

Gastrointestinal Stromal Tumor (GIST)

Gastrointestinal stromal tumor (GIST) is a life-threatening cancer, generally located in the soft tissue of the gastrointestinal (GI) tract. Until recently, GIST was thought to be extremely rare. However, recent advances in diagnosis and classification methods have demonstrated that GIST may be more prevalent, and more aggressive, than previously believed. These same advances also have played a role in the development of new treatments for GIST and other cancers.

GIST: The Most Common GI Sarcoma

GIST is the most common form of GI sarcoma, a life-threatening cancer of the GI tract. Sarcomas are uncommon cancers that begin in the connective tissues (fat, muscle, blood vessels, deep skin tissues, nerves, bones and cartilage). The American Cancer Society estimates that in 2008, about 10,390 new cases of soft tissue sarcoma will be diagnosed in the United States¹. However, this number may be underestimated, especially because a large proportion of patients with GIST may not have been counted in tumor registry databases before 2001².

The GI tract includes the mouth, pharynx, esophagus, stomach, small intestine, large intestine (colon) and anus. Experts believe that GISTs start in cells called interstitial cells, or stroma, which are found in the walls of the GI tract, and are part of the system that signals the body to help move food through the digestive tract. Approximately 50-70% of GISTs occur in the stomach, 20-30% in the small intestine and the remaining percent in the colon, esophagus, rectum and anus³.

Incidence and Diagnosis

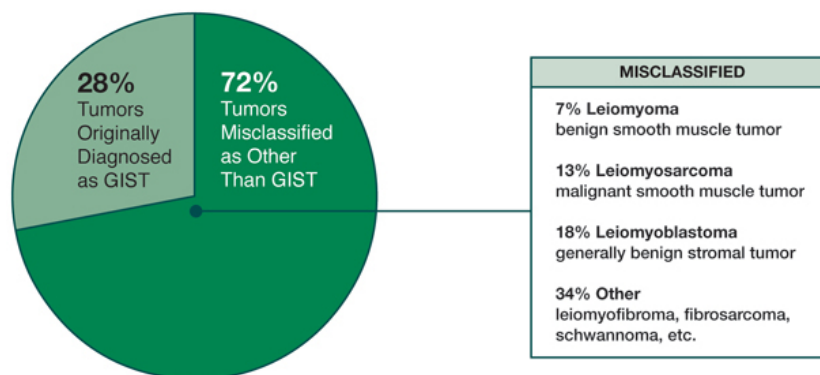
GISTs are often first diagnosed during work-up for other more common, benign disorders. They frequently do not cause any physical symptoms until the disease is well advanced and more difficult to treat. The most common symptoms of GIST are vague abdominal pain, early satiety (feeling of being full), vomiting, abdominal bleeding, or blockage and fatigue due to anemia³. With the high potential for metastases and generally poor outcome, a missed diagnosis may be devastating.

There are no known genetic or environmental risk factors for GIST.

Until recently, a lack of consensus criteria for defining and diagnosing GIST frequently resulted in misdiagnosis or misdesignation as another type of GI sarcoma. (Figure 1)

SWEDISH EPIDEMIOLOGY STUDY⁴

72% OF GISTs HISTORICALLY MISCLASSIFIED



The pie chart above reviews data from an epidemiology study conducted in Sweden. The study found that 72% of GIST tumors were misclassified as other than GIST.

Figure 1: Percentage of GISTs historically misclassified

Improvements in diagnostic tools and procedures have made it easier for physicians to distinguish GIST from other types of GI sarcomas and benign tumors. As a result, experts believe that GIST may be more prevalent than was previously estimated.

Estimates of the incidence of GIST in the US vary. Experts believe there are between 4,500 and 6,000 new cases per year³.

US consensus data have shown that nearly all GISTs have malignant potential, with even small tumors (< 2 cm) recurring or metastasizing after complete resection. GISTs are now graded as having “low risk,” “intermediate risk,” or “high risk” for metastatic spread based on tumor size, tumor location, and mitotic index. (Figure 2). Mutational status has also emerged as a potential risk factor for GIST⁵.

