Advances in the management of gastrointestinal stromal tumours

Authors S. Van Lierde, M. Peeters, N. Van Damme, K. Geboes, S. Laurent, I. Dero, P.Pauwels

Key words GIST tumours, imatinib, KIT mutations, PDGFRA mutations, resistance, sunitinib

Summary

Gastrointestinal stromal tumours (GIST) represent the most common mesenchymal malignancy of the gastrointestinal tract. Before 2001, treatment options for this neoplasm were very limited. In patients for whom curative surgery was not feasible, conventional cytotoxic chemo- and radiotherapy were mostly ineffective. An improved understanding of the pathophysiology of these tumours led to a significant breakthrough. The majority of GIST host activated mutations in KIT and PDGFRA, two related receptor tyrosine kinases. These findings led to the use of imatinib, a selective tyrosine kinase inhibitor. It is currently the standard first-line treatment for unresectable and/or metastatic GIST. Imatinib improves survival and delays disease progression. However, effectiveness can be limited by primary and secondary (acquired) resistance. Alternative targeted therapies such as sunitinib and nilotinib, multitarget tyrosine kinase inhibitors, were recently introduced and showed to be effective options in second-line treatment. Furthermore, identification of c-KIT and PDGFRA mutations is useful in predicting clinical response to therapy. Standard molecular classification of gastrointestinal stromal tumours is recommended for optimisation of treatment (for example appropriate dose selection) and clinical outcome.

(BJMO 2008;Vol 2;6:299-307)

Introduction

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract, accounting for 70% to 90% of these tumours. Nevertheless, they are relatively rare, representing only 2% of all neoplasms of the GI tract.

Over the past few years, GIST have been identified as a distinct clinical and histopathological entity. The immunohistochemical staining by the marker CD117 antigen (KIT) has resulted in a more accurate diagnosis of GIST.[1-3] Many GIST have historically been misdiagnosed as leiomyosarcoma or other spindle cell tumours.[1,2] The current histopathological definition of GIST led to an increase in the number of diagnosed tumours.[2] An estimation of the yearly new cases in the United States ranges between 5,000 and 6,000.[1] Both in Europe and the US, the reported incidence is in the range of 10-20 cases per million.[2-4]

Although GIST occur over a wide age distribution, a peak incidence is seen between 40 and 60 years of age. Some studies indicate a higher incidence among men, others show no predilection for either sex.[4]

Pathology of GIST

Gastrointestinal stromal tumour cells share several immunophenotypical and ultrastructural characteristics with interstitial cells of Cajal. These cells are located in the gut wall and act as gut pacemakers. They participate in a complex cellular communication network between the autonomic nervous system and smooth muscle and are thought to coordinate peristalsis throughout the GI tract.[2,4,5] These findings have led to the hypothesis that GIST share a common stem cell with the interstitial cells of Cajal.[4]

GIST have two major histological patterns. Between 60% and 70% have a spindle cell morphology, while

