Review article: the biology, diagnosis and management of gastrointestinal stromal tumours

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SUMMARY

Background
Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract with an increasing incidence.

Aims
To review the biology, diagnosis and treatment of gastrointestinal stromal tumours.

Methods

Results
The diagnosis of GIST is established by histology supplemented by the immunohistochemical marker CD117, which is positive in 95% of cases. The most common site of the tumour is the stomach. Most GIST are benign with 20–30% malignant. Five-year survival for malignant GIST ranges between 35% and 65% and depends primarily on tumour size, mitotic index and location. The malignant behaviour of GIST is best assessed by invasion of adjacent structures and distant metastases. The gold standard for treatment is surgical resection. Imatinib, a tyrosine kinase inhibitor, is the primary therapy for unresectable, recurrent or metastatic disease.

Conclusions
Gastrointestinal stromal tumours are rare tumours of the gastrointestinal tract and they vary in presentation. When surgical resection is not achievable, imatinib is the treatment of choice.

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EPIDEMIOLOGY

According to the Surveillance, Epidemiology, and End Result (SEER) cancer data registry between 1993 and 2002, the incidence of Gastrointestinal stromal tumours (GIST) in the United States was 0.32 per 100 000 people with an average 15-year prevalence of 1.62 per 100 000 and a 3-year survival of 73%. A database spanning 30 years in Norway demonstrated an increasing incidence of GIST with 1.8 cases per million in the 1980s and 12.5 per million during 2000–2004. This study estimated the prevalence of GIST to be 129 cases per million. A registry in the Netherlands revealed a similar increase in annual incidence of 2.1 cases per million in 1995 to 12.7 per million in 2003. This increase in incidence can be attributed to recent advances in diagnosis using histological and immunohistochemical markers as well as advances in radiographic imaging and endoscopy of the small bowel.

Gastrointestinal stromal tumours are typically diagnosed in people between 60 and 70 years old. In the Norwegian database, a median age of 67 years with a range of 15–88 years was reported. Although case reports of paediatric GIST do exist, occurrence before age 30 is extremely rare. Most studies report no gender differences, although a case series in Norway of 52 patients with GIST between 1980 and 2009 reported a female predominance (62% female vs. 38% male). A national registry from 122 sites throughout the United States included 882 patients with GIST and reported that 78% of patients were Caucasian, 15% African American, 3% Asian and 3% Hispanic. The majority (63%) of GIST are found based on patients’ symptoms, although about a third can be found incidentally during abdominal imaging, endoscopy or surgery. GIST most commonly occur in the stomach (50–60%), less frequently in the small bowel (20–40%) and rarely (10%) in the rectum. GIST may also occur as a primary tumour of the omentum, mesentry or retroperitoneum. Most GIST are benign with only 20–30% malignant. The 5-year survival ranges between 35% and 65% and depends primarily on tumour size, mitotic index and location.

CLINICAL PRESENTATION AND DIAGNOSIS

Gastrointestinal stromal tumours are submucosal tumours, which can invade through the mucosa leading to ulcers and bleeding (Figure 1). They can also invade through the serosa and spread to nearby structures, nodes and distant organs. The clinical presentation of GIST is highly variable and depends on tumour location, size and growth pattern. Small GIST, generally less than 2 cm, rarely cause symptoms and are most frequently discovered incidentally by endoscopy or radiological imaging. Lau et al. reported that 22% of GIST are found incidentally. On endoscopy, a submucosal bulge is identified with overlying normal mucosa if no ulcers have occurred. If symptomatic, the most common presenting symptoms are related to gastrointestinal bleeding (52% of patients) including melena, haematemesis or symptomatic anaemia. Other symptoms can include abdominal fullness, early satiety, a palpable mass or pain. GIST can also cause altered bowel function, bowel obstruction or perforation, and symptoms of cholangitis if they occur at the ampulla of Vater. Proximal gastric tumours can present as dysphagia and tumours near the pyloric region may present as gastric outlet obstruction. Nishida et al. studied 271 patients with stromal tumours and found that 66% of patients had symptoms that correlated with tumour size. They speculated that submucosal origin and tendency towards extraluminal growth was the reason that GIST rarely cause intestinal obstruction even when very large. Rectal GIST, although rare, most commonly present with haematochezia. GIST may occur as part of a syndrome, such as Carney’s triad (gastric GIST, paraganglioma, pulmonary chondroma). Neurofibromatosis type 1 (with predominately spindle cell type of GIST) or Von Hippel Lindau disease.

