Gastrointestinal stromal tumors: Review on morphology, molecular pathology, diagnostics, prognosis and treatment options

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common non-epithelial mesenchymal tumors of the gastrointestinal tract. GISTs represent a specific group of mesenchymal tumors with uncertain biological behaviors. These tumors are assumed to originate from progenitor cells, usually unable to self-regenerate, which differentiate towards Cajal cells. Apart from common GISTs that occur predominantly in adulthood, a heterogeneous group of tumors has been described that are morphologically identical with GIST, but have a specific clinical presentation and biological properties.

Approximately 30% of newly diagnosed GISTs are malignant or have a high potential for malignancy. Currently, GISTs are routinely identified with histological, immunohistochemical, and molecular genetic assays. However, clinical diagnoses, particularly of small or intramural GISTs, might be difficult. The most useful techniques for imaging and monitoring disease progression are endoscopic examinations and fused PET/CT imaging. Surgical treatment is the first-line treatment and the only method that might lead to full remission in patients with a primary GIST. There is currently no consensus on the issues of whether to perform resections in patients with positive margins or resections of metastases. Endoscopic resection could represent a relatively simple and less aggressive alternative as compared to traditional surgery in the treatment of small sized GISTs. Biological therapy with imatinib mesylate is recommended for patients with newly diagnosed, locally advanced, inoperable, or metastasizing gastrointestinal GISTs that express the c-KIT protein. Treatment may reduce a primary tumor to a size small enough for surgical excision. Current research is focusing on the development of new therapies for the treatment of advanced disease and/or disease prophylaxis. (Acta gastroenterol. belg., **2010**, 73, **349-359**).

Key words : Gastrointestinal, Stromal, Tumor, Morphology, Diagnostics, Treatment

Introduction

Gastrointestinal stromal tumors (GIST) are the most common non-epithelial mesenchymal tumors of the gastrointestinal tract. GISTs consist of spindle cells, epithelioid cells, or both. GISTs are assumed to originate from progenitor cells, usually unable to self-regenerate, which differentiate towards Cajal cells. Interstitial Cajal cells are integral to the intestinal wall and generate peristaltic slow waves in the gastrointestinal tract ('peristaltic pacemakers') (1,2)

Although GISTs comprise 60% of mesenchymal gastrointestinal tract tumors, they represent approximately 2-5% of all gastrointestinal tract tumors (3,4). The yearly estimated GIST incidence is 10-20 cases per 106 inhabitants. The median age at diagnosis is 60 years old (5). These tumors are rare in young adults and children (< 1%) (6).

Historical overview

Historically, GISTs were classified as smooth-muscle-cell tumors and were referred to as leiomyoma, bizarre leiomyoma, leiomyoblastoma, or leiomyosarcoma (7,8). In 1983, Mazur and Clark characterized and established this type of tumor as a unique entity termed a 'stromal tumor' (9). This group of stromal tumors included mesenchymal gastrointestinal tumors that did not show any signs of neurogenic or smooth muscle cell differentiation.

Similarities between GIST and intestinal wall cells of Cajal led to the hypothesis that GISTs originated from these cells (10,11). The term GIPACT (Gastro Intestinal Pacemaker Cell Tumor) was proposed for these tumors, but the term did not become widely accepted in the literature (12).

In 1998, the presence of the KIT protein (CD117) in GIST cells was established with immunohistochemical methods (13). The cellular KIT protein is a transmembrane cytokine receptor with an intracellular region that functions as a tyrosine kinase. KIT protein is coded through the *kit* gene. The *kit* gene was first isolated as a Hardy-Zuckerman feline sarcoma retroviral oncogene (feline sarcoma viral oncogene, v-*kit*) (14). The term KIT was derived from the English word 'kit', short for kitten, in reference to the feline sarcoma. Subsequently, the *c-kit* proto-oncogene (a cellular gene that can be modified into an oncogene) was also documented in humans. The human *c-kit* is located on the long arm of chromosome 4 and consists of 21 exons (15).

In 1998, Hirohita *et al.* found that the majority of GISTs possessed activation mutations ('gain-of-function') for the *c-kit* gene (16). Consequently, the term GIST came to refer to tumors that (apart from the usual

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morphologic signs) were positive in immunohistochemical KIT assays.

