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World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Oncology
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjgo@wjgnet.com
http://www.wjgnet.com

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REVIEW

A gist of gastrointestinal stromal tumors: A review

Ashwin Rammohan, Jeswanth Sathyanesan, Kamalakannan Rajendran, Anbalagan Pitchaimuthu, Senthil-Kumar Perumal, UP Srinivasan, Ravi Ramasamy, Ravichandran Palaniappan, Manoharan Govindan

Ashwin Rammohan, Jeswanth Sathyanesan, Kamalakannan Rajendran, Anbalagan Pitchaimuthu, Senthil-Kumar Perumal, UP Srinivasan, Ravi Ramasamy, Ravichandran Palaniappan, Manoharan Govindan, The Institute of Surgical Gastroenterology and Liver Transplantation, Centre for GI Bleed, Division of HPB Diseases, Stanley Medical College Hospital, Chennai 600001, India

Author contributions: Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A and Perumal SK contributed to the conception and design, acquisition, analysis and interpretation of data; Rammohan A, Sathyanesan J, Srinivasan UP and Ramasamy R drafted the article and revised it critically for important intellectual content; Sathyanesan J, Palaniappan R and Govindan M gave the final approval of the version to be published.

Correspondence to: Dr. Ashwin Rammohan, The Institute of Surgical Gastroenterology and Liver Transplantation, Centre for GI Bleed, Division of HPB Diseases, Stanley Medical College Hospital, Old Jail Road, Chennai 600001, India. ashwinrammohan@gmail.com

Telephone: +91-988-4173583 Fax: +91-44-25289595
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Abstract

Gastrointestinal stromal tumors (GISTs) have been recognized as a biologically distinctive tumor type, different from smooth muscle and neural tumors of the gastrointestinal tract (GIT). They constitute the majority of gastrointestinal mesenchymal tumors of the GIT and are known to be refractory to conventional chemotherapy or radiation. They are defined and diagnosed by the expression of a proto-oncogene protein detected by immunohistochemistry which serves as a crucial diagnostic and therapeutic target. The identification of these mutations has resulted in a better understanding of their oncogenic mechanisms. The remarkable antitumor effects of the molecular inhibitor imatinib have necessitated accurate diagnosis of GIST and their distinction from other gastrointestinal mesenchymal tumors. Both traditional and minimally invasive surgery are used to remove these tumors with minimal morbidity and excellent perioperative outcomes. The revolutionary use of specific, molecularly-targeted therapies, such as imatinib mesylate, reduces the frequency of disease recurrence when used as an adjuvant following complete resection. Neoadjuvant treatment with these agents appears to stabilize disease in the majority of patients and may reduce the extent of surgical resection required for subsequent complete tumor removal. The important interplay between the molecular genetics of GIST and responses to targeted therapeutics serves as a model for the study of targeted therapies in other solid tumors. This review summarizes our current knowledge and recent advances regarding the histogenesis, pathology, molecular biology, the basis for the novel targeted cancer therapy and current evidence based management of these unique tumors.

Key words: Gastrointestinal stromal tumors; c-KIT; Imatinib mesylate; Surgery; Review

Core tip: Gastrointestinal stromal tumors have been recognized as a biologically distinctive tumor type, different from smooth muscle and neural tumors of the gastrointestinal tract. This review summarizes our current knowledge and recent advances regarding the histogenesis, pathology, molecular biology, the basis for the novel targeted cancer therapy and current evidence based management of these unique tumors.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors that arise predominantly in the gastrointestinal tract (GIT). In the past, there has been considerable debate regarding its nomenclature, cellular origin, diagnosis and prognosis[1-3]. Due to their similar appearance by light microscopy, GISTs were previously thought to be smooth muscle neoplasms and most were classified as leiomyomas, leiomyoblastomas, leiomyosarcomas or schwannomas[3]. It was in 1998, after the discovery of gain-of-function mutations in the c-KIT proto-oncogene that these tumors were reliably distinguished from other histopathological subtypes of mesenchymal tumors[1,4]. This review attempts to provide an overview of the histogenesis, molecular pathogenesis, clinical picture, investigations, surgical and non surgical management of GIST specific to the GIT.

