Treatment of rare cancers: gastrointestinal stromal tumours

Gastrointestinal stromal tumour, the most common mesenchymal malignancy of the gastrointestinal tract, is a rare cancer that until recent years had severely limited therapeutic options. This article looks at its epidemiology, aetiology, pathophysiology, diagnosis, current treatment and potential new treatment options on the horizon.

Until recently, strategies for treating gastrointestinal stromal tumour (GIST) were severely limited; these tumours were unresponsive to conventional chemo- and radiotherapy, and surgical resection was not always possible.

However, the development of novel, multi-targeted tyrosine kinase inhibitors has meant that patients with metastatic disease can now benefit from pharmacotherapeutic interventions. This article highlights the vital clinical advances which have finally improved the prognosis of this problematic disease.

Epidemiology and aetiology

GIST is the most common mesenchymal malignancy of the gastrointestinal tract. Its true incidence is unknown, but population estimates suggest that GIST is associated with an annual incidence of 20 cases per million (Kindblom et al, 2003). These figures suggest that GIST affects around 1200 UK patients each year (Office for National Statistics, 2005).

Patients can contract GIST at any time, but the median age for presentation is around 60 years (Corless et al, 2004). GISTs predominantly arise in the stomach and small intestine (60% and 25% respectively), but can also occur in the rectum, oesophagus, appendix, gallbladder, pancreas, mesentery, omentum and retroperitoneum (Miettinen et al, 2000; Corless et al, 2004).

Table 1. Prognosis of primary gastrointestinal stromal tumours

Risk	Size (cm)	Mitotic count (per 50 HPF)
Very low risk	< 2	< 5
Low risk	2–5	< 5
Intermediate risk	< 5	6–10
	5–10	< 5
High risk	>5	> 5
	>10	Any mitotic rate
	Any tumour	> 10

HPF = high power field

GIST prognosis appears to be dependent upon the size and mitotic count of the primary tumour (*Table 1*) (Fletcher et al, 2002). This hypothesis has been supported by a retrospective study of 200 patients with surgically resected GISTs. The investigators found that although the removal of a primary tumour with a diameter <5 cm was associated with a relatively high 5-year, disease-specific survival rate of approximately 60%, the survival rate for a tumour >10 cm was as low as 20% (DeMatteo et al, 2000).

Up to 30% of newly diagnosed GISTs are overtly malignant, or have features that indicate a high malignant potential (Miettinen et al, 2002). In addition, 47% of patients present with metastases (DeMatteo et al, 2000). GISTs often recur at the site of resection (overall recurrence rates: gastric 76%, bowel 64%), and even with low-risk GISTs, recurrences have been reported up to 20 years post-resection (Pidhorecky et al, 2000; Corless et al, 2004). For this reason, no GIST should ever be regarded as truly benign, but should be stratified in terms of malignancy risk (*Table 1*; Corless et al, 2004).

Pathophysiology

Approximately 95% of GISTs stain positively for KIT (CD117). KIT is a 145-kD transmembrane glycoprotein that serves as a receptor for stem cell factor (SCF) and has tyrosine kinase activity (Besmer et al, 1986; Yarden et al, 1987). KIT is a member of the receptor tyrosine kinases and is closely related to the receptors for platelet-derived growth factor (PDGF), macrophage colony-stimulating factor, and FLT3 ligand (Rousset et al, 1995).

Binding of SCF to KIT results in receptor homodimerization, tyrosine kinase activation, and phosphorylation of a variety of substrates (*Figure 1*) (Bourne, 1998). In many cases, these substrates are protein tyrosine kinases and serve as effectors of intracellular signal transduction. This in turn triggers cell proliferation and differentiation (Blume-Jensen et al, 1991).