In 2003, Heinrich *et al*. found an activation mutation for the platelet-derived growth factor receptor alpha (PDGRF-α) gene in patients with GIST that had no *c-kit* mutations (17). Subsequent studies confirmed the presence of these mutations in 30-60% of tumors that satisfied histological criteria for GIST, but were KIT-immunonegative (18,19,20). Therefore, KIT immunopositivity is no longer perceived as a prerequisite for a GIST diagnosis.

In 2001, imatinib mesylate was introduced for the treatment of metastatic GIST, representing another important historical milestone. Imatinib is a selective inhibitor of tyrosine kinases, including that harbored in the KIT protein. The treatment efficacy of imatinib was confirmed in two independent clinical studies in the same year (21, 22).

Morphology

Macroscopic picture

When located within the digestive system, tumors grow out from the submucosal layers of the gastrointestinal wall, most frequently from the *muscularis propria*, and arch into the lumen or onto the serous surface of the affected organ. Ulceration of the surrounding mucosa is common. Tumors are often well-defined and are sometimes covered with a thin pseudocapsula. The pseudocapsula may also project a septum into the tumor, dividing it into pseudolobulae. These tumors typically have an elastic consistency. The structure of a biospecimen section is usually homogenous to fibrous and white in color. This structure might be distorted secondarily by regressive modifications from necrosis, bleeding, calcification, or pseudocystic changes (2).

Microscopic picture

Conventional light microscopy enables a high level of certainty of GIST diagnosis in most cases, even before immunohistochemical testing is conducted. GISTs are divided into two main groups : spindle cell and epithelioid. Arrangements of these two types of cells might be fascicular, storiform, diffuse, alveolar, or they may form organoid structures. The tumors are often pleomorphic (2,23,24).

Currently, due to the diagnostic accuracy of immunohistochemical and molecular genetic examinations, electron microscopy does not play a significant diagnostic or prognostic role in GIST diagnosis (25,26).

Molecular genetics

c-kit gene

The *c-kit* gene is located on the long arm of chromosome 4 and encodes a transmembrane tyrosine kinase. The *c-kit* gene product plays an important role in the production of mast cells, melanocytes, hematopoietic stem cells, germinal cells, and Cajal´s cells (27,28). A broad range of mutations of this gene have been found in a number of neoplastic processes, including GIST, myeloproliferative diseases, acute myeloid leukemia, mastocytosis, and paranasal sinus lymphomas (16,29). A *c-kit* mutation is typically found in GISTs smaller than 1 cm, confirming that this is an early oncogenic event (30, 31). The *c-kit* mutations, particularly those in exon 11 (approx. 67%) and exon 9 (approx. 10%), are found in 75-80 % patients with GIST (32). *C-kit* gene mutations also occur within exons 8 (1%), 13 (1%) and 17 (1%), which encode the tyrosine kinase domain (32).

These overactive tyrosine kinase receptors represent promising targets for developing therapies. Currently, imatinib mesylate, originally developed for the treatment of chronic myeloid leukemia, is the most important tyrosine kinase inhibitor. Furthermore, imatinib mesylate selectively inhibits the tyrosine kinases of KIT and PDGFR-α proteins (2, 21, 22).

pdgfr-α gene

The *pdgfr-α* gene is located on the long arm of chromosome 4, close to the *c-kit* gene ; both have very similar structures. The main function of PDGFR-α protein is the facilitation of glial and mesenchymal cell proliferation and differentiation. The PDGFR-α protein is selectively inhibited by imatinib mesylate in vitro (17,33,34). The PDGFR-α mutations are found 5-10 % patients with GIST (32).

In general, activating mutations are found in 85% of GISTs, in either KIT for 75-80% or PDGFR-α for 5-10% (32).

