Gastrointestinal stromal tumor (GIST)

H. Joensuu

Department of Oncology, Helsinki University Central Hospital, Finland

Gastrointestinal stromal tumors (GISTs) may be defined as morphologically spindle cell, epithelioid, or occasionally pleomorphic mesenchymal tumours of the gastrointestinal tract that usually express the KIT protein and harbour mutation of a gene that encodes for a type III receptor tyrosine kinase (either KIT or PDGFRA). In Caucasian populations their annual incidence is 10 to 15 cases per million. Approximately 80% of GISTs have mutated KIT and 5% mutated PDGFRA. Most KIT mutations occur in untreated GISTs in the juxtamembrane exon 11 and only rarely in the kinase domain, whereas in imatinib-treated patients secondary mutations are frequent in exons encoding for the ATP/imatinib binding pocket or the kinase activation loop. Surgery is the standard treatment of local GIST. Tyrosine kinase inhibitor imatinib is the standard treatment for metastatic disease with few exceptions. A majority (80–90%) of patients with metastatic disease respond to imatinib or achieve durable tumour growth stabilisation with continuous therapy using a daily dose of 400 mg to 600 mg. Treatment with imatinib increases survival of patients with advanced disease with a few years and is associated with only moderate toxicity. Imatinib is being evaluated as adjuvant treatment following surgery, and other tyrosine kinase inhibitors as treatments of advanced GIST.

historical aspects and definition of gastrointestinal stromal tumor (GIST)

Gastrointestinal stromal tumor (GIST) is a recently recognised tumour entity. In the past, these tumours were classified as leiomyomas, leiomyosarcomas and leiomyoblastomas, but it is now evident that GIST is a separate tumour entity and the most common sarcoma of the gastrointestinal tract.

The term GIST was first used in 1983 by Mazur and Clark to encompass gastrointestinal non-epithelial neoplasms that lacked the immunohistochemical features of Schwann cells and did not have the ultrastructural characteristics of smooth muscle cells [1]. GISTs continued to be rarely diagnosed until about the year 2000, when they became a focus of intense research. Hirota et al. [2] reported in 1998 that gain-of-function mutations in the KIT (c-kit) proto-oncogene are present in most GISTs. KIT gene encodes the KIT protein, which is the transmembrane receptor for the cytokine known as stem cell factor (SCF). The intracytoplasmic portion of KIT functions as a tyrosine kinase. GISTs were found to be generally resistant to cancer chemotherapy and associated with poor outcome, until in 2001 imatinib mesylate was found to be highly active against chemotherapy-resistant GIST [3]. Imatinib is a selective inhibitor of certain tyrosine kinases including KIT, platelet-derived growth factor receptors (PDGFRs), BCR-ABL, ABL, ARG and c-FMS. In 2003 activating mutations were detected also in PDGFRA in some GISTs [4]. PDGFRA encodes PDGFRα, which, like KIT, belongs to the family of type III receptor tyrosine kinases.

At present GISTs may be defined as morphologically spindle cell, epithelioid, or occasionally pleomorphic, mesenchymal tumours that usually arise from the gastrointestinal tract, usually express the KIT protein (~95% stain positively for KIT in immunohistochemistry) and that often harbour mutation of a gene that encodes for a type III receptor tyrosine kinase (either KIT or PDGFRA, up to 90% of the cases). The KIT protein is readily detectable by immunohistochemical assays, and the gene mutations can be detected by mutation analysis usually based on DNA sequencing. Other useful diagnostic features for GIST are negative immunostaining for desmin (>95%), and absence of lymph node and lung metastases (>95%, Table 1).

epidemiology

Epidemiology of GIST is incompletely known. Three studies that used up-to-date diagnostic criteria found the annual incidence of GIST to be 14.5 per million in south-west Sweden, 11 per million in Iceland, and 12.7 per million in the Netherlands [5–7]. Approximately 10% of cases were detected at autopsy in these series, and 20% at endoscopy, imaging of the abdomen, or at surgery for other conditions.