In 1998, Hirota et al found that most GISTs not only expressed KIT proteins but that their KIT genes con-

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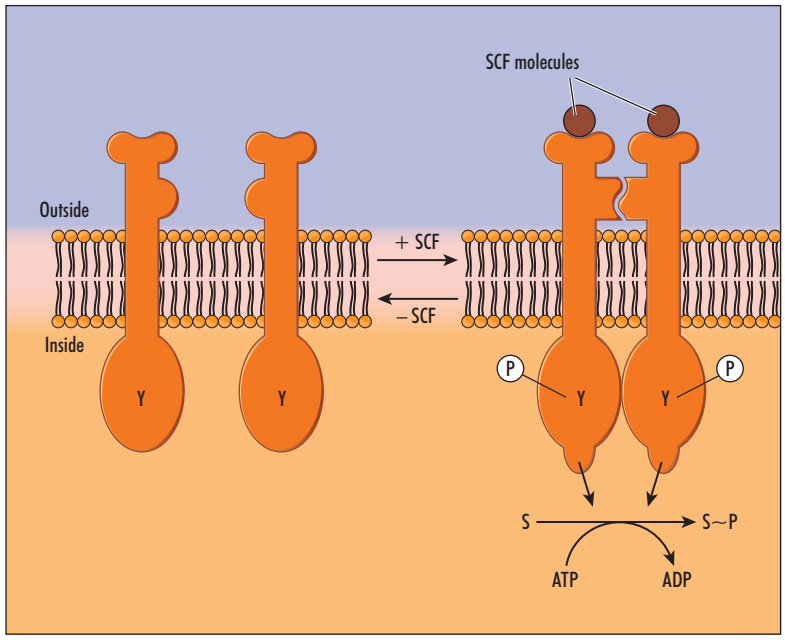


Figure 1. Mechanism of action of the KIT receptor tyrosine kinase, which is associated with 95% of gastrointestinal stromal tumours. The receptor polypeptide has extracellular and cytoplasmic domains, depicted above and below the plasma membrane. Following stem cell factor (SCF) binding, the receptor converts from its inactive monomeric state to an active dimeric state. The cytoplasmic domains become phosphorylated (P) on specific tyrosine residues (Y) and their enzymic properties are activated. This catalyses the phosphorylation of substrate proteins (S) including various protein tyrosine kinases. ADP = adenosine diphosphate; ATP = adenosine 5'-triphosphate.

tained a mutation in the juxtamembrane domain (exon 11). Mutations have also now been discovered in the extracellular domain (exon 9), kinase I domain (exon 13), and activation loop (exon 17). It has been hypothesized that mutation type can be used to predict malignancy risk, but in order to verify this claim, further studies are required (Antonescu et al, 2003; Wardelmann et al, 2003).

KIT-negative GISTs are associated with a similar pathological pathway. These GIST sub-types contain mutations on the PDGFα receptor tyrosine kinase, and like their KIT-positive counterparts, these mutant isoforms can be constitutively phosphorylated in the absence of their hormonal ligand and share the same intracellular transduction process (Corless et al, 2004).

Differential diagnosis

Approximately 80% of the cells within a GIST are spindle shaped, with the other 20% being epitheloid (Nishida and Hirota, 2000; Pidhorecky et al, 2000). As GISTs have a relatively broad morphological spectrum, they are often mistaken for other mesenchymal, neural or neuroendocrine abdominal neoplasms. These include: leiomyoma, leiomyosarcoma, schwannoma, malignant peripheral-nerve sheath tumour, solitary fibrous tumour, inflammatory myofibroblastic tumour, fibromatosis, synovial sarcoma, neuroendocrine tumours, gastric glomus tumour, malignant mesothelioma, angiosarcoma and sarcomatoid carcinoma (Corless et al, 2004).

Advances in metastatic GIST treatment have placed a new priority on accurate diagnosis. As a result, immunohistochemical staining, in combination with standard pathological evaluation, is now the principal diagnostic tool for confirming KIT-positive GIST. The overall immunohistochemical profile of the GIST helps in the differential diagnosis between GISTs and other mesenchymal tumours in the abdomen. Other markers that can indicate GIST include BCL-2, CD34, muscle-specific actin, smooth muscle actin, S-100 and desmin. These markers are present in 80, 70, 50, 35, 10 and 5% of patients respectively (Corless et al, 2004).

Current treatment options

Until recently, therapeutic options for GIST were severely limited. Established anti-tumour interventions such as radiation therapy or conventional chemotherapy proved unsuccessful, with 95% of patients displaying high levels of resistance. In most cases, therefore, the only plausible option was surgery (Pierie et al, 2001), and indeed, for primary resectable tumours, this is the first-line treatment strategy.