Asymptomatic GIST are typically found on upper endoscopy for another indication or as an incidental finding on cross-sectional imaging. For symptomatic
lesions, the presenting signs and symptoms determine the direction of initial evaluation. For example, in the very unusual case of an acute abdomen caused by tumour haemorrhage, perforation or bowel obstruction, emergent surgery will lead to the diagnosis. For patients presenting with significant abdominal pain, cross-sectional imaging studies will usually localise the origin of the tumour (Figure 2). Tissue diagnosis requires endoscopy with the route determined by anatomic location. Standard endoscopic mucosal biopsy samples are generally inadequate for the diagnosis of GIST, and deeper, submucosal tissue is usually required. In a study comparing jumbo forceps biopsy to endoscopic submucosal resection, the diagnostic yield of forceps biopsy was only 17% (vs. 87% for ESR, \( P = 0.001 \)). Device-assisted enteroscopy is now available to sample and mark tumours lying beyond the ligament of Treitz. GIST causing haematemesis or melena are usually found readily on upper endoscopy. A national registry from 122 community and academic centres in the United States reporting data for 2004–2009 found that CT scan was the most commonly (76% of patients) used diagnostic imaging method for initial detection of GIST. CT enterography, which requires a large volume of oral contrast, provides excellent spatial resolution, has multiplanar capabilities and is considered superior to conventional CT for visualisation of the small bowel wall and lumen.

For GIST, which appear confined to the gastrointestinal submucosa, endoscopic ultrasound (EUS) provides important information to establish the diagnosis and stage the tumour. EUS characterises the size, borders, homogeneity, presence of echogenic or anechoic foci and the originating bowel wall layer. Traditionally, GIST appears as a hypoechoic mass arising from the fourth (muscularis propria) or less often the second (muscularis mucosae) layer of the gut wall (Figure 3). EUS-guided fine-needle aspiration (FNA) or core needle biopsies should be obtained where possible. The use of endoscopic FNA to aid in the diagnosis of GIST has been increasing. The risk of peritoneal seeding has previously been considered a contraindication to FNA; however, the risk appears to be negligible, reportedly as low as 0.003–0.009%. Several studies have looked at the diagnostic yield of EUS with FNA for the diagnosis of GIST. The sensitivity and diagnostic yield of this technique ranges between 75% and 85%. EUS can also help to identify extramural lesions and differentiate vascular vs. solid lesions.

**HISTOPATHOLOGY**

The diagnosis of GIST is confirmed histologically and by immunohistochemical staining techniques. The term gastrointestinal stromal tumour was introduced by Mazur and Clark in 1983 as a reference to the main group of mesenchymal tumours of the gastrointestinal tract, which could not be distinguished from smooth muscle or neurogenic origin. Until recently, there existed considerable confusion as to the cell line of differentiation displayed by these tumours. There was evidence that some were myogenic, some neural, while others demonstrated bidirectional differentiation. Histologically, these tumours fall into one of three cell types: spindle cell...
Cells comprising GIST usually undergo a fusiform or epithelioid growth pattern resembling muscular or neural differentiation and display variable cellular density and mitotic activity. Although the prognostic relevance of cell type is limited, it is suggested that the mitotic threshold for malignancy is lower for epithelioid compared with spindle cell tumours. GIST of spindle cell type are composed of relatively uniform eosinophilic cells arranged in short fascicles or whorls with a paler eosinophilic cytoplasm than smooth muscle neoplasms. They often display a fibrillar syncytial appearance. Spindle cell type nuclei tend to be uniform and stromal collagen is minimal in most cases. Delicate thin-walled vessels may be prominent predisposing them to stromal haemorrhage. GIST of the epithelioid type are composed of rounded cells with an eosinophilic or clear cytoplasm. The nuclei tend to be uniform, round or ovoid, and display a nested architecture more often than spindle cell types, which may give them the appearance of an epithelial or melanocytic neoplasm. Lesions of mixed cell type may exhibit an abrupt transition between spindle cell and epithelioid areas, or may have a complex mixing of these cell types throughout, leading to an intermediate ovoid cytologic appearance.