GISTs vary in malignancy potential ranging from small, incidentally detected tumours with excellent outcome to aggressive sarcomas. The proportion of overtly malignant or high-risk GISTs is 20–35% of all GISTs [5, 8] suggesting that the annual incidence of GISTs with a high malignancy potential is about 5 per million. It is likely that many small GISTs are not reported to cancer registries. A study based on the Surveillance, Epidemiology and End Results (SEER) registry data from the USA from 1992 to 2000 found the age-adjusted yearly incidence of GIST to be 6.8 per million [9].
GISTs might constitute approximately one sixth to one third of all soft tissue sarcomas, depending on whether there is an accounting for small and incidental GISTs. Many small, asymptomatic GISTs may remain undetected. In one study, two GISTs were found per 1000 autopsies performed [5], suggesting that asymptomatic GISTs of low malignancy potential may not be uncommon tumours in the elderly general population, and that these GISTs might be much more frequent than GISTs with a high malignancy potential. The frequency of reported GISTs may change with time because of evolving diagnostic criteria and the greater awareness of GIST [7].

Table 1. Useful differential diagnostic features of gastrointestinal stromal tumor (GIST)

<table>
<thead>
<tr>
<th>Feature category</th>
<th>Typical of GIST</th>
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<tbody>
<tr>
<td>Clinical presentation</td>
<td>Origin in the GI tract (&gt;95%)&lt;br&gt;Large GISTs often grow between the abdominal organs&lt;br&gt;Intra-abdominal implants and liver metastases frequent&lt;br&gt;Lung and lymph node metastases absent</td>
</tr>
<tr>
<td>Histopathology/immunohistochemistry</td>
<td>Spindle cell, epithelioid cell or mixed morphology&lt;br&gt;Immunostaining for KIT (CD117) positive (~95%)&lt;br&gt;Immunostaining for CD34 positive (~70%)&lt;br&gt;Immunostaining for PKC-θ positive (&gt;70%)&lt;br&gt;Immunostaining for desmin negative (&gt;5%)&lt;br&gt;Immunostaining for S-100 negative (~95%)</td>
</tr>
<tr>
<td>Gene mutation analysis</td>
<td>KIT mutation usually detectable (~75–85%)&lt;br&gt;PDGFRA mutation sometimes detectable (~5%)</td>
</tr>
<tr>
<td>Therapeutic features</td>
<td>Controlled with imatinib therapy (CR/PR/SD ~80–90%)&lt;br&gt;Responds rarely to conventional chemotherapy (~5%)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease.

**presenting symptoms and signs**

The median age at diagnosis is 66–69 years in population-based studies. These series include tumours detected incidentally or at autopsy, which are generally found at an older median age [5, 6]. In the SEER registry data the median age at the time of diagnosis was 63 years [9]. Only ~3% of GISTs are diagnosed before the age of 21 years [10], and GISTs arise only exceptionally in children. In the SEER series 55% of GISTs occurred in males [9] whereas an equal gender distribution was found in a population-based analysis from Sweden as well as in a large series from Korea [5, 11]. No predisposing factors have been described.

The most common symptom at presentation is bleeding [10]. Large GISTs often protrude from the site of origin and grow between the bowel loops and the abdominal organs, but they may also erode the gastrointestinal tract lumen. Bleeding may take place either into the abdominal cavity causing acute abdominal pain and severe anaemia and sometimes leading to emergency surgery, or into the gastrointestinal tract lumen causing haematemesis, melena and anaemia. Patients with GIST may also have various other symptoms, such as abdominal pain or discomfort, early satiety, bloating, obstructive jaundice, dysphagia, fever and anaemia-related symptoms such as fatigue and palpitations [10], or they may present with an abdominal tumour with no symptoms. Between 10% and 25% of patients present with metastatic disease [5, 9].

GISTs can originate anywhere in the GI tract. The stomach (40–60%) and small intestine (30–40%) are the most common locations. The colon, rectum, oesophagus, and rarely mesentery, retroperitoneum and other intra-abdominal organs are other sites of origin. In the SEER data, 51% of the cases arose from the stomach, 36% from the small intestine, 7% from the colon, 5% from the rectum, and 1% from the oesophagus [9]. Based on a multi-institutional survey from Korea, differences in clinical and histological features of GIST between Korean and Western populations appear to be minor [11].