Immunohistochemical examination

Immunohistochemical detection of the KIT protein (CD117) with the enzyme-linked immunosorbent assay (ELISA) is considered a standard technique for GIST diagnosis ; however, negative results cannot rule out the diagnosis. CD117 is generally positive, although a proportion of true GIST (in the 5% range) is CD117-negative. Mutational analysis for known mutations involving *c-kit* and *pdgfr-α* genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117-negative suspect GIST). In addition, mutational analysis has predictive and prognostic value, so that it is strongly recommended in the diagnostic work-up of all GISTs (35,36, 37). In addition, mutational analysis affects the oncological treatment ; the 800 mg dose is the standard recommended dose in patients with exon 9 mutation, whereas the 400 mg dose is recommended in all other cases (35).

Assessments of *c-kit* and *pdgfr-α* mutations are performed with temperature gradient gel electrophoresis of cDNA and direct nucleotide sequence determination. Sequencing techniques are based on the incorporation of

fluorescent-labeled dideoxynucleotides ; each dideoxynucleotide binds to a different fluorochrome, and can be differentiated on the basis of various emission spectra (38).

For a tumor with the typical morphology of GIST, it is not necessary to evaluate KIT protein expression or mutations in *c-kit* or *pdgfr-α* for a GIST diagnosis. Instead, GIST can be diagnosed by morphology after excluding other gastrointestinal mesenchymal lesions (1,2,3).

KIT expression is absent in approximately 4% to 15% of GIST and this can complicate the diagnosis of GIST in patients who may benefit from treatment with receptor tyrosine kinase inhibitors (39). Recently, the novel gene DOG1 has been found to be overexpressed in most gastrointestinal stromal tumors (GISTs) specifically within the field of soft tissue tumors. The name "DOG1" comes from the name of the antiserum against one GIST-specific gene, encoding for the hypothetical protein FLJ10261, which was named "*D*iscovered *O*n *G*IST 1" (40). DOG1 might play a role in development of GISTs and have potential as a diagnostic marker and therapeutic target. Using immunohistochemistry with antiserum and in situ hybridization with DOG1-specific probes, was showed that DOG1 is highly expressed not only in typical GISTs but also in KIT-mutation-negative GISTs (39,40).

Further studies demonstrate that DOG1.1 is a sensitive immunohistochemical marker for GIST, comparable with KIT, with the additional benefit of detecting 36% of KIT-negative GISTs. DOG1.1 is also a sensitive marker for unusual GIST subgroups lacking KIT or PDGFR-α mutations (39,40,41). In tumors that are negative for both KIT and DOG1.1, mutational screening may be required to confirm the diagnosis of GIST (41).

Specific clinical variants of GIST

Apart from common GISTs that occur predominantly in adulthood, a heterogeneous group of tumors has been described that are morphologically identical with GIST, but have a specific clinical presentation and biological properties.

Familial GIST

Familial GIST is a rare, autosomal dominant, genetic disease with a penetrance of almost 100% (42,43,44). Affected cell populations include cells of Cajal, melanocytes, and mast cells. The causes of familial GIST include various combinations of hyperplastic changes and tumorous proliferations. A number of families with GISTs affecting multiple relatives have been described in recent years. Most affected families have been shown to carry a KIT germline mutation **(**42,43, 44). One GIST family has recently been identified with a germline PDGFR-α mutation (45).

The GIST families tend to have several affected relatives with multiple primary neoplasms, multifocal lesions and tumors that present at earlier ages than corresponding sporadic GISTs. The affected kindreds manifested wide spectrum of cutaneous lesions including melanoma, benign melanocytic nevi and other diverse pigmented skin lesions (urticaria pigmentosa, café-au-lait macules, perioral hyperpigmentation) (44).

In one family with multiple GISTs a new type of germline mutation of KIT gene, and dysphagia was recently reported. The mutation was observed at Asp-820 in tyrosine kinase II domain. The members of the family suffered with dysphagia but no mechanical obstruction was found and the esophagus was not remarkably dilated. The endoscopic ultrasonography at the esophagocardiac junction showed a thickened hyperechoic layer between the circular and longitudinal muscle layers, suggesting hyperplasia of interstitial cells of Cajal at the myenteric plexus layer. Manometry showed low resting lower esophageal sphincter pressure and abnormal simultaneous contractions of the esophagus without normal peristalsis. These findings indicate that the dysphagia of the family was different from typical achalasia (46).

