Imatinib treatment for gastrointestinal stromal tumour (GIST)

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Received: October 1, 2009; Accepted: November 20, 2009

Abstract

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. GISTs are believed to originate from interstitial cells of Cajal (the pacemaker cells of the gastrointestinal tract) or related stem cells, and are characterized by KIT or platelet-derived growth factor receptor alpha (PDGFRA) activating mutations. The use of imatinib has revolutionized the management of GIST and altered its natural history, substantially improving survival time and delaying disease progression in many patients. The success of imatinib in controlling advanced GIST led to interest in the neoadjuvant and adjuvant use of the drug. The neoadjuvant (preoperative) use of imatinib is recommended to facilitate resection and avoid mutilating surgery by decreasing tumour size, and adjuvant therapy is indicated for patients at high risk of recurrence. The molecular characterization (genotyping) of GISTs has become an essential part of the routine management of the disease as KIT and PDGFRA mutation status predicts the likelihood of achieving response to imatinib. However, the vast majority of patients who initially responded to imatinib will develop tumour progression (secondary resistance). Secondary resistance is often related to secondary KIT or PDGFRA mutations that interfere with drug binding. Multiple novel tyrosine kinase inhibitors may be potentially useful for the treatment of imatinib-resistant GISTs as they interfere with KIT and PDGFRA receptors or with the downstream-signalling proteins.

Keywords: gastrointestinal stromal tumour • GIST • imatinib • KIT • mutation • PDGFRA • sunitinib

Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract, comprising the majority of tumours previously diagnosed as leiomyomas, leiomyoblastomas, leiomyosarcomas, neurofibromas and schwannomas. GISTs are believed to originate from interstitial cells of Cajal (the pacemaker cells of the gastrointestinal tract) or related stem cells, and are characterized by KIT or platelet-derived growth factor receptor alpha (PDGFRA) activating mutations [1–6].

Recent population-based studies in Europe revealed annual incidences of 10–20 per million, and the prevalence was estimated at 129 per million [7–9]. About 4500–6000 new cases of GIST are diagnosed each year in the USA [10].

GISTs have an equal sex predilection, and most tumours occur in individuals over the age of 50. GISTs are very rare in children (<1%) [1, 2, 11, 12].

GIST occurs throughout the gastrointestinal tract. The most common sites are the stomach (50%) and small bowel (25%). Approximately 10% of GISTs arise in the colon and rectum and 5% within the oesophagus. About 10% of the cases occur outside of the gastrointestinal tract (extra-gastrointestinal GISTs), mainly in the mesentery, omentum, retroperitoneum and pelvis [1, 2, 13–20].

The most common clinical presentation of GIST is gastrointestinal bleeding. Acute abdomen due to tumour rupture, obstruction, appendicitis-like pain, early satiety, bloating or fatigue related to anaemia can occur. Smaller GISTs are often incidental findings during surgery, radiologic studies or endoscopic procedures. Aggressive tumours generally metastasize to the liver or disseminate throughout the abdomen, and they rarely metastasize to lymph nodes or spread outside of the abdominal cavity [1, 2, 13].
GISTs range in size from less than 10 mm (GIST tumorlets) to very large lesions (>350 mm), and the median size is approximately 50 mm. Small GISTs often form solid subserosal, intramural or polypoid intraluminal masses. Larger GISTs form external, pedunculated masses attached to outer aspect of gastrointestinal structures. They are usually uninnodal but multiple nodules may occur. Cystic degeneration, haemorrhage or necrosis can be found, generally in larger tumours [1, 2].

GISTs are usually cytologically monomorphic and exhibit spindle cell or epithelioid cell cytomorphology, as well as a mixed pattern consisting of both spindle and epithelioid cells [10]. Epithelioid and mixed spindle and epithelioid GISTs are more common in the stomach [16]. Spindle cell GISTs are generally arranged in fascicles, and epithelioid tumours are often arranged in nests or sheets. The stroma can be hyalinized or myxoid. Histological features that can be seen in GISTs are parancular vacuoles, nuclear palisading mimicking schwannoma, neuroendocrine-like morphology mimicking paranglioma or carcinoid tumour, and ‘skeinoid’ fibres, hyaline eosinophilic cytoplasmic structures that are found predominantly in small bowel GISTs [1, 2, 13].