EPIDEMIOLOGY

GISTs represent the most common mesenchymal neoplasms of the GIT. With an annual incidence of 11-14 per 10^6, they form 0.1%-3.0% of gastrointestinal malignant tumors[5,6]. The median age at diagnosis is 60 years. There is usually no predilection for either gender but some series suggest a slight male predominance. GIST occurring in the familial form is autosomal dominant[5-7]. 5% of GISTs occur in patients with neurofibromatosis type 1 syndrome, occurring mostly in the small intestine and without KIT mutations. GIST also occurs as a part of Carney triad along with paraganglioma and pulmonary chordoma in young females[6-9].

HISTORY

Stromal tumors were referred to as smooth muscle neoplasms of GIT but immunohistochemistry (IHC) demonstrated that these tumors lacked features of smooth muscle differentiation and, while some had markers of neuronal differentiation, some had neither[1-3,7,8]. Mazur *et al*[3] coined the term "gastrointestinal stromal tumors" to collectively refer to a group of mesenchymal tumors of neurogenic or myogenic differentiation which lacked the immunohistochemical features of Schwann cells and did not have the ultrastructural characteristics of smooth muscle cells.

DISCOVERY OF KIT

In 1986, a new acute transforming feline retrovirus, the Hardy-Zuckerman 4 feline sarcoma virus (HZ4-FeSV), was isolated from feline fibrosarcoma. The viral genome of HZ4-FeSV contained a new oncogene that was designated v-KIT, which encoded a transmembrane tyrosine kinase receptor called KIT. c-KIT is the cellular homologue of the oncogene v-KIT[10]. Huizinga *et al*[11] showed that mice with mutations in the *KIT* gene lacked the network of interstitial cells of Cajal associated with Auerbach's nerve plexus and intestinal pacemaker activity and hence it was shown that the interstitial cells of Cajal express the KIT receptor. Hirota *et al*[4] were investigating the mutational status of c-KIT in mesenchymal tumors of the GIT and reported that GISTs contained activated c-KIT mutations, which play a central role in its pathogenesis, and that mutations of c-KIT resulted in gain of function of the enzymatic activity of the KIT tyrosine kinase.

MOLECULAR PATHOGENESIS

What is KIT?

KIT is a 145-kDa glycoprotein. The KIT receptor can be detected by immunohistochemical staining for CD117, which is the epitope on the extra-cellular domain of the KIT receptor. Steel factor (SLF) AKA stem-cell factor is a ligand for KIT. On binding of SLF to KIT, KIT undergoes receptor homo-dimerization, which leads to activation of KIT tyrosine kinase activity, effecting intracellular signal transduction[4,7,8]. Membrane receptor tyrosine kinase cellular signaling pathways regulate key cell functions, including proliferation, differentiation and anti-apoptotic signaling. Auto-phosphorylation of c-KIT causes ligand-independent tyrosine kinase activity, leading to an uncontrolled cell proliferation due stimulation of downstream signaling pathways. An unregulated activation can lead to various forms of cancer/benign proliferative conditions. SLF-KIT interaction is essential for development of melanocytes, erythrocytes, germ cells, mast cells and ICCs. Hence, mutations involving c-KIT produce cellular defects in hematopoiesis, melanogenesis, gametogenesis and in the interstitial cells of Cajal. Mutations of different exons of the *c-KIT* gene (exon 11, exons 9 and exon 13) cause constitutive activation of the tyrosine kinase function of c-KIT[4-9,12].