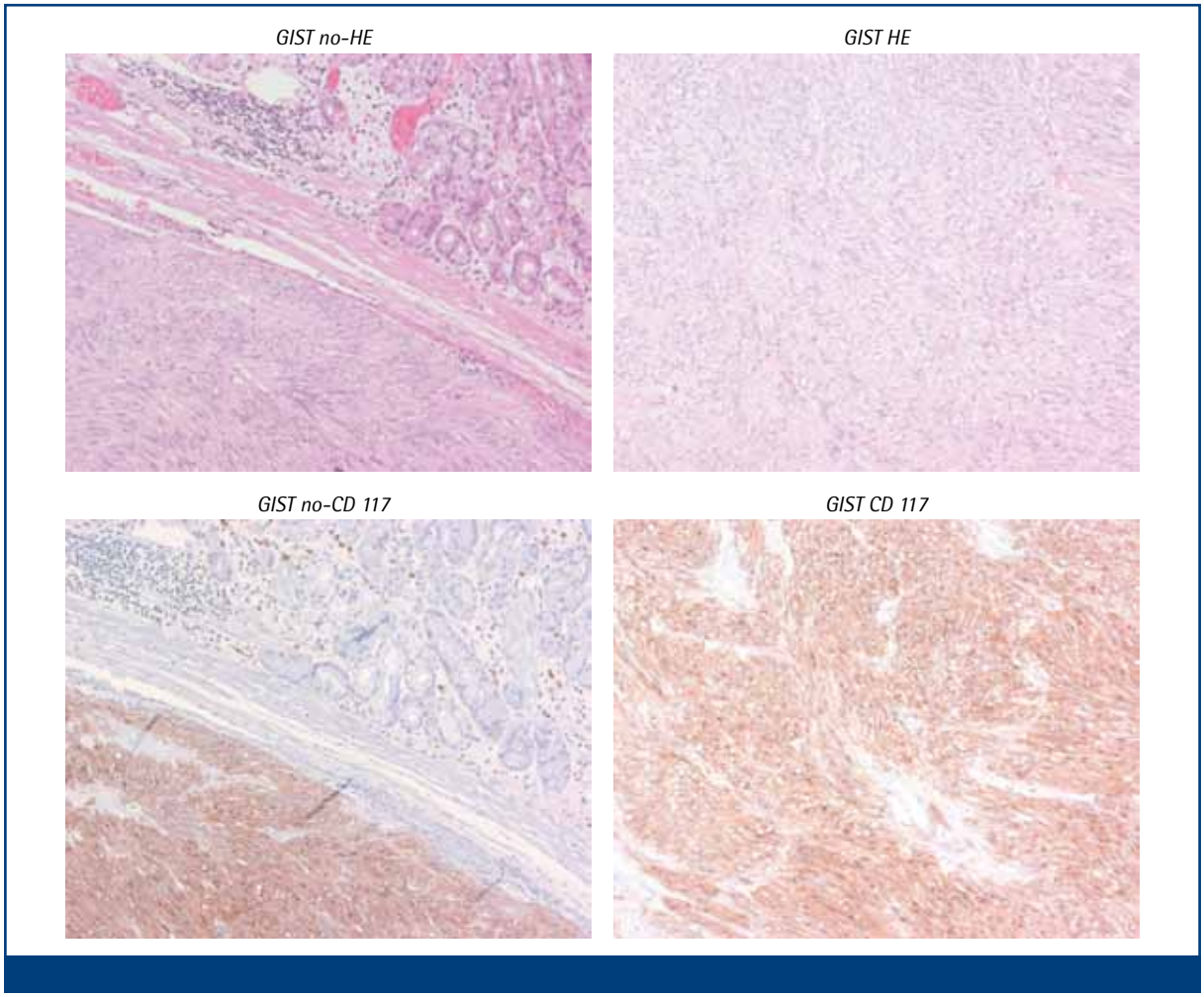

Figure 1. Different patterns of GIST immunohistochemistry.

20% to 30% have an epitheloid morphology. Less than 5% of GIST are pleomorphic.[1,4] Sometimes it is difficult to differentiate GIST from smooth muscle tumours. Advances in immunohistochemical staining and molecular profiling are often needed to come to a definite diagnosis.[4] Over 90% of reported cases of GIST express KIT (CD117) (*Figure 1*). KIT is a type III transmembrane receptor tyrosine kinase. It is the protein product of the KIT proto-oncogene and is the most specific and sensitive marker for GIST. This specificity however can be lost by applying antigen retrieval techniques. KIT plays a critical role in different cell functions. Relevant downstream pathways affected by KIT stimulation include proliferation and anti-apoptosis. However, a minority of GIST are KIT-negative. A small proportion of c-KIT-negative GIST are associated with mutations in a related tyrosine-kinase receptor, plateled-derived growth factor receptor alpha (PDGFRA). Downstream activation targets of KIT associated with tumour progression are also activated by mutant forms of PDGFRA in GIST. As a result, a subset of patients with KIT-negative GIST benefit from PDGFRA targeted therapy. Therefore, screening for KIT/PDGFRA mutations is helpful in confirming the diagnosis of GIST.[1,4,6,7] Some GIST express CD34 (mesenchymal/hematopoietic precursor cell marker; 60-70%), smooth muscle actin (30-40%), S-100 (5%), desmin (1-2%) and keratin (1-2%).