For patients with unresectable or metastatic tumours, the choice of therapy was even more restricted. Despite well-documented poor response rates, chemotherapy represented the only viable option. A variety of regimens were investigated, involving doxorubicin, dacarbazine, interferon-alpha and thalidomide, but successes were minimal and prognosis poor (Casper, 2000; Pidhorecky et al, 2000; Joensuu and Dimitrijevic, 2001; Pierie et al, 2001).

In 2001, a major breakthrough occurred. For many years, researchers had speculated that selective inhibition of the KIT protein may halt GIST progression, and phase II studies involving the tyrosine kinase inhibitor imatinib showed that this agent could reverse KIT-driven abnormal growth and achieve objective clinical responses. For example, imatinib's clinical efficacy (400–600 mg/day) was objectively assessed in an open-label, randomized study involving 147 patients with unresectable or metastatic KIT-positive GIST, aged between 18 and 83 years.

Around 40% of patients achieved a partial therapy response (defined as at least a 50% decrease in the summed products of the largest perpendicular diameters of all measurable target lesions, no progression of evaluable disease, and no new lesions), while a further 42% remained stable (measurable increased or decreased response below 50%). These results were maintained for up to 24 months, provided that patients continued to benefit (Novartis Pharma AG, data on file, 2002).

Further phase III studies resulted in imatinib being granted an accelerated licence for the treatment of adult

patients with KIT-positive unresectable and/or metastatic GISTs. It has now become the first-line treatment for this GIST patient sub-group.

The efficacy of imatinib in treating metastatic and unresectable GIST has prompted clinicians to investigate its role in improving the outcome of surgery and rendering more tumours operable. Encouraging results have already been observed in small studies, including one reported at the American Society of Clinical Oncology meeting in June 2003. Imatinib was administered to 112 GIST patients, 18 of whom eventually underwent resection of residual tumours. Complete resection was achieved in seven of eight patients whose tumours were responding to imatinib at the time of surgery and in two of 10 patients with progressive disease. The investigators recommended that initially inoperable patients who achieve a partial response with imatinib therapy should receive early surgery evaluation while their disease is responsive or stable (Hohenberger et al, 2003).

The role of surgery in metastatic/inoperable GIST post imatinib is not entirely clear. It seems to benefit those patients in whom the tumours have shown metabolic and histological response. In these situations surgery may minimize the risk of rupture. It is increasingly recognized that some patients develop a resistant clone with an isolated site of progressive disease. In these patients, resection of the new lesion may allow continuing disease control on imatinib. In patients where the tumours have globally progressed on imatinib, surgery has a very limited role. Resection of individual masses is attempted with a palliative intent, e.g. for pain, bleeding.

Although imatinib has undoubtedly improved patient prognosis, further specifically targeted agents are required. Up to 20% of GIST patients exhibit primary resistance to imatinib, 7% develop toxicity, and the vast majority develop secondary resistance (Fletcher et al, 2003; Sawaki and Yamao, 2004; Verweij et al, 2004). This resistance may be attributable to additional KIT or PDGF-α mutations (Corless et al, 2004).

Imatinib resistance: new hope for clinicians

The emergence of imatinib resistance has inevitably led to calls for the development of second-generation molecularly-targeted pharmacological compounds.

One the most promising pharmacotherapeutic agents is sunitinib malate (Sutent, Pfizer Limited, Sandwich, Kent), a novel tyrosine kinase inhibitor with direct anti-tumour and anti-angiogenic activity. This multitargeted molecule inhibits both PDGF and KIT receptor tyrosine kinases, and also vascular endothelial growth factor receptor (VEGFR-1 and 2). It has shown promise in patients with imatinib-resistant GIST.