GISTs frequently give rise to numerous intra-abdominal metastases located on the peritoneal, omental, mesenteric and other serosal surfaces, and to liver metastases, whereas extra-abdominal metastases are rare. In the late phases of advanced disease this results in a characteristic clinical presentation with a greatly enlarged abdomen coupled with muscle wasting. GISTs have a high tendency to seed. The intra-abdominal lesions probably result from tumour cell seeding into the abdominal cavity, whereas liver metastases probably from haematogenous spread. GIST patients may have metastases in surgical scars and sometimes even in needle tracts. Lymph node metastases are rare.

**histopathology**

GISTs range in size from a few millimetres to 35 cm, with a median size of between 5 cm and 8 cm [5, 6]. GISTs probably originate from the interstitial cells of Cajal or their precursors [12]. Cells of Cajal are the pacemaker cells of the GI tract controlling gut motility. GISTs are usually well circumscribed and surrounded by a pseudocapsule. Microscopically, GIST cell morphology is usually spindle-shaped (70%), but some GISTs consist of rounded cells (epithelioid type, 20%) or a mixture, but they can also be pleomorphic [13]. Large GISTs often show cystic degeneration or central necrosis.

Most (~95%) GISTs stain positively in immunostaining for the KIT protein (the CD117 antigen, an epitope of the KIT tyrosine kinase), exhibiting a diffuse, focal or mixed staining pattern [5, 8]. Detectable KIT expression, judged together with other immunohistochemical stainings and tumour morphology, is a very useful feature in distinguishing GISTs from other mesenchymal neoplasms that do not usually express KIT. Most (70%) GISTs express CD34, a sialylated transmembrane glycoprotein also found in haematopoietic progenitor cells and endothelial cells. An isoform of protein kinase C, PKC-θ, is highly expressed and constitutively phosphorylated in many GISTs [14–16], and PKC-θ may be useful for identifying KIT-expression-negative GISTs [16]. GISTs may stain positively for smooth muscle actin (SMA, 30–40%), but they are usually negative (~95%) in immunostaining for S-100 (a neural cell
marker) and for desmin (~98%, an intermediate filament protein typical of muscle).

**molecular biology**

Constitutively activating mutations of *KIT* are often present in GIST, and result in increased cell proliferation and enhanced cell survival. Mutations occur most commonly in the juxtamembrane exon 11 of the gene (in ~65% of all GISTs), whereas ~10% of GISTs have *KIT* exon 9 mutations and 2% exon 13 or exon 17 mutations [17]. Approximately 5% of GISTs have a constitutively activating mutation in *PDGFRA* [18].

*KIT* and *PDGFRA* mutations appear to be mutually exclusive; GISTs with a mutation in both of these genes do not exist or are very rare. Most (~80%) *PDGFRA* mutations are found in exon 18, and the rest either in exon 12 (10–15%) or 14 (1–5%, Table 2).

No *KIT* or *PDGFRA* mutation is present in 10–15% of GISTs. The molecular biology of the GISTs that are wild type with respect to *KIT* and *PDGFRA* is incompletely understood, but the *KIT* tyrosine kinase appears to be activated in many of these tumours despite lack of detectable *KIT* mutation. In one study, *KIT* mutations were found in 11 (85%) of 13 morphologically benign GISTs that were only 4–10 mm in diameter, suggesting that *KIT* mutations are present early in the development of most GISTs [19]. Transgenic mice generated by insertion of *KIT* genes containing exon 11 or 13 mutations and expressing activated forms of *KIT* develop diffuse hyperplasia of interstitial cells of Cajal and GISTs [20]. A few kindreds, i.e. genealogically related groups, presenting with GISTs and with a germline mutation in *KIT* or *PDGFRA* have been described.

Three rare subgroups of GISTs only rarely have *KIT* or *PDGFRA* mutations. Patients with neurofibromatosis have a higher risk of being diagnosed with GIST as compared with the general population [21]. The GISTs are often multiple, located in the bowel, and generally carry favourable prognosis. Neurofibromatosis-associated GISTs usually do not have *KIT* or *PDGFRA* mutations, but they sometimes have mutated *NF1*.