Carney's triad

Carney's triad is defined as a non-familial syndrome of unknown etiology that presents as a combination of GIST (usually located in the stomach), pulmonary chondroma, and extra-adrenal paraganglioma (47). The majority of patients do not present with the fully developed triad ; the most common combination is GIST and pulmonary chondroma (48). Other combinations may include the occurrence of adrenal cortex adenoma and probably also esophageal leiomyoma (49).

Carney – Stratakis syndrome

Carney-Stratakis syndrome (familial paraganglioma syndrome with GIST) has only recently been described. Two patients with this syndrome had originally been included in a group of 79 patients with Carney triad. However, later, they were included in a different group of twelve patients from five families in whom the coincidence of GIST and paraganglioma differed from Carney triad by its familial occurrence, lack of predominance in young women, and higher incidence of paraganglioma (50,51,52).

Neurofibromatosis type I

Neurofibromatosis type I (von Recklinghausen disease) is an autosomal dominant hereditary disease caused by a congenital mutation of the neurofibromin 1 (*nf1*) gene on chromosome 17. The main signs include 'café au lait' spots on the skin, pigmented hamartomas of the iris, and multiple neurofibromas on various parts of the body. Bone cysts, meningiomas, optic nerve

gliomas and other tumors might also occur in these patients. GIST, often multiple, is present in 5-25% of patients with neurofibromatosis type I. In the gastrointestinal tract, the disease most frequently affects the small intestine (53,54,55).

Sporadic pediatric GIST

GISTs in young people, children, or newborns form a specific clinical group of tumors, morphologically indistinguishable from GISTs in adult patients. These tumors mostly occur in the stomach antrum of young females. Mutations in genes encoding KIT and PDGFR-α proteins are rare in sporadic pediatric GISTs, and this distinguishes them from the adult forms. The lack of gene mutations supports the assumption that these tumors have different pathogenic etiologies (56,57,58). The biological behavior of a sporadic pediatric GIST is characterized by a tendency to metastasize into the liver ; nevertheless, patients exhibit relatively long survival times (over ten years) despite liver impairment (59,60).

Tumor localization and clinical presentation

GISTs can occur in most gastrointestinal tract organs and also extra-gastrointestinally. The highest incidence rates of GIST are found in the stomach (60-70%), small intestine (20-25%), colon (5%), and esophagus (< 5%) (29,61). GISTs occur less frequently outside the digestive system, specifically in the mesentery, omentum, and retroperitoneum, rarely in the pancreas and gallbladder, exceptional cases of primary GISTs were reported in the serous lining of the bladder and in the vagina (62,63,64, 65,66,67,68). These tumors are sometimes called EGIST (extra-gastrointestinal stromal tumors), and they most frequently metastasize to the liver, soft tissue of the abdominal cavity (omentum, peritoneum), and retroperitoneum. Generalizations into lymph nodes, lungs, and skeleton are rare (62,69).

The most frequent disease symptom is bleeding into the gastrointestinal tract, which occurs in 20-50% of the cases (2). Tumor-associated bleeding is typically intraluminal and it manifests (according to localization) as hematemesis, enterorrhagia, or melena. However, an erosion of veins from an extraluminally growing tumor might occur with subsequent bleeding into the abdominal cavity ; this may manifest as an acute abdominal pain and severe anemia and frequently requires urgent laparotomy (2,61). Other symptoms of GIST include chronic abdominal pain (20-50%) with possible palpable resistance and chronic anemia (10%). The disease might also present with a range of non-specific symptoms, including fatigue, asthenia, anorexia, night sweats, palpitations, weight loss, and paraneoplastic fever (2,5). About 20% of patients have no clinical signs. The disease is diagnosed through the manifestation of metastases in about 17% of cases (5, 9, 70).

Clinical diagnostics

Clinical diagnostics are based on endoscopic examinations and imaging techniques. Gastroscopy and colonoscopy are the main examination techniques for large tumors located in the stomach or colon, respectively.