**MOLECULAR BIOLOGY**

Notable progress in the diagnoses of GIST was made when Hirota et al. first proposed a gain-of-function mutation in the c-KIT proto-oncogene, which is found in most GIST. The KIT gene encodes the c-KIT protein, a tyrosine kinase transmembrane receptor for the cytokine known as stem cell factor (SCF). The epitope of the c-KIT protein (its antigenic determinant) is the CD117 antigen. CD117 is expressed in virtually all (approximately 95%) GIST, both spindle and epithelioid types, and is absent in other tumours such as leiomyomas and schwannomas. Therefore, CD117 is a reliable phenotypic marker. The c-KIT proto-oncogene belongs to the platelet-derived growth factor receptor (PDGFR) superfamily, mapping to chromosome 4 (4q11-q12). All haematopoietic stem cells, including mast cells, melanocytes and germ cells, express high levels of c-KIT. The binding of SCF to c-KIT results in receptor dimerisation, which in turn activates the tyrosine kinase enzymatic activity of the intracellular portion and results in auto-phosphorylation of the receptor. The activated kinases then cross-phosphorylate tyrosine residues in the opposed homo-dimer partner, leading to additional c-KIT structural alterations and further activation of the receptor. These steps culminate in activation of an intricate cell-signalling cascade that control crucial cell functions in tumourigenesis, including proliferation, adhesion, apoptosis and differentiation.

Mutations most commonly occur in the juxtamembrane exon 11 of the gene in chromosome 4 (approximately 65% of all GIST). These mutations have been reported to be of higher grade and associated with poorer outcome compared with GIST lacking these mutations. Other less commonly involved KIT mutation sites are on exon 9 (10%) and exon 13 (2%) in the same chromosome. A less common mutation is of...
the alpha-type platelet-derived growth factor receptor (PDGFRA) present in only 5% of GIST. It is very rare for both c-KIT and PDGFRA mutations to occur simultaneously. Similarly, it is rare for GIST to occur without either mutation; however, it has been reported in patients with Neurofibromatosis or Carney’s Syndrome.

Other important cell-cycle proteins frequently associated with the pathogenesis or progression of GIST are the tumour suppressor proteins p53 and bcl-2. Feakins reported that out of 105 GIST, 28% were p53 positive and 77% were bcl-2 positive. Expression of p53 is associated with increased size, epithelioid shape, nuclear atypia, mucosal invasion and mitotic count >5/50 high power field. El-Rifai et al. reported that 9p deletion, 8q amplification and 17q amplification were exclusively found on high-grade (malignant) GIST. Sheehan et al. demonstrated variable cyclooxygenase-2 (COX-2) protein expression in the cytoplasm of GIST cells. The percentage of cells expressing COX-2 was 60% in spindle cell GIST tumours, 85% in epithelial cell tumours and 47.5% in mixed type tumours. More recent studies have repeatedly shown a correlation between COX-2 expression and tumour cell proliferation, but no associations have been found between COX-2 expression and mortality, metastasis, tumour size, response to tyrosine kinase inhibitors or survival.

IMMUNOHISTOCHEMICAL STAINING

Positive staining of c-KIT serves as a strong and universal marker of GIST (Figure 4c). Staining patterns may be diffuse, focal or mixed. The expression of this protein, judged together with other immunohistochemical stainings and tumour morphology, is a very useful diagnostic feature in distinguishing GIST from other mesenchymal neoplasms that do not express c-KIT. However, in the last decade, drawbacks related to the use of c-KIT staining have emerged such as those associated with a small group of c-KIT-negative GIST (approximately 5% – especially related to PDGFRA mutant tumours) and false positivity related to the development of unreliable c-KIT antibody assays. To overcome this, it is recommended to regularly validate the quality of the most widely used polyclonal c-KIT antibody assays. Recently, a complementary stain with similar sensitivity and specificity to c-KIT staining was developed, which has proved useful in the histochemical diagnosis of GIST. A calcium-regulated chloride channel protein was identified from transcriptional gene expression profiling studies on GIST. This protein is known as DOG1 (discovered on GIST-1) and polyclonal antibodies against this protein have been found to label GIST independent of c-KIT/PDGFRA mutational status (Figure 4d).