Carney’s triad is a rare syndrome of unknown cause that primarily affects young women, and consists of gastric, typically epitheloid type of GISTs, extra-adrenal paraganglioma, and pulmonary chondroma. GISTs of patients with the Carney’s triad do not harbour *KIT* or *PDGFRA* mutations.

The third group is the rare paediatric GISTs. They occur often in girls, are located in the stomach, have the epitheloid type tissue morphology, lack or have unusual *KIT* and *PDGFRA* gene mutations, and often have a protracted clinical course.

**estimation of risk of recurrence and outcome**

Many GISTs have an uncertain malignancy potential. Estimation of the risk of recurrence will become important provided that adjuvant therapy becomes a standard praxis in the management.

The most commonly used scheme to assess the risk of recurrence is the consensus approach, which is based on the primary tumour diameter and the mitotic count (Table 3) [13].

Patients whose tumour has ruptured into the abdominal cavity either before surgery or at surgery have a very high risk of tumour recurrence. On the other hand small (<1 cm), incidentally found GISTs behave, almost invariably, in a benign fashion.

Tumours arising from the small bowel, colon, rectum or mesentery are generally associated with less favourable outcome than those arising from the stomach.

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**Table 2. Frequency and clinical significance of *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumor (GIST)**

<table>
<thead>
<tr>
<th>Mutation site</th>
<th>Approximate proportion of all GISTs</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>KIT</em> exon 9 (extracellular domain)</td>
<td>5–15%</td>
<td>Many tumours originate from the intestine. Many respond to imatinib, but primary resistance more common than with <em>KIT</em> exon 11 mutants. Patients may benefit from a high (800 mg) imatinib dose; many respond to sunitinib as second-line therapy.</td>
</tr>
<tr>
<td><em>KIT</em> exon 11 (juxtamembrane domain)</td>
<td>60–70%</td>
<td>Frequency not related to tumour site of origin. Most responsive to imatinib; durable responses frequent.</td>
</tr>
<tr>
<td><em>KIT</em> exon 13 (tyrosine kinase domain 1)</td>
<td>~1%</td>
<td>Clinical responses to imatinib observed.</td>
</tr>
<tr>
<td><em>KIT</em> exon 17 (tyrosine kinase domain 2)</td>
<td>~1%</td>
<td>Clinical responses to imatinib observed.</td>
</tr>
<tr>
<td><em>PDGFRA</em> exon 12 (juxtamembrane domain)</td>
<td>~1%</td>
<td>Rarely originate from the intestine. Clinical responses to imatinib observed.</td>
</tr>
<tr>
<td><em>PDGFRA</em> exon 14 (tyrosine kinase domain 1)</td>
<td>rare, &lt;1%</td>
<td>Unknown, only few tumours described in the literature.</td>
</tr>
<tr>
<td><em>PDGFRA</em> exon 18 (tyrosine kinase domain 2)</td>
<td>~5%</td>
<td>Most originate from the stomach. D842V not sensitive to imatinib; other mutation types may be sensitive.</td>
</tr>
<tr>
<td>Wild type</td>
<td>10–15%</td>
<td>Primary resistance to imatinib more common than with <em>KIT</em> exon 11 mutants; ~40% respond to imatinib.</td>
</tr>
<tr>
<td>Paediatric GISTs</td>
<td>~3%</td>
<td>Special clinical features. <em>KIT</em> and <em>PDGFRA</em> mutations usually not present.</td>
</tr>
<tr>
<td>Carney triad</td>
<td>rare, &lt;1%</td>
<td>Gastric epitheloid-type GISTs, paraganglioma, pulmonary chondroma. <em>KIT</em> and <em>PDGFRA</em> mutations have not been reported.</td>
</tr>
<tr>
<td>NF-1-related GISTs</td>
<td>~1%</td>
<td>Multiple low-grade GISTs often present; frequently arise from the intestine. <em>KIT</em> and <em>PDGFRA</em> mutations rare. <em>NF1</em> mutation may be present.</td>
</tr>
</tbody>
</table>
Tumour Ki-67 antigen expression in immunohistochemistry may be comparable or superior to the mitotic count in prognostication.

