disease progression. The estimated 1-year survival rate for all patients was 88%. In all patients with response, the uptake of FDG into the tumor detected by PET had decreased markedly from baseline as early as 24 h after a single dose of imatinib mesylate, and some metastatic lesions became cystic, showing tissue with myxoid degeneration and scarring in needle biopsies. The clinical response of GISTs to imatinib mesylate is often rapid, and patients have decreased cancer-related symptoms within a few days of starting the drug.

## Treatment of patients who progress during imatinib mesylate treatment

Imatinib mesylate has been shown to be highly effective, but resistance and disease progression have been observed [5, 25]. The existence of progressive disease may be verified by CT, MRI, and eventually FDG-PET scans, and the histology of the lesion should be examined. In the case of localized progressions (Fig. 2), local treatment options include surgery and laser or radiofrequency ablation. Imatinib mesylate therapy should not be discontinued on partial progression. For systemic progression (Fig. 3), the imatinib mesylate dose can be increased up to 800 mg/day. Patients with progression should be enrolled in a clinical trial for recurrent GIST. To manage resistant clones, the addition of other drugs should be considered. Investigational agents that are being studied in combination with imatinib mesylate include the mammalian target of rapamycin (mTOR) inhibitor RAD001 and the protein kinase C inhibitor PKC412. In addition, SU11248, which is an inhibitor of tyrosine kinases, including the vascular endothelial growth factor receptor, platelet-derived growth factor, Kit and FLT3 receptor tyrosine kinases, is currently being explored as therapy for imatinib mesylate-resistant GIST.

## Conclusion

Although 30 years ago leukemia was thought to be inevitably fatal; it is now considered to be a curable disease. There are no effective modalities for treating unresectable GIST, but now imatinib mesylate has appeared as a contender. Early clinical trials suggest a survival benefit and imatinib mesylate has rapidly become the first-line treatment for patients with unresectable GIST.

There are, however, a number of problems regarding the use of imatinib mesylate in patients with GIST. The first problem is the acquisition of resistance to imatinib mesylate in responsive patients with GIST. Gene amplification and additional mutations have already been identified in the development of resistance to imatinib

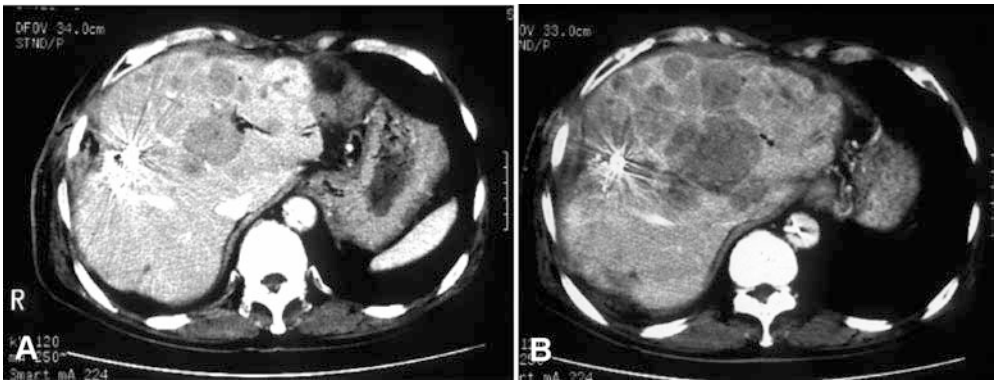


**Fig. 2A, B** CT images show multiple intrahepatic metastases. There is no change in size or enhancement with contrast medium compared with pretreatment (**A**), and every metastasis has increased to twice the diameter after 16 months of imatinib mesylate administration (**B**)

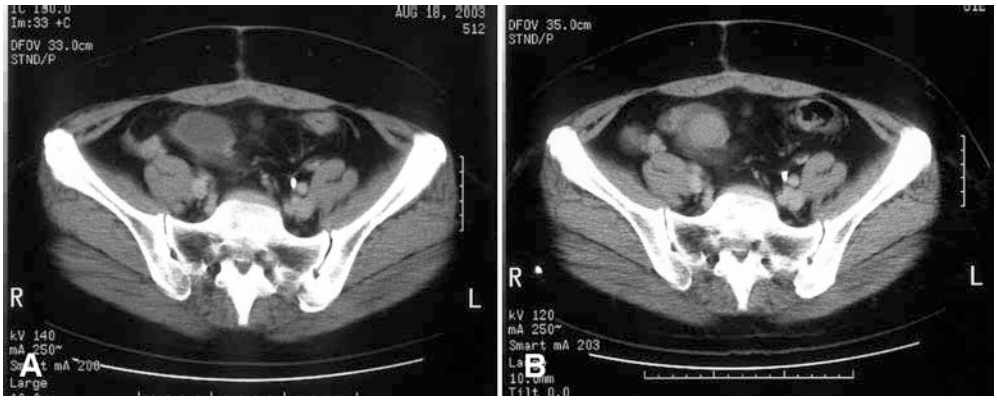


**Fig. 3A, B** CT images demonstrate intraperitoneal metastasis as a low density area (**A**), and enhancement with contrast medium reveals the tumor (**B**)

mesylate in cases of CML. Other problems include incomplete response with imatinib mesylate therapy, adequate duration of administration in imatinib mesylate-sensitive patients, and the absence of any response to imatinib mesylate in approximately 20% of patients. All of these issues should be clarified by the current clinical trials and the associated laboratory studies. The resolution of these problems could lead to the development of more effective therapies against GIST.

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