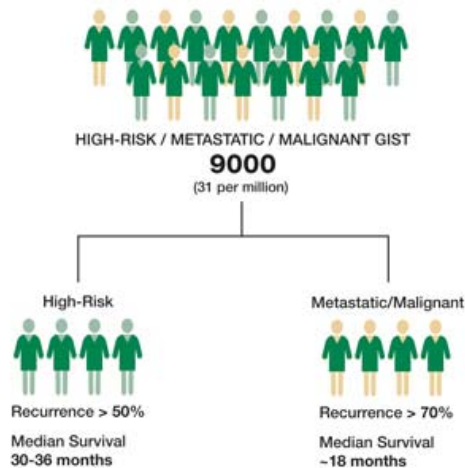


Figure 2: Estimated prevalence of GIST in U.S. based on Swedish epidemiology study.⁴

Scientists have discovered that a mutation in the protein called Kit (also known as CD117) – located on the surface of normal cells – is one of the major causes of GIST. Greater than 90% of GISTs are positive for Kit⁶.

Normally, the role of Kit is to signal cells to grow and divide in a controlled fashion. In 1998, Japanese researchers discovered that nearly all of the GISTs they studied contained a mutation in the DNA, which caused Kit to be continuously activated. Left “on” all the time, Kit signals cells to constantly grow and divide.

Treatment Options

Surgery (also called resection) remains the cornerstone of therapy for GIST because conventional chemotherapy and radiotherapy have minimal utility in the treatment of primary or recurrent disease.

Patients most frequently undergo surgery when possible and receive close, ongoing follow-up. A surgeon who has experience in GIST management should ideally perform the surgery.

Many GISTs cannot be surgically removed at all, because they are too large or have already spread to other parts of the body prior to diagnosis. Often, even when surgery is performed, the resection is incomplete.

Despite surgery, the overall rate of recurrence is 90% and five-year survival is 48-65%⁶.

The discovery of malfunctioning Kit and its role in GIST paved the way for the development of new treatments designed to control the activity level of Kit receptors. In 2008, Gleevec became the first and only FDA approved post-surgery treatment indicated to delay or prevent the recurrence of this highly-aggressive cancer, filling a major unmet need in the GIST community.

As is the case with many forms of cancer, once metastases occur, however, the median survival decreases. According to a report published in the May 2004 issue of the *Journal of the National Comprehensive Cancer Network (JNCCN)*, optimal management of GIST patients can only be addressed by a multidisciplinary disease management approach combining medical oncology, surgery and imaging experts.

About Gleevec

Gleevec tablets are now indicated for the adjuvant treatment of adult patients following complete surgical removal of Kit (CD117)-positive gastrointestinal stromal tumors (GIST). Gleevec® is also indicated for the treatment of patients with Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Important safety information⁷

Fetal harm can occur when Gleevec is administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking Gleevec tablets and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking Gleevec should use adequate contraception. If the patient does become pregnant while taking Gleevec, the patient should be advised of the potential hazard to the fetus.

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

Dose adjustments may be necessary due to hepatotoxicity, other non-hematologic adverse reactions or hematologic adverse reactions. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months).

A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended. Gleevec should be used with caution in patients with severe renal impairment.

In the Phase III GIST studies 13% of patients reported (NCI Grades 3/4) hemorrhage at any site. In the Phase II GIST study 5% of patients were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life-threatening. There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and GI perforation.

Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of Gleevec at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

Consider potential toxicities—specifically liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.

Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6 and CYP2C9. Dosage of Gleevec should increase by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin. Examples of commonly used drugs that may significantly interact with Gleevec include ketoconazole, acetaminophen, warfarin, erythromycin and phenytoin. (Please see full Prescribing Information for other potential drug interactions).

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron.

Common side effects of Gleevec tablets

In the Phase III adjuvant GIST trial, the majority of both Gleevec and placebo-treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations, including patients with unresectable and/or malignant metastatic GIST.

The most commonly reported adverse events, Grade 3 and above, reported in post-surgery patients treated with Gleevec, were edema (periorbital, 1.2%; peripheral, 0.3%; facial, 0.3%), diarrhea (3.0%), abdominal pain (3.0%), rash (exfoliative, 2.7%; rash, 0.9%), nausea (2.4%), vomiting (2.4%), and fatigue (2.1%).