Double-balloon enteroscopy is becoming increasingly common for the diagnosis of GISTs located in the small intestine (71). When the location of the suspected tumor is uncertain, invasive perioperative enteroscopy might be used, with the introduction of an endoscope into the lumen of the small intestine by way of an enterotomy (72). Endoscopic sonography plays an important role in the diagnosis of small intramural tumors, mainly those located in the gastric wall. Tumors smaller than 2 cm are easily detected with this method, the threshold diameter size is around 1 cm for reliable tumor imaging (73,74).

Contrast-enhanced spiral CT imaging might be useful in detecting tumors that are 2 cm or larger, particularly for extraluminal tumors or tumors with calcifications, necroses, or substantial vascularisation (75). In addition, CT scanning plays an important role in the detection and monitoring of post-treatment metastasis regression (76). Alternatively, magnetic resonance imaging might contribute to a more precise localization of a tumor and determination of its resectability (75).

Furthermore, positive emission tomography (PET) plays an important role in GIST diagnostics. Fluorin-18-fluorodeoxy glucose PET (FDG-PET) allows differentiation of metabolically active tumor tissues from other tissues. Importantly, FDG-PET allows the evaluation of the GIST response to imatinib mesylate treatment (77). A recent study has shown that an unremarkable finding on a primary FDG-PET image signals primary resistance of the tumor to imatinib (76).

At present, fused PET/CT imaging is the most useful imaging technique with respect to primary diagnostics, post-operative monitoring, and, in the case of imatinib treatment, also post-therapeutic monitoring and disease prognosis prediction (76,77,78).

Surgical treatment

Surgical resection is the first-line treatment and the only treatment approach that might lead to full remission in patients with a primary GIST. Surgical treatment is associated with low morbidity for tumors smaller than 10 cm located in the stomach or intestines (79).

The benefit of large resections has not been confirmed. Wedge resection is considered sufficient in the stomach area, and segmental resection is considered appropriate in the small intestine. Surgery must aim to achieve microscopic negative margins of resection (R0 resection) (80). In contrast, enucleation represents an unsuitable surgical approach (80,81). Negative margins of resection are achieved in 70-95% of cases with pri-

mary tumor surgery, and primary resection is feasible in 85% of patients (81, 82).

'En bloc' resection is indicated in cases when GIST adheres closely to the surrounding organs (83). Since adjuvant treatment is indicated in these cases, the extent of resection should always be carefully considered with an emphasis on preserving functionality of the involved organs ; the surgery should not aim to preclude adjuvant treatment (84).

Should the tumor be encapsulated in a pseudocapsula, it is important to preserve the integrity of the pseudocapsula. Tumors are often soft and crumbly ; thus, it is necessary to operate with particular care to avoid ruptures and subsequent increases in the risk of implantation metastases (81).

A positive microscopic resection margin significantly affects patient lethality. Survival of patients with a perioperative tumor rupture is similar to that of patients with positive margins of resection (85).

A laparoscopic resection of GIST is possible and is preferred in some centers (86,87,88). However, a laparoscopic procedure should not be performed when there is a risk of post-surgery distortion of tumor integrity. It is imperative to always adhere to the general rules of oncologic surgery. When the laparoscopic procedure does not represent an indisputable benefit to the patient after considering the extension of resection and the risk of pseudocapsula perforation, it is necessary to either select a classical operation or perform early conversion of the procedure (84). In most cases ; laparoscopic resection is recommended in tumors smaller than 2-5 cm in diameter (37,79,84).

Metastasizing of GIST into lymph nodes is rare ; thus, a routine lymphadenectomy is not indicated. Sentinel lymphadenectomy is performed only when preoperative investigations confirm the involvement of lymph nodes (69,89).

There is no consensus on the issues of whether to perform resections in patients with positive resection margins or whether to perform resections of metastases. When selecting the procedure, the biological characteristics of the tumor have to be taken into account. Patients with a well-differentiated tumor and a 'disease-free' interval longer than a year might profit from these procedures (90,91). A combination of cytoreductive surgery and subsequent adjuvant therapy is meaningful in cases of tumors that are non-resectable with radical surgery (92).

Surgical indication for metastatic GIST treated with imatinib is not yet established. Surgery for focal progressive lesions could be considered as part of the second-line/third-line armamentarium in selected cases. Surgery of residual disease upon best clinical response seems associated with survival benefit compared with historical controls in similar patient collectives treated with imatinib alone. However, evidence from prospective randomized trials is needed to make definite recommendations (93).