Approximately 96% of GISTs are positive for KIT (CD117) by immunohistochemistry. CD34 can be expressed by 60–70% of the tumours, and smooth muscle actin (SMA) expression is detected in 30–40% of the cases. S100 protein, keratins and desmin are rarely expressed in GISTs (up to 5%) [1–3, 10, 13, 21–23]. Recently, gene expression profiling studies found that the DOG1 (‘Discovered On GIST-1’) protein was ubiquitously expressed in GISTs, regardless of mutation status [24]. Subsequently, several studies found that DOG1 is a sensitive immunohistochemical marker for GIST, being rarely expressed in other mesenchymal tumours [25–27].

The main differential diagnosis of GIST includes smooth muscle tumours (leiomyoma and leiomyosarcoma), nerve sheath tumours (schwannoma and neurofibroma), inflammatory fibroid polyp and desmoid fibromatosis. These tumours are almost invariably negative for KIT (CD117) by immunohistochemistry. Moreover, smooth muscle tumours and nerve sheath tumours are diffusely positive for desmin and S100 protein, respectively. Inflammatory fibroid polyp can be positive for CD34, but there is no expression of KIT. Desmoid fibromatosis generally expresses fl-catenin in the nuclei of the spindle cells. It is important to state that KIT (CD117) is not expressed by GIST only. Other tumours that are consistently KIT-positive are mastocytoma, seminoma and granulocytic sarcoma. Melanoma, Ewing sarcoma family of tumours, angiosarcoma and some carcinomas can also express KIT [1, 2, 28, 29].

It is generally agreed that the most important prognostic factors in GIST are size of the tumour and mitotic count, which defines the risk of aggressive behaviour. The most commonly used scheme to assess this risk is the National Institutes of Health (NIH) consensus approach [10]. However, it is known that tumours arising in the intestines are generally associated with less favourable outcome than those arising in the stomach with similar size and mitotic index parameters (see Table 1) [15, 30].

Patients whose tumour has ruptured into the abdominal cavity have a high risk of tumour recurrence [31].

Surgery is the standard treatment for all non-metastatic GISTs. Regional lymph node resection is of no value as GISTs rarely give rise to lymph node metastases. The tumour should be removed en bloc with its pseudocapsule to yield an adequate resection margin. Imatinib, a tyrosine kinase inhibitor of KIT and PDGFRA receptors, is considered as the standard treatment for metastatic and/or unresectable GIST. The neoadjuvant use of imatinib is recommended to avoid mutilating surgery and/or yield complete resection of the tumour. Adjuvant treatment with imatinib may benefit patients presenting high risk of recurrence of the tumour after surgery [32–36]. Sunitib, a multiple tyrosine kinase inhibitor, may be useful for the treatment of GIST after disease progression under imatinib therapy or intolerance to imatinib [37].

Molecular pathogenesis of GIST

KIT and PDGFRA genes, located pericentromerically at 4q11-q12, encode for similarly named highly homologous receptor tyrosine kinase proteins (KIT and PDGFRA) [38]. KIT and PDGFRA have structural characteristics of type III receptor tyrosine kinase family [39]. Activating mutations of KIT and PDGFRA genes permit ligand-independent phosphorylation of the receptor tyrosine kinases, perpetuating the receptor-initiated signal and causing activation of the downstream effectors (Fig. 1). Increase in cellular proliferation and decrease in apoptosis are the end results of such activation, ultimately leading to enhanced cell survival and the development of neoplasia. Mutually exclusive mutations in KIT or PDGFRA are observed in more than 80% of GISTs (see Table 2) [4, 40, 41].