GISTs can develop anywhere along the GI tract from the esophagus to the rectum; however, stomach (60%) and small intestine (30%) are the most common locations for GIST. Only 10% of GISTs are found in the esophagus, mesentery, omentum, colon or rectum. Up to 30% of GISTs exhibit high-risk (malignant) behavior such as metastasis and infiltration[8,9,13,14]. The metastatic pattern is predominantly intra-abdominal, with spread throughout the peritoneal cavity and to the liver. Lymph nodal invasion is uncommon. GISTs with indolent (low-risk) behavior are typically found as small submucosal lesions. True smooth muscle tumors/leiomyomas also occur throughout the GI tract but are now thought to be rare in comparison to GISTs, except in the esophagus where they are more common[6,7,9,13-15].

CLINICAL PRESENTATION

Only 70% of the patients with GIST are symptomatic. While 20% are asymptomatic and the tumors are detected incidentally, 10% of the lesions are detected only at autopsy. Symptoms and signs are not disease specific, they are related more to the site of the tumor[6,7,16]. Bleeding (30%-40%) comprises the most common symptom after

vague abdominal discomfort (60%-70%). Bleeding is attributed to the erosion into the GIT lumen. Bleeding occurring into the peritoneal cavity due to a ruptured GIST can lead to acute abdominal pain presenting as a surgical emergency. Bleeding into the GI tract lumen, causing hematemesis, melena or anemia, is usually more chronic on presentation. Most of the patients present with vague symptoms, such as nausea, vomiting, abdominal discomfort, weight loss or early satiety. Symptoms are usually site specific. These include dysphagia in the esophagus, biliary obstruction around the ampulla of Vater or even intussusception of the small bowel[6,7]. Lymph node metastases are uncommon in GIST. Distant metastases most commonly occur in GISTs of the peritoneum, omentum, mesentery and the liver. GISTs have a high tendency to seed and hence intraperitoneal or even scar metastases are known to occur[6,7,16].

PATHOLOGY

GIST vary greatly in size from a few millimeters to more than 30 cm, the median size being between 5 and 8 cm. Macroscopically, GIST usually has an exophytic growth and the common intra-operative appearance is that of a mass attached to the stomach, projecting into the abdominal cavity and displacing other organs[5,7,9,17]. Mucosal ulceration may be present at the summit of the lesion in 50% of cases. On gross appearance they are smooth gray and white tumors which are well circumscribed, usually with a pseudocapsule. A small area of hemorrhage or cystic degeneration and necrosis may be visible[7,18]. Gastric GISTs have a solid or nested form, often with a hyalinized stroma that shows myxoid change. GISTs in the small intestine are more often spindled than epithelioid and may show a paraganglio-matous pattern. Another characteristic is the eosinophilic structures, composed of collagen, which are stained brightly with periodic acid-Schiff (PAS) stain[18,19].

GISTs (> 95%) are positive for CD117. In 60%-70% of the patients, IHC for CD34 (mesenchymal/hematopoietic precursor cell marker) is also positive[7,8,13,15]. Vimentin and smooth muscle actin is positive in 15% to 60%. GISTs (10%-15%) have no detectable KIT or *PDGFRA* mutations [wild-type GIST (WT-GIST)]. Absence of mutations does not exclude the diagnosis of GIST[7,8,13,15,19]. DOG1 is a calcium dependent, receptor activated chloride channel protein expressed in GIST; this expression is independent of mutation type and can be used in the diagnosis of KIT-negative tumors[20,21].

INITIAL EVALUATION AND WORKUP

Due to the vague and protean presentation of GIST, initial diagnosis can be delayed. Imaging in the form of contrast enhanced computed tomography (CECT) is the modality of choice; it is used to characterize the lesion, evaluate its extent, and assess the presence or absence of metastasis at the initial staging workup. CECT is also used for monitoring response to therapy and performing follow-up surveillance of recurrence[15,18,20]. On CECT, GISTs appear as a large, well-defined soft tissue mass with heterogeneous enhancement. Tumors are usually of varying density and show patchy enhancement after intravenous contrast. Varying degrees of necrosis may frequently be demonstrated within the mass, more so in tumors responding to chemotherapy. Response to therapy is assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) or the Choi criteria (Table 1). According to the Choi criteria, responsive tumors show a 10% decrease in tumor size and 15% decrease in tumor density on CECT. This criteria has been shown to be better than RECIST criteria in assessing the response of GIST to tyrosine kinase inhibitor (TKI) therapy[18,22,23].