Prediction of prognosis of GIST has been studied intensively. Tumour size and mitotic activity (measured per 50 high-power fields, HPF) are the most useful morphological features in predicting malignant behaviour.[8] The risk stratification system originally proposed by *Fletcher and colleagues* indicates that high mitotic rates associated with large tumour size represent a high risk of tumour recurrence and metastatic spread.[1] Moreover, high mitotic rates with large tumour size are associated with a poor progno-

Table 1. Predicting the malignant potential of GIST.[1]		
Risk	Size	Mitotic Rate
High	Any size > 10 cm > 5 cm	> 10/50 HPF Any rate > 5/50 HPF
Intermediate	5-10 cm < 5 cm	< 5/50 HPF 6-10/50 HPF
Low	2-5 cm	< 5/50 HPF
Very low	< 2 cm	< 5/50 HPF
HPF: High-power fields.		

sis (*Table 1*). However, even tumours classified as low risk (small tumour size and low mitotic activity) can become metastatic. In addition to size and mitotic rate, also the site of origin has been identified as a prognostic factor. Several studies noted that patients with small bowel tumours have a poorer prognosis than patients with primary gastric tumours of similar size and mitotic activity.[9,10] Most oesophageal and colon GIST are highly malignant, whereas only 25% of gastric GIST show a malignant behaviour.[9,10] No GIST can truly be called benign an recurrences have been observed 30 years or more after the primary diagnosis.[1] There are no published data supporting specific policies for follow-up and routine follow-up schedules differ across institutions. A routine follow-up (clinical and/or with imaging) every 6 months for 3 years, and yearly afterwards can be proposed.

Clinical presentation

Many GIST are asymptomatic and are discovered at endoscopy or computed tomography (CT). GIST are associated with a multiform clinical course, which is largely dependent on the size and extent of the tumour on initial presentation.[11] Vague abdominal pain or discomfort are the most frequent symptoms (50-70%). Gastrointestinal haemorrhage occurs in 34% to 40% of the patients. A palpable tumour is a less frequent but ominous sign. A smaller percentage of patients presents with intestinal obstruction or with an intestinal perforation. However, many patients have non-specific symptoms such as anorexia, weight loss, nausea and anaemia related fatigue.[8,11,12]

GIST can develop anywhere along the GI tract. They are most commonly found in the stomach (60%), in the small bowel (25%) and colorectal (5%). Only 2% are discovered in the oesophagus. GIST located in the mesenterium, omentum, retroperitoneum or pelvis account for 8% of all cases.[9] Cases have also been described in the uterus and the prostate.

Up to 47% of patients with newly diagnosed GIST have metastatic disease at presentation. The metastatic pattern of aggressive GIST is predominantly intra-abdominal, with spread throughout the peritoneal cavity and to the liver. Surprisingly, these tumours rarely metastasise to lymph nodes. Metastases in the lungs and the bone are also very rare.

Diagnostic work-up

The possibility of a GIST is often suggested by contrast-enhanced CT or endoscopy. Unfortunately, standard biopsies mostly provide insufficient tissue for a definite diagnosis. Endoscopic ultrasound (EUS) is very accurate in locating lesions in the wall of the GI tract and distinguishing them from other submucosal lesions.[13] Fine needle aspiration by EUS for accessible lesions gives adequate material in the majority of cases.[14] The risk of tumour rupture and peritoneal spread precludes a percutaneous biopsy as a diagnostic option. Open biopsy is sometimes useful for lesions that are not accessible by endoscopy.[15] However, a preoperative biopsy is not always necessary, especially if the tumour is operable.

CT is widely available and is currently the imaging modality of choice for the diagnostic workup. CT can be used to characterize suspected GIST. It is especially important in evaluating the extent of the mass, detecting possible metastasis, and assessing the resectability of the tumour. A triphasic (arterial, venous, and portal phase) technique is preferred at baseline and for follow-up.[16,17] Magnetic resonance imaging (MRI) offers no diagnostic benefit compared to CT, but may be an alternative when there are contra-indications for an optimal CT scan. ^{18}F-fluoro-deoxyglucose Positron Emission Tomography (^{18}F-FDG-PET) can be used for metabolic imaging.[18,19] As GIST show high metabolic active they are easily detected with PET. However, this technique is not specific for GIST. As a result, PET is most useful to evaluate the extent of the disease and to screen for metastatic locations. In addition, ^{18}F-FDG-PET has been very effective in assessing response to therapy with imatinib.[18,19] It may be helpful to distinguish the difference between recurrent tumour and scar tissue, or to highlight early functional changes and response to treatment.[19]

Table 2. Mutation status and prognosis of GIST.[25-27]