Endoscopic treatment

In several recent studies endoscopic resection has emerged as minimally invasive treatment for small GISTs (94,95,96,97,98). Endoscopic resection using band ligation could represent a relatively simple and less aggressive alternative as compared to traditional surgery in the treatment of small sized GISTs with the shape of the polyp (94,95).

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are other advanced techniques of therapeutic endoscopy for superficial GIST. The methods have recently been applied to esophageal and gastric GISTs (96,97,98).

Application of endoscopic methods is limited to lesions with no risk of nodal metastasis and mostly for the tumors smaller than 3 cm. If the GIST is completely removed by endoscopic method and histopathological examination discloses that the risk for malignancy is low, no further treatment is necessary (95,96,97).

Oncological treatment

The treatment of GIST with currently available chemotherapeutics has been ineffective. Radiotherapy is equally ineffective. The biological treatment with imatinib is the therapy that has achieved a significantly positive response in 40-70% of patients with metastasizing or inoperable disease.

Imatinib mesylate (Glivec EU / Gleevec US, Novartis Pharmaceuticals AG, Basel, Switzerland) inhibits the tyrosine kinase domains on various receptors, including c-KIT (CD117) and PDGFR-α. Receptor tyrosine kinases (RTK) are widely expressed transmembrane proteins that act as receptors for growth factors, neurotrophic factors, and other extracellular signaling molecules (99).

Therapy with imatinib is recommended for the treatment of patients with newly diagnosed, locally advanced, inoperable, or metastasizing GISTs that express the c-KIT protein. Treatment may reduce the primary tumor to a size small enough to remove with a surgical excision (92,99). Imatinib treatment is also indicated after an incomplete surgical resection or for patients with a high risk of post-operative morbidity or mortality consequent to the presence of co-morbidities (99,100). The daily imatinib dose is 400 or 800 mg (divided into 2 × 400 mg, morning and evening). Treatment is continued to prevent eventual disease progression (100).

Introduction of imatinib into the treatment of advanced GISTs can prolong the time to disease progression and, in particular, the overall survival time. According to a large phase III clinical study (B2222) and a more recent study, the overall survival times were 57 and 64 months, respectively, compared to only 19 months survival without imatinib (99, 101, 102, 103). Another study (BRF14) confirmed that, subject to com-