Another investigated antigen initially envisioned as a reproducible marker of GIST was CD34, which is a sialylated transmembrane glycoprotein also found in haematopoietic progenitor cells and endothelial cells. Unfortunately, only 60–70% of GIST are CD34+. In addition, colorectal and oesophageal malignancies may also express CD34, which in itself makes it nonspecific for the accurate diagnosis of GIST. Finally, other proteins such as smooth muscle actin (40%), S100 (5%) and desmin (2%) have been identified as potential GIST markers, but they lack reliability.

PROGNOSTIC FEATURES

Assessment of the malignant potential of a primary GIST lesion is difficult in many cases and even small GIST (<2 cm in diameter) have an uncertain malignant potential. Tumour size (with threshold levels of 2 cm, 5 cm and 10 cm) and mitotic index are common features used to assess prognosis. Investigative tools include the measurement of cellular proliferation using the markers proliferating cell nuclear antigen (PCNA) or Ki-67 and assessment of DNA aneuploidy. Tumour site has been considered an important independent prognostic indicator, as patients with small bowel GIST have a higher rate of recurrence than those with gastric tumours. There are also differences in the rate of disease progression based on location in the stomach. The most significant is the higher frequency of malignant behaviour for GIST located in the gastric fundus and at the gastro-oesophageal junction-cardia region, compared with the antrum. This finding could be from variation in the proliferation characteristics of different subsets of ICC's or differences in gastric smooth muscle stem cells present in different subregions of the stomach. This conflicts with the findings of Yan et al. who looked at 69 cases of GIST and found no statistical difference in survival based on primary tumour location. Presentation may also be associated with survival. In a cohort study of 146 patients with GIST who underwent complete resection, Hassan et al. found that symptomatic presentation, as opposed to incidentally diagnosed tumours, was independently associated with a poorer outcome and significantly decreased disease-specific 5-year survival.

Malignancy is clearly established if there is tumour spread beyond the organ of origin. The liver is the most common site of metastases followed by the peritoneum. Other sites of reported metastasis include the retroperitoneum, pleura, lungs, bone and subcutaneous tissue.
THERAPEUTIC APPROACH

The current treatment of patients with GIST requires a multidisciplinary team including a medical and surgical oncologist.\(^67\) Surgery is the mainstay therapy for GIST with a primary goal of complete resection with negative tumour cell margins and preservation of an intact capsule to avoid tumour rupture or haemorrhage.\(^67,\)\(^68\) For GIST <2 cm, which are considered to be low risk and are mostly found incidentally on endoscopy or radiological imaging, EUS evaluation annually to assess for growth is the usual practice. There are no strict guidelines for surveillance and patient preference, as well as co-morbidities, should be taken into account.\(^23\) In general, surgical excision is recommended if there is growth in size or for any tumours \(\geq 2\) cm (Figure 5). For rectal GIST found on colonoscopy, EUS followed by surgical excision biopsy is recommended regardless of size.\(^69\)

As GIST tend to arise from the organ of origin without diffuse infiltration, wedge resection of gastric and segmental resection of intestinal GIST are considered adequate therapy, while en bloc resection for omental or mesenteric tumour is usually recommended.\(^59\) In a retrospective review of 186 patients with surgically treated primary GIST, 87 of 104 patients (84%) with gastric tumours were treated with wedge resection or local excision; only 15 patients (14%) underwent antrectomy with Billroth anastomosis or gastrectomy. For 16 patients with duodenal GIST, six (38%) required pancreatoduodenectomy, six (38%) required duodenectomy with local excision and four (25%) required segmental resection. Forty-five of 53 patients (85%) with small bowel GIST had segmental resection with primary anastomosis. The 5-year disease-free survival of the 146 patients with localised GIST with histologically complete resections was only 65%.\(^64\) Katrin et al. achieved a higher rate of complete resection using laparoscopic surgery than open surgery (97.5% vs. 85.2%), as well as a lower morbidity, complication rate, length of surgery and length of hospitalisation.\(^68\)