Other factors suggested to be associated with an adverse outcome include presence of tumour necrosis, high cellularity and marked pleomorphism, a high S-phase fraction, DNA aneuploidy, presence of telomerase activity, and presence of KIT exon 11 deletion mutation. KIT immunoreactivity or staining pattern and CD34 expression do not appear to be independent prognostic factors for survival.

According to the SEER data, the relative 5-year survival rate for GIST patients diagnosed in the USA from 1992 to 2000 was 45% [9]. The 5-year survival rate ranges from 50% to 65% after complete resection of localised primary tumour [22], but 40–90% of surgical patients have a postoperative recurrence or metastasis. The median survival time of patients with metastatic or locally recurrent GIST was 10–20 months before the imatinib era [22], although a small proportion of patients with intra-abdominal metastases survived up to 20 years [10].

### management of local disease

Surgery is the standard treatment for non-metastatic GISTs. The tumour should be removed en-bloc with its pseudocapsule to yield an adequate resection margin. The optimal width of the tumour-free margin has not been defined. Regional lymph node resection is of unproven value, since GISTs rarely give rise to lymph node metastases. Extensive lymphadenectomy is not recommended. Tumour rupture is associated with an increased risk for development of peritoneal implants.

En-bloc resection is recommended whenever feasible in cases where contiguous organs are involved. The associated morbidity may be substantial when this requires total gastrectomy, pancreaticoduodenectomy or an abdominopereineal resection. In such patients preoperative treatment with imatinib may be considered, although at present there are no studies to support this practice. Two clinical trials are currently underway to address the safety and efficacy of preoperative imatinib. A diagnostic coarse needle biopsy performed through the abdominal wall may increase the risk of tumour cell seeding into the abdominal cavity, which can often be avoided when a needle biopsy is taken at endoscopy.

### management of recurrent and metastatic GIST

Imatinib is considered as the standard treatment of metastatic GIST. Approximately 65–70% of patients achieve a partial response, and another 15–20% have stable disease [23–25]. The median time to response is 12–15 weeks, but many patients obtain subjective benefit within a few days after starting imatinib, and an 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan may cease to show uptake as quickly as within 24 h. On the other hand, some GISTs shrink slowly and it may take up to a year to achieve tumour

### Table 3. Assessment of the risk of recurrence in resectable gastrointestinal stromal tumor

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Size</th>
<th>Mitotic count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&lt;5 cm</td>
<td>6–10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>5–10 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;10 cm</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>any size</td>
<td>&gt;10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt;5 cm</td>
<td>&gt;5/50 HPF</td>
</tr>
</tbody>
</table>

*Adapted from Fletcher et al., 2002 [13]. HPF, high power field.

### Table 4. Key principles in the management of gastrointestinal stromal tumor (GIST)

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local disease (one tumour)</td>
<td>Complete surgical removal of the tumour with tumour-free (usually a few centimetre) margins. Avoid tumour rupture. Adjuvant and neoadjuvant treatment with imatinib are being investigated in clinical trials and are considered experimental at present. Neoadjuvant imatinib may be considered for selected patients to achieve organ preservation. Adjuvant imatinib is recommended in case of tumour rupture. Adjuvant radiation therapy or conventional chemotherapy have no proven value.</td>
</tr>
<tr>
<td>Recurrent/metastatic disease;</td>
<td>Imatinib daily until treatment failure; the starting dose is usually 400–600 mg/day. Monitor blood cell counts, blood chemistry and treatment response (e.g. CT of the abdomen 1 month after starting imatinib, then at about 3-month intervals). Surgical resection of residual tumours of responding patients may be considered in selected cases, but the benefit is unproven. Removal of bleeding, infected or obstructing metastases may be necessary.</td>
</tr>
<tr>
<td>first line therapy</td>
<td></td>
</tr>
<tr>
<td>GIST progresses during</td>
<td>(i) Escalate imatinib dose up to 800 mg/day if feasible. Consider surgery for solitary growing metastases. (ii) Sunitinib considered for second-line therapy (especially when KIT exon 9 mutation is present). (iii) Consider participation in a clinical trial with novel agents. (iv) Many patients may benefit from imatinib despite of GIST progression during imatinib therapy. Consider palliative surgery or radiation therapy in selected cases.</td>
</tr>
<tr>
<td>imatinib therapy</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography scan.
GIST liver metastases often respond turning into hypodense, cyst-appearing lesions on CT-scan that contain mostly hyaline degeneration and a few KIT-positive tumour cells in a tissue biopsy [3]. The median response duration exceeds 2 years. The longest ongoing responses have exceeded 5 years at the time of writing. Patients who achieve a partial response (PR) and those with stable disease have roughly similar survival, whereas patients who show primary resistance to imatinib generally have poor outcome. The median survival time of patients diagnosed with metastatic GIST and treated primarily with imatinib is not yet known; in the USA–Finland randomised phase II study it was 4.8 years and had not yet been reached in the subgroup of patients with GIST with KIT exon 11 mutation [25].