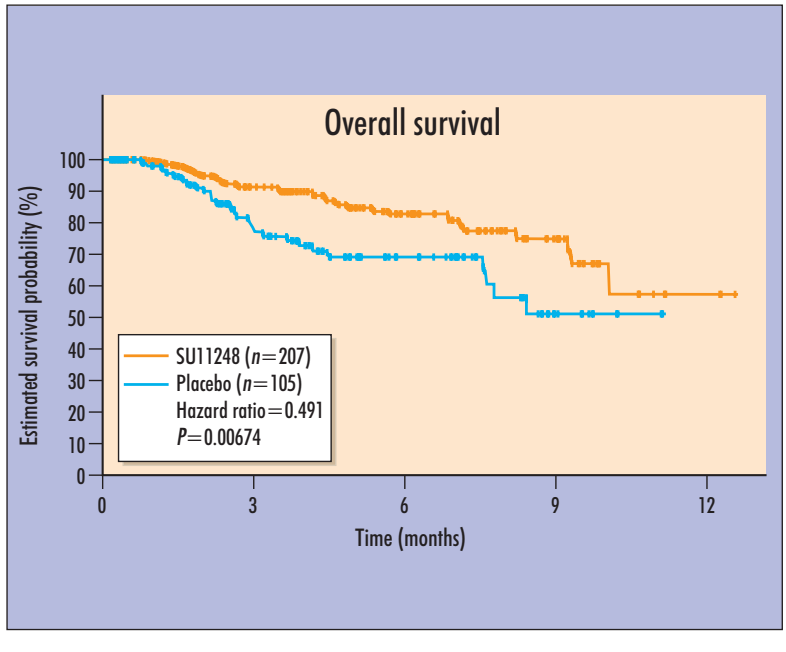
For example, interim results from a phase III, double-blind, multicentre, randomized, placebo-controlled trial involving 312 imatinib-resistant patients, were presented at the American Society of Clinical Oncology in May 2005, and more recently at the European Cancer Conference. Patients in the sunitinib cohort (n=207; median age 58 years) received between one and nine (median = two) 6-week treatment cycles (4 weeks of daily sunitinib administration treatment followed by 2 weeks drug free) using a target dose of 50 mg per day.

The researchers found that compared to placebo, sunitinib resulted in more than a four-fold increase in median time to progression (6.3 *vs* 1.5 months, P<0.00001; hazard ratio = 0.335; Demetri et al, 2005). Estimated overall survival also significantly improved *vs* placebo (50% risk reduction, P=0.00674; *Figure 2*; Demetri et al, 2005). In addition, it was noted that as 59 patients in the placebo arm were subsequently offered treatment with sunitinib, and as this crossover was included in the survival analysis, the survival benefit for sunitinib may have been underestimated. Sunitinib was reasonably well tolerated throughout the study (grade 3 neutropenia=8%, grade 3 anaemia=4%, grade 3 thrombocytopenia=5%).

The researchers concluded that sunitinib represents a useful treatment for GIST patients who are resistant to or intolerant of imatinib (Demetri et al, 2005).

Research into GIST gene expression and signalling pathways may provide further pharmacotherapeutic options. It is now believed that activation of the P13K/mTOR protein kinase pathway is essential to KIT-mediated oncological signalling, and studies have shown that selective inhibition of this pathway reduces proliferation and increases apoptosis (Duensing et al, 2003).

Figure 2. Difference in overall survival between patients treated with the novel receptor tyrosine kinase inhibitor, sunitinib (SU11248), and placebo.



Conclusions

Until 2001 the choice of therapy for GIST was severely restricted. The discovery that GIST expresses KIT and PDGF receptor tyrosine kinases led to the development and use of novel pharmacotherapeutic treatments. Imatinib, currently the only licensed therapy for the treatment of adult patients with KIT-positive unresectable and/or metastatic GISTs, has greatly improved patient prognosis and now a second generation of pharmacotherapeutics looks to promise hope for those who experience imatinib resistance. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Until recently, strategies for treating gastrointestinal stromal tumours (GIST), the most common mesenchymal malignancy of the gastrointestinal tract, were severely limited.
- The discovery that GIST expresses oncogene (KIT) and platelet-derived growth factor (PDGF) receptor tyrosine kinases has led to the development and use of novel pharmacotherapeutic treatments.
- Imatinib is currently the only licensed therapy for the treatment of adult patients with KIT-positive unresectable and/or metastatic GISTs.
- The emergence of imatinib resistance has led to a demand for second-generation GIST pharmacotherapies recommend to use targeted therapies instead.
- Sunitinib, a multitargeted KIT and PDGF receptor tyrosine kinase inhibitor, is the most promising of the forthcoming compounds. Mammalian target of rapamycin (mTOR) inhibitors may also prove to be of benefit.