Table 1 Response Evaluation Criteria in Solid Tumors

Complete response	Disappearance of all target lesions
Partial response	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter
Progressive disease	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started

Originated from [23], with permission.

Endoscopic ultrasound (EUS) has been used in the diagnosis of GIST; it assesses the depth of invasion and is useful in obtaining a tissue sample. Preoperative percutaneous biopsy should not be used because of a significant risk of tumor rupture or dissemination[15,20]. Conventional endoscopic sampling techniques such as forceps biopsy are limited in their clinical utility given the difficulty of sampling lesions in a subepithelial location and the increased risk for perforation. The efficacy of EUS guided fine needle aspiration (EUS-FNA) has been pointed out in several studies and the reported accuracy is 80%-85%[18,24]. A clear role for EUS guided Trucut biopsy has yet to be defined, given the inconsistent results in providing adequate tissue yield. However, at present, EUS-FNA should be considered the procedure of choice to secure a tissue diagnosis of GIST[15,18,24]. EUS features of GIST which are predictive of an adequate tissue yield include a size of 10 cm, round/oval shape and location in a specific sonographic wall layer. EUS features of a high grade GIST include irregular extra-luminal borders, heterogeneous echo patterns, presence of cystic spaces and echogenic foci[25].

GISTs are positron emission tomography (PET) avid tumors because the receptor tyrosine kinase increases the glucose transport protein signaling[20]. PET is useful in revealing small metastases which would otherwise not have been picked up on CECT[9]. It helps differentiate an active tumor from necrotic or inactive scar tissue. PET also differentiates malignant from benign tissue and recurrent

Table 2 European Organization for Research and Treatment of Cancer metabolic response criteria for tumors evaluated with positron emission tomography

Complete metabolic response	Complete resolution of [^{18}F]-FDG uptake within the tumor volume indistinguishable from surrounding normal tissue
Partial metabolic response	Reduction of a minimum of 15%-25% in tumor [^{18}F]-FDG SUV after one cycle of chemotherapy Reduction of a minimum of > 25% in tumor [^{18}F]-FDG SUV after more than one treatment cycle
Progressive metabolic disease	Increase in [^{18}F]-FDG tumor SUV > 25% within the tumor region, visible increase in the extent of [^{18}F]-FDG tumor uptake (> 20% in the longest dimension) Appearance of new [^{18}F]-FDG uptake.
Stable metabolic disease	Increase in tumor [^{18}F]-FDG SUV < 25%, decrease of < 15%. No visible increase in extent of [^{18}F]-FDG tumor uptake (< 20% in the longest dimension)

Originated from [26], with permission. PET: Positron emission tomography; [^{18}F]-FDG: ^{18}F-fluoro-de-oxyglucose; SUV: Standardized uptake value.

tumor from nondescript benign changes. Changes in the metabolic activity of tumors precede anatomic changes on CECT; it is hence used to assess the response to TKI therapy. PET helps to clarify ambiguous findings seen on computerized tomography (CT) or magnetic resonance imaging and to assess complex metastatic disease in patients who are being considered for surgery. Routine use of PET for surveillance after resection is not yet recommended. The European Organization for Research and Treatment of Cancer metabolic response criteria is based on tumor evaluated with PET[9,20,22,26] (Table 2).

PRINCIPLES OF BIOPSY AND PATHOLOGICAL ASSESSMENT

Routine preoperative biopsy is not mandatory but biopsy is necessary prior to the initiation of preoperative therapy with TKI. EUS-FNA biopsy of the primary site is preferred over percutaneous biopsy as it reduces the risk of tumor hemorrhage and intra-abdominal tumor dissemination[24,25,27,28]. Percutaneous image guided biopsy can be used while confirming the presence of metastatic disease. While assessing a specimen, a pathology report should include the anatomic location, size and mitotic rate measured in the most proliferative area of the tumor and reported as the number of mitoses in 50 high power fields (equivalent to 5 mm^2 of tissue). The specimen should be subjected to IHC for KIT and molecular genetic testing to identify mutations in the *KIT* or *PDGFRA* genes[8,20,27].