Follow-up after resection of primary tumour is as follows: low-risk tumours – CT scan every 6 months for 5 years; intermediate or high-risk tumours – CT scan every 3–4 months for 3 years, every 6 months until 5 years, then annually thereafter.\(^59\) Several variables have been identified to guide risk of recurrence post-operatively (Table 1). Surgical resection in patients with primary GIST is associated with a 5-year survival rate of 48–70%;\(^14,\)\(^70–72\) however, 40–80% of GIST recur despite

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**Figure 5** | Flow diagram of GIST management.
Table 1 | Factors associated with prognosis when evaluating a GIST post-operatively

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Poor</th>
<th>Intermediate</th>
<th>Favourable</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Tumour size</td>
<td>≥10 cm</td>
<td>5–10 cm</td>
<td>&lt;5 cm</td>
<td>12</td>
</tr>
<tr>
<td>Tumour location</td>
<td>Colon</td>
<td>Small intestine</td>
<td>Stomach</td>
<td>12</td>
</tr>
<tr>
<td>Mitosis (total number per 50 hpf)</td>
<td>≥5</td>
<td>&lt;5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Growth</td>
<td>Local invasion</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal cancer index (PCI)</td>
<td>≥4</td>
<td>1–3</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Surgical resection cytoreduction</td>
<td>Incomplete</td>
<td>Complete</td>
<td>63</td>
<td></td>
</tr>
</tbody>
</table>

PCI: The summation of the lesion size score in each of 13 abdominopelvic regions. Lesion size score: 0 (absence of tumour), 1 (tumour nodules < 0.5 cm), 2 (0.5–5 cm tumour nodules), 3 (nodules > than 5 cm).

Histopathologically complete tumour resection.73 There is no agreement regarding whether surgery should be attempted to remove residual metastatic disease or stable primary disease that is controlled with imatinib (see below). If clinical response is achieved after imatinib therapy for previously unresectable tumours or in cases where gross residual disease is present after surgery, then re-evaluation for resectability should be performed. Imatinib therapy should not be interrupted, or only for the shortest possible time.59

Standard cytotoxic chemotherapy is not effective in treating GIST.14 With the introduction of tyrosine kinase inhibitors (TKI), there has been a dramatic increase in survival. In 2002, the FDA approved imatinib mesylate (Gleevec, Novartis Pharmaceuticals, East Hanover, NJ, USA) for the treatment of surgically unresectable or metastatic GIST.74 Imatinib mesylate is a selective inhibitor of tyrosine kinase signalling enzymes including c-ABL, BCR-ABL, c-KIT and PDGFRα.75, 76 Tuveson et al. demonstrated that this inhibition of mutant c-KIT will lead to growth arrest and eventual apoptosis in GIST cells.77 Imatinib was first used for chronic myelogenous leukaemia (CML).78–80 Henrich et al. studied mast cell leukaemia with a similar c-KIT mutation as seen in GIST and found that imatinib can inhibit kinase action of the mutant c-KIT protein.81 In a randomised, open-label, multicentre clinical trial looking at the safety and efficacy of imatinib for histologically confirmed and metastatic or unresectable GIST, no patients had complete tumour response, 53.7% had partial response, 27.9% had stable disease and 13.6% had disease progression. Patients also had improvement in functional status assessed by the Eastern Cooperative Oncology Group (ECOG) scale. Imatinib was generally well tolerated, although 74.1% of patients had oedema (mostl periorbital), 52.4% nausea, 44.9% diarrhoea, 25.9% abdominal pain. Other side effects included musculoskeletal pain (39.5%), fatigue (34.7%), rash (30.6%) or headache (25.9%).82