KIT contains a total of 21 exons, but mutations can be mainly detected in four exons: 9, 11, 13 and 17. Exon 9 encodes the extracellular transmembrane domain of KIT receptor. Exon 11 encodes the intracellular juxtamembrane domain. Exons 13 and 17 encode the tyrosine kinase domain: the first portion of the split kinase domain in encoded by exon 13, while exon 17 encodes the kinase activation loop (second tyrosine kinase domain) [4, 42, 43]. KIT exon 11 mutations are the most common (60–70% of GISTs), mainly in-frame deletions of variable sizes, but substitutions (point mutations), duplications and insertions may occur. Exon 9 mutations are the second most common and are detected in 10% of GISTs, most of them located in the small bowel. Exon 9 mutations represent mainly in-frame tandem duplication (Ala502_Tyr503dup). Substitutions have been reported in KIT exons 13 and 17, but primary mutations in those exons are rare (up to 2% of GISTs) [1, 2, 4, 5, 41, 43–48].

Approximately 5–10% of GISTs have PDGFRA mutations instead of KIT mutations. The mutations that are found in PDGFRA involve exon 18 (second tyrosine kinase domain), exon 12 (juxtamembrane domain) and exon 14 (first tyrosine kinase domain). Exon 18 mutations are the most common (up to 6% of GISTs),
while exon 12 and exon 14 mutations are rarely found (< 2% of GISTs). Single nucleotide substitutions are the most common PDGFRA mutations in GIST. In exon 18, the most common mutation is a single nucleotide substitution known as Asp842Val (D842V). In-frame deletions have also been detected in exon 18. PDGFRA exons 12 and 14 mutations involve substitutions, insertions and deletions [1, 2, 6, 48–50]. PDGFRA mutations show a strong predilection for the stomach, epithelioid morphology, myxoid stroma, nuclear pleomorphism and variable (occasionally absent) expression of KIT (CD117) [1, 2, 6, 13, 22, 51–55].

No KIT or PDGFRA mutation is detected in 10–15% of GISTs (wild-type GISTs). Notably, wild-type genotype is a characteristic feature of the vast majority of GISTs diagnosed in children and adolescents and GISTs associated with familial syndromes such as neurofibromatosis, Carney–Stratakis syndrome or the Carney triad [41]. The molecular biology that drives the growth of wild-type GISTs is incompletely understood, but the KIT tyrosine kinase appears to be activated (phosphorylated KIT) in many of these tumours despite lack of detectable KIT mutation. An activating mutation either in a receptor tyrosine kinase that is analogous to KIT/PDGFRA receptor tyrosine kinases independent of ligand SCF (stem cell factor), perpetuating the receptor-initiated signal and causing activation of the downstream effectors. The result is enhanced cell survival.

Table 1 Assessment of risk of aggressive behaviour in GIST by mitotic index, size and tumour location

| Morphologic parameters | % of patients with progressive disease |
|------------------------|---------------------------------------|
| Size (cm) | Stomach | Jejunum/ileum | Duodenum | Rectum |
| ≤2 | ≤5/50 HPFs | 0 | 0 | 0 | 0 |
| >2 and ≤5 | ≤5/50 HPFs | 1.9 | 4.3 | 8.3 | 8.5 |
| >5 and ≤10 | ≤5/50 HPFs | 3.6 | 24 | 34 | 57 |
| >10 | ≤5/50 HPFs | 12 | 52 | – | 54 |
| ≤2 | >5/50HPFs | 0 | 50 | – | – |
| >2 and ≤5 | >5/50HPFs | 16 | 73 | 50 | 52 |
| >5 and ≤10 | >5/50HPFs | 55 | 85 | 86 | 71 |
| >10 | >5/50HPFs | 86 | 90 | – | – |

Table 2 Molecular classification of GIST

| Genotype | Frequency | Tumour location |
|----------|-----------|-----------------|
| KIT mutation | 70–80% | Small bowel, colon |
| Exon 9 | 10% | All sites |
| Exon 11 | 60–70% | All sites |
| Exon 13 | 1% | All sites |
| Exon 17 | 1% | All sites |
| PDGFRA mutation | 5–10% | Stomach |
| Exon 12 | 1% | All sites |
| Exon 14 | <1% | Stomach |
| Exon 18 D842V | 5% | Stomach, mesentery, omentum |
| Exon 18 (other than D842V) | 1% | All sites |
| Wild-type | 10–15% | All sites |

Modified from Miettinen and Lasota, 2006 [30].