MANAGEMENT OF GIST

Small GIST

Tumors which are less than 2 cm in the widest dimension are defined as small GIST. They are usually discovered incidentally on endoscopy[29]. If these lesions are symptomatic, complete surgical resection is recommended. Small asymptomatic gastric GISTs (less than 2 cm) with no high-risk EUS features can be managed conservatively with endoscopic surveillance at 6 to 12 mo intervals[27-29]. Endoscopic resection of these small tumors would be another option. With the recent advent of endoscopic resection techniques, endoscopists can now remove mucosal or submucosal tumors by endoscopic mucosal resection (EMR). Complete resection of subepithelial tumors larger than 2 cm in size and those originating from the muscularis propria layer still remain difficult by EMR[30-32]. A study performed in elderly and high risk surgical patients showed that EUS guided band ligation of small duodenal tumors is a safe and efficient therapeutic method[33].

PRINCIPLES OF SURGERY

Surgery is the primary treatment of choice in localized or potentially resectable GIST. It is imperative to avoid tumor rupture. The tumors are fragile and should be handled with care, with an aim to achieve complete gross resection of the tumor with an intact pseudocapsule. Multivisceral and radical surgery should be avoided where possible. Segmental or wedge resection with an aim to obtain histologically negative margins is sufficient. Resection should be accomplished with minimal morbidity. Re-resection is not indicated for patients with an R1 resection. Lymphadenectomy is not required as GISTs have a low incidence of nodal metastases[15,18,29].

ROLE OF LAPAROSCOPY

Although prospective trials are lacking, small series and retrospective analyses have shown low recurrence rates, shorter hospital stay and low morbidity with a laparoscopic approach[9,15,18,29]. It has been recommended for selected GISTs present in favorable anatomic locations like the anterior wall of the stomach, jejunum and ileum. The same surgical principles as open surgery are applicable in laparoscopic surgery for GIST. The specimen is removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites. Endoscopic resection of small GISTs is more controversial due to the risks of positive margins, tumor spillage and intact specimen retrieval[9,15,18,29]. During laparoscopic partial gastrectomy for GIST of the stomach, it is important to avoid an excessive surgical resection of the gastric wall as this can cause a deformity of the stomach[34-36]. Laparoscopic and endoscopic cooperative surgery (LECS) is a procedure which enables tumor resection with minimal surgical margin[35-38]. The LECS procedure involves seromuscular resection by laparoscopy with endoscopic dissection for the mucosal to submucosal layers, making it possible to standardize gastric submucosal tumor resection independent of tumor location, such as in the vicinity of the esophagogastric junction or pyloric ring[34-38].

IMATINIB MESYLATE

Imatinib mesylate is a tyrosine kinase inhibitor with activity against ABL, BCR-ABL, KIT, PDGFRA, PDGFRB and CSF1R. Its structure mimics adenosine triphosphate (ATP) and it binds competitively to the ATP binding site of the target kinases. This prevents substrate phosphorylation and signaling, thereby inhibiting proliferation and survival[9,15,18,27]. Patients with advanced GIST started on imatinib have shown a 35%-49% 9 year survival. The presence and the type of *KIT* or *PDGFRA* mutation status are predictive of response to imatinib. Exon 11 mutations occur in the KIT juxtamembrane domain and are the most common mutations in GISTs. Tumors with exon 11 mutations have better response rates to imatinib, with a longer progression free survival (PFS) and overall survival (OS). Exon 9 mutations occur in the KIT extracellular domain; these mutations are specific for intestinal GIST. Exon 9 mutations are associated with a decreased response to imatinib and a poorer PFS. *PDGFRA* mutations are common in gastric GIST. Mutations in PDGFRA affect exon 18 in the tyrosine kinase domain[9,15,18,27,39-44]. There have been multiple trials testing the most appropriate dosing of imatinib. 400 mg/d has been found to have equivalent response rates and OS compared to higher doses, which are associated with more side effects. Indications for a higher dosing (800 mg/d) include patients with an exon 9 KIT mutation or those with tumors which continue to progress on the standard 400 mg/d dosage[41-45].