In 2008, imatinib was approved by the FDA as adjuvant therapy for the treatment of c-KIT-positive GIST based on a randomised, double-blind phase III, placebo-controlled multicentre trial of 713 patients after surgical resection for a GIST ≥3 cm. Patients were treated for 1 year following surgical resection with either imatinib 400 mg or placebo. The use of imatinib 400 mg daily compared to placebo showed a significant improvement in recurrence-free survival of 98% vs. 83% (HR = 0.35, 95% CI 0.22–0.53; P < 0.0001). There was no difference in overall survival. In a subset analysis, it was found that the significant increase in recurrence-free survival persisted across all size categories (3–6 cm vs. 6–10 cm vs. >10 cm). Severe adverse events (classified as Grade 3 or 4) were more common in the imatinib group and these included abdominal pain [12 patients (3%) vs. 6 patients (1%)], diarrhoea [10 patients (2%) vs. 5 patients (1%)], dermatitis [11 patients (3%) vs. 0] and neutropaenia [12 patients (3%) vs. 4 patients (1%)]. The most common adverse events overall were as follows: oedema (77%), fatigue (43%), diarrhoea (31%) and nausea (30%).83

Imatinib is started at a dose of 400 mg once daily with a meal until progression of disease or patient intolerance occurs. In the past, if patients did not respond to imatinib therapy, dose escalation was commonly recommended. However, Blanke et al. studied the effect of imatinib 400 mg twice daily vs. 400 mg once daily in patients with metastatic or surgically unresectable GIST and found no statistically significant difference in response rate, progression-free survival or overall survival. Toxicities occurred more frequently in the higher dose group.84 A meta-analysis of 1640 cases of advanced GIST comparing 400 mg daily vs. 800 mg...
daily doses also found no difference in overall survival (HR = 1.00, \( P = 0.97 \)); however, they did find a small difference in progression-free survival (HR 0.89; 95% CI 0.79–1.00, \( P = 0.04 \)), which was attributed to patients with KIT exon 9 mutations.\(^{85} \) Currently, the standard of care is imatinib at 400 mg daily for advanced GIST, with an increase in dose to 800 mg daily for patients with disease progression or those with an exon 9 KIT mutation.\(^{86} \)

Sunitinib malate (Sutent, Pfizer Inc., New York, NY, USA) is a second-line TKI used for patients with imatinib intolerance or resistance. Primary resistance to imatinib is defined as progression within the first 6 months of treatment; secondary resistance occurs after the first 6 months. Partial resistance includes one or more limited sites of metastasis, or a growing nodule within a larger mass. Multifocal resistance is overt progression of most or all tumour sites.\(^{59, 70, 87} \) Similar to imatinib, sunitinib targets c-KIT and PDGFR but additionally blocks vascular endothelial growth factor (VEGF).\(^{86} \) In a randomised, double-blind, placebo-controlled, multicentre trial assessing the efficacy of sunitinib for unresectable, imatinib-resistant GIST, sunitinib treatment resulted in significantly longer time to tumour progression (27.3 vs. 6.4 weeks, HR 0.33, 95% CI 0.23–0.47; \( P < 0.0001 \)).\(^{86} \) Secondary endpoints included overall survival, progression-free survival, time to tumour response and duration of response. Fourteen patients (7%) in the sunitinib group showed partial response to treatment (vs. 0% for placebo); 120 patients (58%) had stable disease (vs. 48% for placebo) and 39 patients (19%) had progressive disease (vs. 37% for placebo). Fifty-nine patients originally in the placebo group crossed over to sunitinib and six had partial response to treatment and four had stable disease at 26-week follow-up. The most common serious adverse events were neutropaenia (10%), lymphopaenia (9%), thrombocytopaenia (4%), anaemia (4%) and fatigue (5%). The most common nonhaematological adverse events included diarrhoea, nausea, anorexia, dysgeusia, fatigue, skin discolouration and hand–foot syndrome – all of which were more common in the sunitinib group.\(^{88} \) Currently, daily dosing is the standard of treatment for sunitinib in patients who failed imatinib therapy.\(^{86} \)