HPFs, high-power fields.

* >5 and ≤10 cm and >10 cm groups are combined because of small number of cases.

Fig. 1 Schematic representation of molecular pathogenesis of GIST. Activating mutations of KIT and PDGFRA genes permit phosphorylation of KIT/PDGFRA receptor tyrosine kinases independent of ligand SCF (stem cell factor), perpetuating the receptor-initiated signal and causing activation of the downstream effectors. The result is enhanced cell survival.
KIT and PDGFRA or in a downstream signalling molecule of the KIT/PDGFRA signalling cascade could be involved. Recently, a primary BRAF V600E mutation was detected in 7% of adult GIST patients lacking KIT/PDGFRA mutations. The BRAF-mutated GISTs showed predilection for small bowel location and high risk of malignancy [1, 56, 57].

**Imatinib and implications of mutation status for the treatment of GIST**

The use of imatinib has revolutionized the management of unresectable and metastatic GISTs and altered its natural history, substantially improving survival time and delaying disease progression in many patients [58, 59].

Imatinib (STI571) was the first targeted therapy approved for the treatment of GIST, and it has become the treatment of choice for advanced GIST. Imatinib is an orally available tyrosine kinase inhibitor of KIT and PDGFRA receptors first developed as a treatment for chronic myeloid leukemia by inhibiting the intracellular kinases ABL and BCR-ABL fusion protein [60–63]. Imatinib blocks the transfer of phosphate groups from adenosine triphosphate to tyrosine residues of the substrates. This results in interruption of the downstream signalling cascade that regulates cell proliferation (Fig. 2) [63].

Imatinib is considered as the standard treatment of metastatic GIST. A partial response is observed in approximately 65–70% of the patients, and 15–20% have stable disease. Only 5% or less achieve a complete response. The median response duration exceeds 2 years [59, 64]. The standard starting dose of imatinib is 400–600 mg daily, even though 600 mg proved not to be superior to 400 mg [59], and continuous administration of imatinib is recommended in the treatment of advanced disease with no upper limit for treatment duration as discontinuation of treatment was associated with disease progression. Only tumour progression, intolerance or patient refusal should encourage interruption of treatment [65].

Response monitoring is carried out using computed tomography (CT), magnetic resonance imaging (MRI) and/or metabolic imaging with fluorodeoxyglucose-positron emission tomography (FDG-PET). GIST liver metastases generally turn into hypodense lesions with cystic degeneration on CT scans [66].

Adverse effects of imatinib therapy are usually mild to moderate. The most common are oedema (particularly periorbital), muscle cramps in fingers and feet, diarrhoea, nausea and vomiting, fatigue and rash. Haematological disturbances may occur, including anaemia and neutropenia. Elevation in liver transaminase levels is also common [32].

The success of imatinib in controlling advanced GIST led to interest in the neoadjuvant and adjuvant use of the drug. The neoadjuvant (preoperative) use of imatinib is recommended to facilitate resection and avoid mutilating surgery by decreasing tumour size. The use of neoadjuvant imatinib therapy was considered safe with encouraging outcomes [58, 67–73]. Adjuvant therapy is indicated for patients at high risk of recurrence. It was demonstrated that imatinib at 400 mg daily for 1 year following surgical resection prolongs recurrence-free survival and is associated with improved overall survival [58, 73–75].