Mutation site	Response	Prognosis
KIT exon 11	favorable response	PR 61.3%-83.5%
KIT exon 9	intermediate response	PR 29.3%-47.8%
Wild-type or PDGFRA D842V	low response	ORR 0%-25%

PR: partial response; ORR: overall response rate

Molecular pathogenesis

The KIT receptor tyrosine kinase has an essential role in normal biological functions such as hematopoiesis, melanogenesis, fertility and gametogenesis and gut motility. However, gain-of-function mutations in KIT result in a constitutive activation of the c-KIT receptor and can lead to the development of GIST.[21] Approximately 80% of the GIST have mutations in the KIT proto-oncogene, that lead to constitutive activation of c-KIT, a receptor tyrosine kinase. Most KIT mutations involve exon 11 (juxtamembrane domain) and result in spontaneous (ligand-independent) receptor dimerisation and receptor activation. Mutations can also be present in the extracellular domains of KIT (exons 8 and 9), and in the kinase I and II domains (exons 13 and 17).[12] Of the small percentage of GIST that are KIT-negative, a subset (approximately 35%) have mutations in PDGFRA.[20] Wild-type KIT and PDGFRA genes are present in approximately 12% of all GIST.

Familial gain-of-function KIT mutations have been shown to result in a high incidence of GIST.[22] Furthermore, in addition to sporadic occurrence, GIST - mostly in the small intestine - are increasingly being recognized in association with neurofibromatosis type 1. The underlying pathogenic mechanism remains elusive.[23] These tumours are generally KIT positive on immunohistochemistry but fail to demonstrate KIT mutations.[24].

KIT and PDGFRA mutations are common (85-90%) in GIST and are the best predictors of clinical response to imatinib (Gleevec®) therapy**.** Three prognostic groups are related to imatinib mesylate response (*Table 2*). The presence of KIT exon 11 mutations predicts a favourable response to imatinib treatment.[25-27] GIST with KIT exon 9 mutations show an intermediate level of response to imatinib therapy.[25] On the other hand, wild-type GIST and also stromal tumours with the presence of PDGFRA exon 18 mutation with the substitution D842V have been shown to have low sensitivity to therapy with imatinib.[25-27] Several studies described a higher risk of malignant behaviour for GIST with KIT exon 9 mutations compared with KIT exon 11 mutations.[12]

Management of localized GIST

The standard therapy for localized GIST remains surgical resection. The objective of surgery is the complete gross resection with preservation of an intact pseudocapsule.[28] In 86% of the patients, a complete tumour resection can be obtained. During surgery, the abdomen should be explored for metastases with special attention to the peritoneal surface and the liver.[28,29] Furthermore, as GIST generally displace rather than infiltrate surrounding organs, tumours often can be lifted off from surrounding organs during surgery. Due to the very high risk of intra-abdominal dissemination, it is important to avoid tumour rupture.[17,28] It is also important to obtain negative surgical resection margins. However, management of positive margins in GIST remains unclear. The question of repeated resection with wider margins of uninvolved tissue has not been addressed adequately in the literature. Extended lymphadenectomy is not necessary due to the low incidence of lymph node involvement.[17,28] The issue of clinical planning needs to be addressed by a multidisciplinary team.

In general, there is a high rate of recurrence and/or metastasis, even after complete surgical resection. The median time to recurrence ranges from 18 to 25 months. Only 10% of the patients remain disease-free after extended follow-up.[29,30] Before 2001, surgery was the only treatment option. Great improvements occurred with the recognition that approximately 90% of GIST have an oncogenic mutation of KIT or PDGFRA. Mutations occur early in the GIST development and are required for GIST cell growth and survival.[20,31] These findings led to the introduction of a specific inhibitor of KIT tyrosine kinase activity (imatinib).[32] Imatinib is a potent and selective protein-tyrosine kinase inhibitor that has shown effective targeting and competitive blocking of the activity of KIT, ABL, BCR-ABL, PDGFRα, PDGFRβ, ARG and possibly CSF1R in *in vitro* and *in vivo* studies. Inhibiting KIT activity blocks KIT-mediated downstream mitogenic signal transduction pathways.[33] Based on these observations, it was