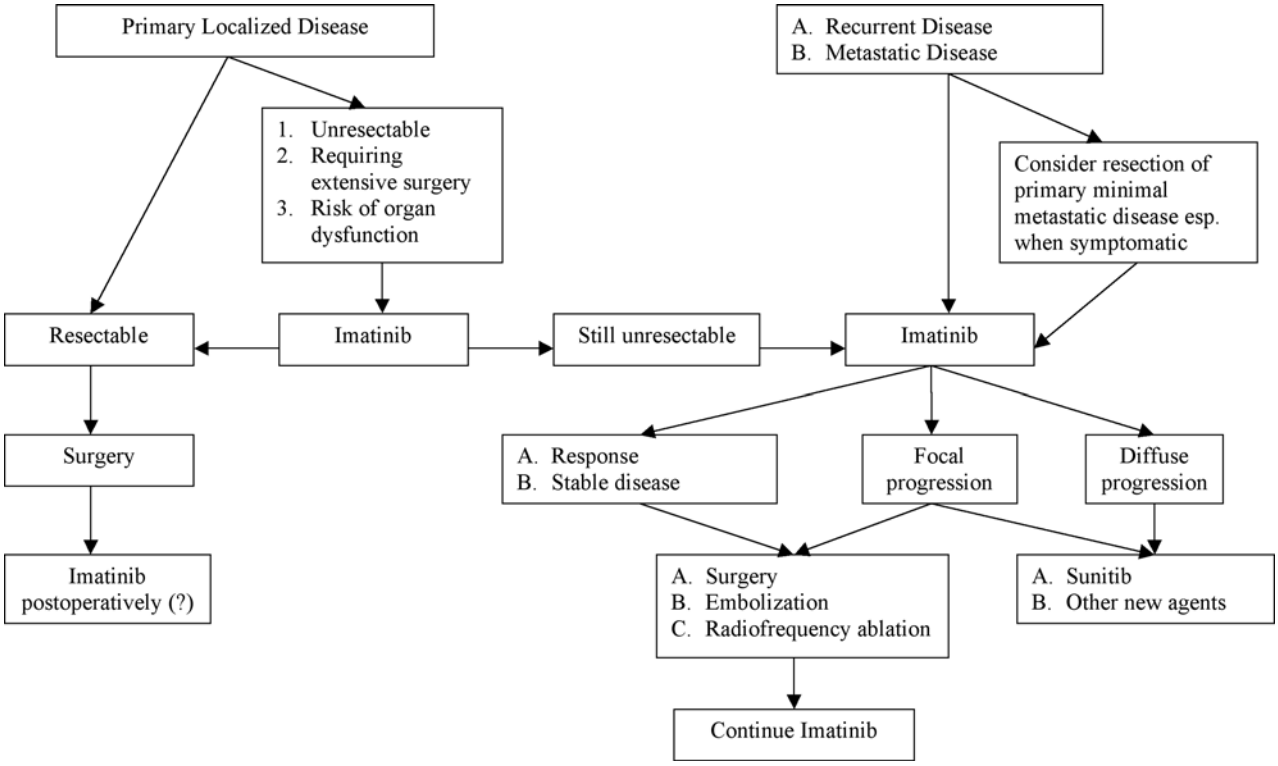

Fig. 1. — Algorithm for the treatment of GIST (101)

plete or partial remission of the advanced disease, continuation with imatinib treatment represents a clear advantage for the patient. The majority of patients experienced rapid relapse of the disease following treatment discontinuation (104,105). Should progression occur despite continued treatment, the 400 mg per day imatinib dose can be increased to 800 mg with high likelihood of further efficacy (106). An algorithm of the recommended treatment course with respect to the stage of the disease is shown in Figure 1.

Recent studies have investigated the effects of adjuvant administration of imatinib following resection of a primary localized GIST. The main aim was to delay tumor recurrence. According to those studies, adjuvant administration of imatinib contributed to extending the recurrence-free period (100). However, other questions remain to be addressed ; for example, what is the ideal length of adjuvant treatment, what are the indications for adjuvant treatment, given the level of risk associated with aggressive tumor behavior, etc. (100,104).

Further disease progression requires a second-line biological treatment with the tyrosine kinase inhibitor, sunitib malate (Stutent, Pfizer Inc, New York, USA) at a dose of 50 mg daily over four weeks, followed by two-weeks of a treatment-free period (107,108).

Sunitinib malate is a multitargeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors 1, 2, 3, PDGFR-α, PDGFR-β,

Table 1. — **Overview of treatment options that might follow imatinib and sunitib failure** (112,121,122,123,124, 125,126,127)

Generic name	**Trade name**	**Biological effect**	**Type of study**	**Phase**
Nilotinib	Tasigna®	Selective tyrosine kinase inhibitor	Nilotinib versus Best Supportive Care (112)	III
Everolimus	Certican®	Inhibitor of mTOR (mammalian target of rapamycin) a serine-threonine kinase	everolimus + imatinib Disease progression despite continued treatment of imatinib (400 mg/day) (121)	I/II
Sorafenib	Nexavar®	Multikinase inhibitor targeting a number of serine/threonine and receptor tyrosine kinases	Disease progression despite continued treatment of imatinib or sunitib (122)	II
Vatalanib	Vatalanib®	Selective inhibitor of the protein kinase domain of vascular endothelial growth factor receptors	Disease progression despite continued treatment of imatinib or imatinib intolerance (123)	II
AZD 2171	Cediranib® Recentin®	Selective vascular endothelial growth factor (VEGF) signaling inhibitor	Imatinib resistance or intolerance (124)	II
Dasatinib	Sprycel®	Selective tyrosine kinase inhibitor	Dasatinib versus sorafenib, nilotinib and IPI-504 (125,126,127)	Pre-clinical

KIT and some other receptors (FLT3, RET, CSF-1) (109). This broad range of activity may confer both antiangiogenic effects and direct antitumor effects depending on the tumor subtype. Recently, an alternative dosing strategy of daily administration of sunitinib 37.5 mg daily (continuous daily dosing), with no planned breaks, has demonstrated comparable benefit in GIST without increase in toxicity (110).