Pathologists play an important role in the molecular characterization (genotyping) of GISTs. GIST genotyping has become an essential part of the routine management of the disease as KIT and PDGFRA mutation status predicts the likelihood of achieving response to imatinib. Clinical observations have shown that KIT exon 11 mutations are associated with better response to imatinib and longer progression-free survival than KIT exon 9 mutations and wild-type genotype. Thus, patients with GISTs presenting KIT exon 9 mutation require a higher dosage of imatinib (800 mg daily instead of the standard dose of 400 mg daily) in order to achieve similar therapeutic results. PDGFRA exon 18 Asp842Val (D842V) mutation is resistant to imatinib treatment. PDGFRA mutations other than Asp842Val (D842V) may be sensitive to imatinib [48–50, 76, 77].

In conclusion, routine tumour genotyping is recommended if tyrosine kinase inhibition therapy is considered for the treatment of GIST.

**Imatinib resistance in GIST**

A minority of patients (10–20%) experience tumour growth on imatinib within the first 6 months of treatment (primary resistance), and PDGFRA D842V and KIT exon 9 (under standard imatinib
dose therapy) mutations as well as wild-type genotype may explain primary resistance. However, the causes for such resistance remain largely unknown [58].

The vast majority of patients who responded to imatinib will develop tumour progression (secondary resistance). Secondary resistance (Fig. 3) often develops due to secondary KIT or PDGFRA mutations that interfere with drug binding. Most secondary KIT mutations represent single nucleotide substitutions affecting codons in exons 13, 14, 15, 16 and 17. Secondary PDGFRA mutations involve exon 18 (Asp842Val). Interestingly, GISTs with primary KIT mutations in exon 11 (tumours with better response rates than other genotypes) reveal secondary mutations more frequently in comparison to tumours with KIT exon 9 mutations, suggesting that the development of secondary KIT mutations is an important escape mechanism for tumour cells. Moreover, several different types of mutations may occur independently indicating polyclonal resistance [48, 78–84].

Another possible mechanism of imatinib resistance is KIT gene amplification [79], and other oncogenes and tumour suppressor genes may also be responsible for sustaining the tumourigenic potential in imatinib-resistant GISTs. Moreover, the constitutive activation of downstream-signalling proteins (kinase pathways) represents a distinct molecular mechanism of imatinib resistance, and the PI3-kinase/AKT may play an important role as an alternate survival pathway [81, 85].

Multi-targeted tyrosine kinase inhibitors for the treatment of GIST

Multiple novel tyrosine kinase inhibitors may be potentially useful for the treatment of imatinib-resistant GISTs as they interfere with KIT and PDGFRA receptors or with the downstream-signalling proteins [86].

Sunitinib (SU11248) was approved for the treatment of imatinib-resistant GIST or imatinib-intolerant patients. Sunitinib...
inhibits multiple receptor tyrosine kinases including KIT, PDGFRα, platelet-derived growth factor receptor beta (PDGFRβ), vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, FMS-related tyrosine kinase 3 receptor, receptor for macrophage colony-stimulating factor and glial cell line-derived neurotrophic factor receptor, presenting both antiangiogenic and antiproliferative activities. Sunitinib is indicated for patients whose disease progressed on imatinib (even after imatinib dose escalation up to 800 mg daily), and it presents better responses in wild-type genotype tumours and GISTs with KIT exon 9 mutation or secondary KIT mutations (exons 13 or 14). The drug is orally available, and the approved schedule is 50 mg per day for 4 weeks followed by a 2-week rest. The most common adverse effects include diarrhoea, mucositis, hair and skin discoloration, high blood pressure, bleeding and fatigue [33, 37, 87–92].

Other candidate tyrosine kinase inhibitors are being tested, including nilotinib, dasatinib, sorafenib, masitinib, vatalanib (PTK787/ZK222584) and motesanib (AMG 706) [36, 93–101].

The PKC inhibitor PKC412, the rapamycin target protein (mTOR in the AKT pathway) inhibitor everolimus and the heat shock protein 90 (HSP90) inhibitor IPI-504 may also turn out to have efficacy in the treatment of GIST [36, 79, 102].

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