KIT and PDGFRA mutational status predicts for the likelihood of achieving response to imatinib. Patients with an exon 11 KIT mutation have a PR rate up to 85–90%, while those with an exon 9 KIT mutation have a PR rate of ~50%. Patients who have GIST with KIT exon 11 mutation also have longer median time to treatment failure as compared to those with GIST harbouring other types of mutations. Patients who have no detectable mutation of KIT or PDGFRA respond less frequently to imatinib than those with exon 11 mutants [26], but, still, up to 39% do respond [27]. The rare patients who have GIST with KIT exon 13 or 17 mutation of PDGFRA mutation may also respond to imatinib.

Taken together, these results suggest that treatment with imatinib should be considered for virtually all patients who present with metastatic GIST regardless of the mutational status of the tumour. The rare patients who have GIST with a mutation known to be resistant to imatinib, such as the PDGFRA exon 18 mutation D842V, may be the only exception to this rule.

A 400–600 mg daily dose of imatinib is considered as the standard starting dose. Two large randomised trials compared 400 mg administered twice daily (800 mg/day) to 400 mg given once daily [28, 29]. In these trials the 800 mg dose was associated with a longer time to disease progression, but in neither study was the higher dose associated with a superior response rate or improved overall survival (the design included an option for cross-over from the lower dose arm to the higher dose arm at disease progression). The higher dose was associated with greater toxicity. One randomised trial (BFR14) addressed whether imatinib therapy can be discontinued in responding patients after 12 months of treatment, but discontinuation was associated with disease progression in 66% of the patients as compared with 15% of those allocated to continue with imatinib [30]. This suggests that treatment discontinuation is best avoided, although there was no difference in overall survival between the groups at the time of reporting. Imatinib blood concentrations may become smaller in a proportion of patients with prolonged administration [31]. Imatinib dose escalation beyond the 400 mg daily dose might thus benefit some patients with stable or responding disease, but this hypothesis remains unproven. At present, continuous administration of imatinib is recommended in the treatment of advanced disease with no upper limit for treatment duration.

Adverse effects of imatinib therapy are usually mild to moderate. The most common adverse effects are oedema (usually periorbital), occasional muscle cramps in fingers and feet, diarrhoea, nausea/vomiting, fatigue and rash. Anaemia (usually macrocytic), neutropenia and elevation in liver transaminase levels are also common. Imatinib therapy requires close surveillance, especially at the beginning of the treatment, in elderly patients and those with concomitant medications. Response monitoring is carried out using computer tomography (CT) or sometimes with magnetic resonance imaging (MRI). Metabolic imaging with FDG-PET occasionally helps in clinical decision-making, but access to PET is not required for safe administration of imatinib.

There is suggestive evidence that metastasectomy may improve survival in selected patients, and removal of infected, obstructing or bleeding metastases may be mandatory. It is not known whether surgical resection should be performed to remove residual masses that remain following imatinib therapy. This might be an option for patients with low-volume metastatic disease, and the best timing for such surgery may be while the tumours are responding to imatinib.

**Imatinib-resistant GIST**

A majority of patients with metastatic disease ultimately cease to respond to imatinib. The reasons for failure include secondary mutations at the ATP/imatinib binding pocket (exon 13 or exon 14) or in the activation loop (exon 17) of the KIT kinase that prohibit imatinib binding, but may also involve activation of other kinases and signalling routes, target gene amplification, increased imatinib metabolism or development of drug resistance.