A group of new tyrosine kinase inhibitors have been developed for treating further progression ; nilotinib (Tasigna, Novartis Pharma GmbH, Nuremberg, Germany) is the best researched within the group (111). The nilotinib is active in GIST resistant to both imatinib and sunitinib. These results warrant further investigation of nilotinib in GIST (112).

Table 1 provides an overview of treatment options that might follow imatinib and sunitib failure.

Prognostic factors for GIST behavior

To date, no criteria have been identified that would allow a diagnostic exclusion of GIST malignant behavior. Approximately 30% of newly diagnosed GISTs are clearly malignant or have high potential for malignancy (113). Every GIST should, therefore, be considered as potentially malignant. At the 2001 National Institute of Health conference, morphological criteria were identified that could be used to assess the risk of aggressive behavior in GIST. In 2006, new extended criteria were proposed that stemmed from extensive research and took into account different behaviors of stromal tumors of the stomach and small intestine (Table 2) (114).

Table 2. **— The risk of malignant behavior of GIST (114).**

	Tumor parameters		**Risk of aggressive behavior according to localization**	
Group	**Maximal size (cm)**	**Mitotic rate per 50 HPFs***	**Stomach**	**Small intestine**
1	≤ 2	≤ 5	Very low if any	Very low if any
2	> 2 ≤ 5	≤ 5	Low	Low
3a	> 5 ≤ 10	≤ 5	Low	Intermediate
3b	> 10	≤ 5	Intermediate	High
4	≤ 2	> 5	Low	High
5	> 2 ≤ 5	> 5	Intermediate	High
6a	> 5 ≤ 10	> 5	High	High
6b	> 10	> 5	High	High

* HPFs - High Power Fields ; when magnified 40 x

The signs of potential malignancy include tumor location ; for example, stomach tumors have the best prognoses, but tumors of the small intestine and extra-GIT tumors have less favorable prognoses (29,57,115). Furthermore, negative prognoses are indicated with signs of high cellularity, a high proliferation index, infiltrative growth, and necroses with tumor disintegration (5,62,115,116,117).

Although the prognostic value of *c-kit* and *pdgfr-α* mutations is questionable, their reliability in the prediction of the therapeutic response to imatinib mesylate is widely accepted. In general, tumors with a 'regulatory type' mutation (for example, exon 11 of *c-kit* or exon 12 of *pdgfr-α*) are regarded as responsive, while tumors with an 'enzymatic type' mutation (for example, exon 17 of *c-kit* or exon 18 of *pdgfr-α*) are regarded as primarily resistant (118).

To date, several studies have confirmed that imatinib had significant efficacy in GISTs with an exon 11 *c-kit* mutation, and only slightly less efficacy in GISTs with an exon 9 mutation. Other studies showed that mutations in exons 13 and 17 of *c-kit* or exon 18 of *pdgfr-α* were associated with disease stabilization, rather than a response to treatment (119,120).

Summary

GISTs represent a specific group of mesenchymal tumors with uncertain biological behaviors. Approximately 30% of newly diagnosed GISTs are malignant or have a high potential for malignancy.

Currently, GISTs are routinely identified with histological, immunohistochemical, and molecular genetic assays. However, clinical diagnoses, particularly of small or intramural GISTs, might be difficult. The most useful techniques for imaging and monitoring disease progression are endoscopic examinations and fused PET/CT imaging.

Surgical treatment is the first-line treatment and the only method that might lead to full remission in patients with a primary GIST. There is currently no consensus on the issues of whether to perform resections in patients with positive margins or resections of metastases.

Biological therapy with imatinib mesylate is recommended for patients with newly diagnosed, locally advanced, inoperable, or metastasizing gastrointestinal GISTs that express the c-KIT protein. Treatment may reduce a primary tumor to a size small enough for surgical excision.

Current research is focusing on the development of new therapies for the treatment of advanced disease and/or disease prophylaxis.

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