Regorafenib (Stivarga, Bayer Health Care Pharmaceuticals, Wayne, NJ, USA) is another tyrosine kinase inhibitor approved in February 2013 as third-line treatment for GIST. In addition to c-KIT and PDGFR (targeted by both imatinib and sunitinib), as well as VEGFR (targeted by sunitinib), regorafenib also inhibits RET, FGFR and BRAF. The pivotal study for approval was a phase 3, randomised, placebo-controlled, multicentre trial of regorafenib for the treatment of metastatic, unresectable GIST in patients who previously failed imatinib and sunitinib treatment.\(^{84} \) Failure of previous treatment was defined as either intolerance or progression with imatinib and solely progression with sunitinib. Overall, 199 patients were randomised to receive 160 mg of regorafenib daily or placebo for three consecutive weeks followed by 1 week of no treatment in 4-week cycles. There was a statistically significantly greater progression-free survival in the regorafenib group with 60% (95% CI: 51–68) at 3 months and 38% (95% CI: 29–48) at 6 months. Progression-free survival in the placebo group was only 11% at 3 months and 0% at 6 months. Despite these differences, there was no difference in overall survival. The most common adverse events were hand–foot syndrome (56% of patients in regorafenib group vs. 14% in the placebo group), hypertension (23%), skin rash (20%) and diarrhoea (5%).\(^{89} \)

CONCLUSIONS

Gastrointestinal stromal tumours are the most common mesenchymal tumours of the gastrointestinal tract arising from the interstitial cells of Cajal. Pathological diagnostic criteria include histological morphology (spindle cell type, epithelioid type, mixed type) supplemented by immunohistochemistry markers. CD117 (c-KIT) is most common and found in almost 95% of GIST. Clinical presentation varies depending on the site of the tumour. Fortunately, most GIST are benign and only 20–30% are malignant. Malignant behaviour of GIST is defined by invasion of adjacent structures and distant metastasis. The liver is the most common site of metastases followed by the peritoneum, the retroperitoneum, pleura, lungs, bone and subcutaneous tissue.

The mainstay of therapy for localised disease is surgery to attempt complete resection. Localised GIST is associated with a 5-year survival rate of 48–70%; however, 40–80% of GIST recur despite histopathologically complete tumour resection. Following resection, risk stratification is necessary. Patients should be started on the tyrosine kinase inhibitor imatinib 400 mg/day until progression or intolerance in all cases except when there is complete resection of a low-risk tumour. The current management of unresectable GIST is imatinib. The response rate of recurrent or metastatic GIST to imatinib mesylate is 60–70%. Additional tyrosine kinase inhibitors with additional anti-tumour properties have come to market for salvage therapy.
All authors approved the manuscript. Frank Friedenberg, MD reviewed the medical literature and contributed to drafting of the manuscript. Frank Friedenberg, MD contributed to drafting of the manuscript and final edits. All authors approved the final version of the manuscript.
Review: gastrointestinal stromal tumours (GIST)


67. Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumours:
before and after STI-571. *Hum Pathol* 2002; 33: 466–77.

1. Characteristic findings on EUS that suggest a GIST include
   a. originates from the third layer
   b. is hypoechoic
   c. originates from the muscularis propria (4th layer)
   d. is hyperechoic

2. The two most common sites for metastasis from GISTs are:
   a. Brain and lung
   b. Liver and lung
   c. Liver and peritoneum
   d. Pancreas and bones

True or False

3. GISTs arise from the interstitial cells of Cajal

4. Follow up after resection of a GIST consists of panendoscopy every year

5. Small bowel GISTs are more likely to recur than gastric GISTs

6. The most common location of a GIST is in the stomach

7. GISTs are usually diagnosed by endoscopic biopsies of a submucosal mass.

8. First line therapy for GIST is imatinib

9. Positive staining of c-KIT (CD117) is seen in 95% of GIST tumors and can be detected by immunostaining

10. GISTs that measure <2cm should be removed endoscopically to prevent metastasis

11. Imatinib mechanism of action involves inhibition of tyrosine kinase of the mutant c-KIT leading to cellular growth arrest and apoptosis in GIST cells