Drug was discontinued for adverse reactions in 57 of the Gleevec-treated patients (17%) and 11 of the placebo-treated patients (3%). Edema, gastrointestinal disturbances (nausea, vomiting, abdominal distension and diarrhea), fatigue, low hemoglobin and rash were the most frequently reported adverse reactions at the time of discontinuation.

The majority of patients who received Gleevec in the adjuvant GIST study experienced adverse reactions at some time. The most frequently reported adverse reactions (all Grades) were edema (periorbital, 47.2%; peripheral, 26.7%; facial, 6.8%), diarrhea (59.3%), fatigue (57.0%), nausea (53.1%), muscle spasms (16.3%) and myalgia (12.2%), abdominal pain (21.1%) and upper abdominal pain (6.2%), rash (exfoliative, 26.1% and rash 8.9%) and vomiting (25.5%)*.

The majority of patients who received Gleevec in the unresectable and/or metastatic GIST study experienced adverse reactions at some time. The most frequently reported adverse reactions (400 mg/day; 800 mg/day) (all Grades) were edema (77%; 86%), nausea (58%; 65%), muscle cramps (32%; 30%), diarrhea (56%; 58%), fatigue (69%; 75%), abdominal pain (57%; 55%), rash and related terms (56%; 70%), and vomiting (37%; 41%)*.

In previous Phase III unresectable and/or metastatic GIST trials (400 mg/day; 800 mg/day) severe (NCI Grades 3/4/5) lab abnormalities – including neutropenia (3%; 4%), and anemia (5%; 6%) – and severe adverse reactions (NCI Grades 3/4/5), including edema (9%; 13%), fatigue (12%; 12%), abdominal pain (14%; 12%), nausea (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), vomiting (9%; 8%) and myalgia (6%; 4%) were reported among patients receiving Gleevec.

In CML clinical studies, the majority of adult Ph+ CML patients who received Gleevec experienced adverse reactions at some time, but most were mild to moderate in severity. The most frequently reported adverse reactions (all Grades) were superficial edema (60%–74%), nausea (50%–73%), muscle cramps (28%–62%), vomiting (23%–58%), diarrhea (43%–57%), musculoskeletal pain (38%–49%), and rash and related terms (36%–47%)*. In these studies, therapy with Gleevec was discontinued for drug-related adverse reactions in 2.4% to 5% of patients.

In CML clinical studies, severe (NCI Grades 3/4) lab abnormalities—including neutropenia (3.6%–48%), anemia (1%–42%), thrombocytopenia (<1%–33%), and hepatotoxicity (approx 5%)—and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (e.g., pleural effusion, pulmonary edema, and ascites) and superficial edema (1.3%–11%), hemorrhage (1.8%–19%), and musculoskeletal pain (2%–9%) were reported among patients receiving Gleevec*. Severe fluid retention appears to be dose-related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly.

Supportive care may help management of some mild-to-moderate adverse reactions so that the prescribed dose can be maintained whenever possible. However, in some cases, either a dose reduction or interruption of treatment with Gleevec may be necessary.

Gleevec tablets should be taken with food and a large glass of water to minimize GI irritation. Gleevec tablets should not be taken with grapefruit juice and other foods known to inhibit CYP3A4.

Patients should be informed to take Gleevec exactly as prescribed, not to change their dose or stop taking Gleevec unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose.

*Numbers indicate the range of percentages in 4 studies among adult patients, with newly diagnosed Ph+ CML, patients in blast crisis, accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

*For more detailed study information please see full Prescribing Information.

References:

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- ⁶ US Department of Health and Human Services. Agency for Healthcare Research and Quality (AHRQ). Technology Assessment: Report on the Relative Efficacy of Oral Cancer Therapy for Medicare Beneficiaries Versus Currently Covered Therapy, Part 2. Imatinib for Gastrointestinal Stromal Tumors (GISTs). Available at: <http://www.ahrq.gov/clinic/ta/gist/gist1.htm>
- ⁷ Gleevec® (imatinib mesylate) tablets prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Nov 2007.