hypothesized that the selective inhibition of KIT and PDGFRα receptor tyrosine kinases with imatinib would be effective in the treatment of GIST.[32] The success of imatinib in patients with advanced disease has encouraged physicians to evaluate the use of imatinib in an adjuvant and neo-adjuvant setting. Given the favourable efficacy and the low toxicity profile of imatinib, neo-adjuvant therapy may be effective in downsizing tumour size or in tumour shrinkage and treatment of low-volume microscopical disease.[30,34] The *American College of Surgeons Oncology Group (ACOSOG)* initiated 2 adjuvant trials (phase II for high-risk patients [Z9000], phase III for resected primary GIST [Z9001]).[35,36] The aim of the phase III, randomised, double-blind, placebo-controlled *ACOSOG Z9001 trial* was to compare imatinib 400 mg/d and placebo for one year after resection of primary GIST in high risk patients. The primary endpoint of the study was recurrence-free survival (RFS) and the secondary endpoint was overall survival (OS). Overall, at 1 year, 97% of patients in the imatinib arm had RFS compared with 83% of patients in the placebo arm ($p< 0.001$). Similarly, at 2 years, 90% of patients in the imatinib arm had RFS compared with 71% of patients in the placebo arm ($p< 0.001$).[36]

As a consequence of the positive results obtained in the interim analysis, the blinded phase of treatment was terminated. Following unblinding, all patients in the placebo arm were offered 1 year of imatinib.[36] Currently there are two ongoing randomised trials with imatinib in the adjuvant setting.[37,38] The *EORTC 62024 trial* investigates the impact of adjuvant therapy with imatinib during two years, with overall survival as primary endpoint. Furthermore, the goal of the *SSGXVIII trial* is to determine the appropriate adjuvant treatment duration of imatinib (1 year versus 3 years).[37,38]

Another subject of active investigation is the use of neoadjuvant imatinib for patients with non-metastatic but unresectable or borderline resectable tumours in order to try to downsize the primary tumour before surgery.[35] Neoadjuvant imatinib, with or without adjuvant imatinib, to reduce or eradicate micrometastases is also being assessed.[37]

Management of advanced GIST

Conventional cytotoxic chemo- and radiation therapy are ineffective in GIST. Before 2001, treatment options were very scarce for patients with unresectable and/or metastatic GIST and prognosis was infaust. Currently, the first-line treatment for patients with advanced disease is imatinib 400 mg/d. Studies have confirmed the use effectiveness of this agent in advanced GIST.[28] In 70-85% of the patients with advanced GIST, disease control can be achieved with imatinib. In large clinical trials, the estimated median OS with imatinib therapy exceeds 36 months. This is in contrast with a median survival of 19 months in the pre-imatinib era.[29,30] Recently, two randomised phase III trials (*US Intergroup S0033* and *EORTC 62005*) have compared the efficacy of imatinib 400 versus 800 mg daily in patients.[39,40] Primary endpoints were OS and progression free survival (PFS). In the EORTC trial, a modest but significant higher PFS was seen in the 800 mg dose-group.[40] This may be explained by a significant PFS advantage in patients with KIT exon 9 mutations treated with 800 mg. This was reported in a meta-analysis of combined data from studies *62005* and *S0033*. Although both treatments were relatively well tolerated, more patients in the 800 mg group required dose reductions and treatment interruptions. Up to 7% of treatment interruptions were due to hematological toxicity.[40] In both studies, no statistically significant 5-years OS benefit ($P= 0.97$) was detected in the high-dose versus standard-dose group.[41] These findings led to an updating of the NCCN guidelines to recommend that patients with KIT exon 9 mutations should be treated with imatinib 800 mg/day.[42] Other patients should receive the standard dose of 400 mg/day. At present, no reimbursement for high-dose imatinib is foreseen in Belgium.

Another important issue is how to monitor clinical response. Traditionally, response evaluation is based on CT imaging using the *RECIST criteria.* Today we know that these criteria are not applicable for the evaluation of response of GIST treated with imatinib. Therapeutic response is not correlated with imaging response. Indeed, in GIST tumour shrinkage may evolve slowly. After therapy, tumour size can even remain stable because of the replacement of tumour by fibrotic tissue or even show an increase due to intratumoural edema or haemorrhage.[43,44] Furthermore, GIST can exhibit focal progression even if the majority of the tumour is responding. New response evaluation criteria using CT, the so-called *Choi criteria*, have been proposed as an alternative.[45] These criteria showed that a 10% decrease in unidimensional tumour size or 15% decrease in tumour density correlates better with PET scan findings. As already