Resistant lesions can occasionally be detected early by imaging. Such tumours may show a characteristic ‘node within a lesion’ pattern, where a dense growing nodule appears within a liver lesion that has turned hypodense and more homogenous during imatinib therapy. Such nodules often harbour a secondary KIT mutation. When other metastatic lesions continue to respond, surgical resection of the growing lesion should be performed. Radiofrequency ablation may be attempted when surgery is not feasible.

Imatinib dose escalation up to 800 mg/day is recommended whenever feasible in patients who progress on a lower dose of imatinib. Approximately 5% of patients who progress on the standard dose of imatinib achieve a PR after imatinib dose escalation, and another 30% have stabilisation of the disease [29, 32].

Patients who progress despite imatinib dose escalation are candidates for a trial with other tyrosine kinase inhibitors. Sunitinib (SU11248) is an inhibitor of KIT, PDGFRα, fms-like tyrosine kinase-3 and vascular epidermal growth factor receptor-2 (VEGFR2), and has been approved by the Food and Drug Administration (FDA) for the treatment of GIST patients whose disease has progressed on imatinib or who are unable to tolerate treatment with imatinib. In a randomised trial the median time to tumour progression was 6.3 months for patients treated with sunitinib compared to 1.5 months for those given placebo among patients who had failed imatinib therapy.
Adverse effects include diarrhea, hair and skin discoloration, high blood pressure, bleeding and fatigue.

Other tyrosine kinase inhibitors that inhibit KIT, PDGFs and VEGFs and that are currently being studied include vatalanib (PTK787/ZK222584), PKC412 (also inhibits PKC), AMG706 (also inhibits ret), and sorafenib (BAY43-9006, also inhibits RAF). Other compounds such as dasatinib (a dual Src and Abl inhibitor), AMN107 (inhibitor of KIT, PDGFRa and BCR-ABL), SDX-102 (an adenosine monophosphate synthesis inhibitor) and RAD001 (an mTOR inhibitor) may also turn out to have efficacy in the treatment of GIST. Some of these compounds have already shown clinical activity for imatinib-resistant GIST.

palliative treatment of tyrosine kinase inhibitor-resistant advanced GIST

Continuation of imatinib despite disease progression may be beneficial when imatinib sensitive and resistant clones co-exist in the same patient, and in such cases imatinib therapy may be continued for as long as there is evidence of continued benefit. Stopping imatinib before initiation of alternative therapy often results in tumour flare and increased clinical symptoms. Patients treated with imatinib show gradually increasing serum SCF levels over time, which may in part explain the tumour flare [34].

As other sarcomas, GISTs may be moderately sensitive to radiation therapy; selected patients may benefit from palliative irradiation of symptomatic metastases. Surgical removal of obstructing, bleeding or painful metastases may also be worthwhile. Only few (<5%) patients respond to conventional cancer chemotherapy and the response duration is generally short.

adjuvant therapy

Although administration of adjuvant imatinib appears attractive following removal of GIST with a risk for recurrence, this is of unproven value and considered experimental at present. Three ongoing randomised trials address the safety and efficacy of imatinib administered 400 mg once daily in the adjuvant setting. The ACOSOG Z9001 trial compares 12 months of imatinib versus 12 months of placebo following macroscopically complete surgery of a GIST 3 cm or larger in diameter. The EORTC adjuvant study allocates patients with an intermediate- or high-risk or recurrence between 24 months of imatinib or to observation. The Scandinavian Sarcoma Group/AIO study randomises patients with a high risk or very high risk or recurrence (defined as tumour rupture or limited metastatic disease completely removed at surgery) to receive imatinib either for 12 months or for 36 months.

Patients who have tumour rupture into the abdominal cavity and those rendered free from metastatic disease by surgery face a very high risk of tumour recurrence, and should probably be considered as candidates for imatinib therapy, although this praxis has not been evaluated in clinical trials and the optimal duration of administration is unknown. Adjuvant radiation therapy and adjuvant conventional chemotherapy have no proven therapeutic value, and are not recommended.

references