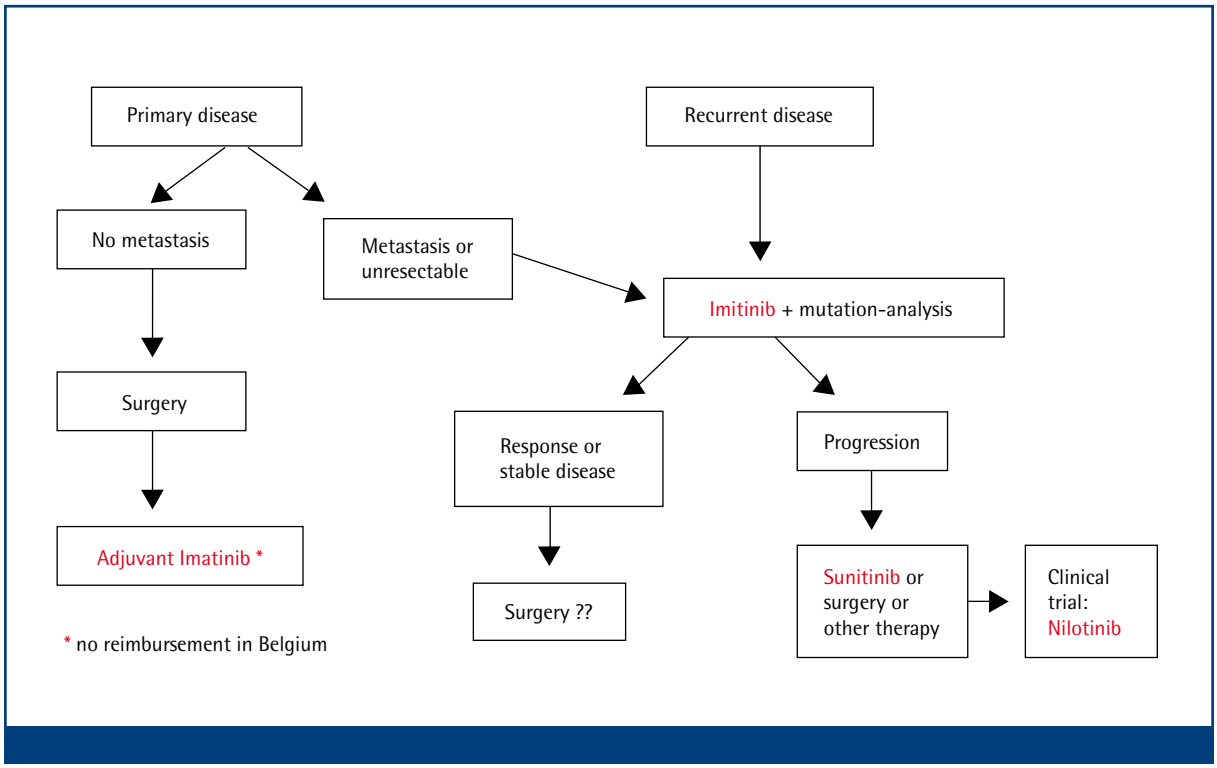

Figure 2. Treatment algorithm for patients with GIST.

mentioned, PET scan can play an important role in the follow-up of GIST. It can provide rapid insights into the sensitivity of lesions to imatinib as well as clarify ambiguous CT results.[18,19] The metabolic data derived from PET scans complement CT data.

Duration of treatment with imatinib is considered to be life-long. This became clear in a French study where a significant higher risk of progression, even in the presence of a radiographic complete response, was seen in patients who discontinued the imatinib therapy. Although this study was not powered to investigate OS, this was not different between both groups.[46] Unless there is significant toxicity, treatment should be continued. Fortunately, imatinib is generally well tolerated with most side effects being less than grade 2. The most common grade 1/2 adverse events are nausea, diarrhoea, periorbital edema, muscle cramps, fatigue, headache, and dermatitis. Severe adverse events (grade 3/4) associated with imatinib occurred in 21% of patients and included gastrointestinal or tumour haemorrhage, anaemia, neutropenia, abdominal pain and fluid retention. Toxicity is generally dose-related.[47]

Management of imatinib-resistant tumours

One can consider primary and secondary resistance against imatinib. Primary resistance is seen in patients who do not achieve a stable disease or progress within 6 months after initial clinical response. Patients who develop disease progression after more than 6 months have secondary resistance. Focal resistance to imatinib therapy can develop in specific lesions. The most common mechanism of secondary resistance is the development of new, acquired kinase mutations in KIT (or PDGFRA) that interfere with imatinib activity. Especially patients with primary mutations in KIT exon 9 can benefit from increasing the imatinib dose from 400 to 800 mg/day.[39,48] In case of imatinib-refractory or intolerant patients, the therapeutic strategy must be discussed at a multidisciplinary oncology meeting. Surgical resection, radiofrequency ablation and hepatic artery chemo-embolisation are alternative treatment options.[49] Furthermore, new biologicals such as sunitinib (Sutent®), a multitarget tyrosine kinase inhibitor, became available.[50,51] Sunitinib not only targets KIT and PGDFRA, but also the vascular endothelial growth factor receptor (VEGFR) resulting in anti-angiogenic effects. In a double-blind phase III trial of sunitinib versus placebo the superiority of sunitinib in patients with refractory disease was definitively demonstrated. Its effect is related to the mutation status of the tumour. A phase I/II

trial revealed a significantly higher partial response rate, as well as PFS and OS in patients with primary KIT exon 9 mutations as compared to KIT exon 11 mutations. Hypothyroidism is a frequent sunitinib-related side effect. Therefore, regular surveillance of the thyroid function is recommended. Other side-effects include diarrhoea, skin discolouration, mucositis, fatigue, hypertension and bleeding.[50,51]

Other kinase inhibitors such as nilotinib, dasatinib, AMG-706, everolimus and IPI-504 are currently being tested in imatinib and/or sunitinib resistant GIST.

Conclusion

Before 2001, treatment options for GIST were limited. GIST are highly resistant to conventional chemotherapy and radiotherapy. The only curative option was surgery. The past few years, a significant breakthrough was achieved with the identification of molecular abnormalities underlying the pathogenesis of these tumours. The majority of GIST have activating mutations in either KIT or PDGFRA, two related receptor tyrosine kinases. The understanding of this process led to the development of an effective systemic therapy, imatinib mesylate. This small molecule targeting the tyrosine kinase has proven activity in recurrent or metastatic GIST. The success of imatinib has prompted interest in its use in the adjuvant and neoadjuvant setting which is now being tested.

Although imatinib improves outcome for many patients with GIST, its effect is limited by primary and secondary (acquired) resistance. Other biologicals, such as sunitinib, a multitarget TKI, and nilotinib, a downstream inhibitor, are available and can be used in imatinib-resistant patients. Moreover, analysis of KIT/PDGFRA mutation status is mandatory to allow treatment selection and adequate dosing (*Figure 2*).

In the future, molecular classification of GIST will be essential for the optimisation of GIST treatment and clinical outcome.

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Key messages for clinical practice

1. GIST are highly resistant to chemo- and radiotherapy and before 2001, surgery was the only treatment option.
2. The identification of activating KIT and PDGFRA mutations led to the introduction of imatinib in the treatment of GIST.
3. Imatinib is effective in the treatment of recurrent and metastatic GIST.
4. The use of imatinib in an adjuvant and/or neo-adjuvant setting is currently under investigation.
5. Primary and secondary imatinib resistance of GIST limits the potential of imatinib in the treatment of GIST.
6. Sunitinib and nilotinib can be used in the treatment of imatinib resistant GIST.

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Correspondence address

Authors: S. Van Lierde[1], M. Peeters[1,3], N. Van Damme[1], K. Geboes[1], S. Laurent[1], I. Dero[1], P. Pauwels[2]
[1]Department of Gastroenterology, Digestive Oncology Unit, Ghent University Hospital, Belgium,
[2]Department of Pathology, Ghent University Hospital, Belgium, [3]Senior Clinical Investigator of the Fund for Scientific Research – Flanders (FWO)

Please send all correspondence to:
Prof. Dr. Marc Peeters
Department of Gastroenterology, Digestive Oncology
Ghent University Hospital
De Pintelaan 185
B- 9000 Ghent, Belgium
marc.peeters@UGent.be

Conflicts of interest: the authors have nothing to disclose and indicate no potential conflicts of interest.