NEOADJUVANT IMATINIB - RESECTABLE DISEASE

Surgery is the primary treatment for all tumors which can be resected without significant morbidity. If this is not the case, then preoperative imatinib should be considered. Imatinib is effective in reducing the size of the tumor prior to resection, increasing the likelihood of negative margins without significant morbidity[27,29,46]. Before starting a patient on neoadjuvant imatinib, a baseline CECT is recommended. The optimal duration of preoperative therapy is yet unknown. In patients responding to therapy, imatinib is continued until maximal response (defined as no further improvement between 2 successive CT scans). This can be as long as 6-12 mo but it is not always necessary to wait for a maximal response prior to surgery. Surgery is recommended when the tumor appears to have downsized to a point where complete resection can be achieved without significant morbidity[9,18,27,29,46-49]. Imatinib should be stopped just before surgery and resumed as soon as the patient is able to tolerate oral medications, regardless of the surgical margins. The recommended dose is 400 mg/d, with dose escalation to 800 mg/d advised in cases of documented mutations in KIT exon 9[29,44,46-50]. In cases where there is no progression, continuation of the same dose of imatinib is recommended and resection is considered. If there is tumor progression, as confirmed with CECT scan, surgery is recommended after discontinuing imatinib[29,44,46-49].

Table 3 Risk stratification of gastrointestinal stromal tumors

Mitotic rate	Tumor size (cm)	Stomach	Jejunum/ Ileum	Duodenum	Rectum
≤ 5/50 HPF	≤ 2	None	None	None	None
	> 2, ≤ 5	Very low	Low	Low	Low
	> 5, ≤ 10	Low	Moderate	High	High
	> 10	Moderate	High		
> 5/50 HPF	≤ 2	None	High	NA	High
	> 2, ≤ 5	Moderate	High	High	High
	> 5, ≤ 10	High	High	High	High
	> 10	High	High		

Originated from [54], with permission. HPF: High-power fields; NA: Not available.

ADJUVANT THERAPY

Although surgery is the therapeutic modality of choice, it does not routinely cure GIST. Complete resection is possible in approximately 85% of patients and 50% patients will develop recurrence or metastasis following complete resection[9,18,25,27,51]. The 5-year survival rate is approximately 50%, while the median time to recurrence after resection of primary high-risk GIST is 2 years. Adjuvant imatinib has been shown to improve PFS and OS in postsurgical patients. In patients who have not received preoperative imatinib and have undergone complete resection, imatinib has been found to be beneficial if continued for 36 mo, especially in patients with an intermediate or high risk of recurrence. Estimation of this risk is based on the tumor size, site, mitotic count and tumor rupture (Table 3). A survival benefit is seen in patients with a high risk of recurrence (mitotic count > 5/50 HPF, size > 5 cm, non-gastric location and tumor rupture)[27,29,35,40,51-55]. In those patients who had received preoperative imatinib and undergone a complete resection, continuation of imatinib at the same dose for 2 years following surgery is recommended. In patients with a positive resection margin, imatinib is continued/started regardless of surgical margins until disease progression is noted[27,29,50].

UNRESECTABLE, METASTATIC OR RECURRENT DISEASE

Imatinib has a very high likelihood of clinical benefit and a positive response in patients with documented unresectable GIST. Imatinib is indicated when primary resection would carry the risk of severe postoperative functional deficit[51]. It is also indicated in those who have a widespread metastatic disease or a recurrence after resection. There is a survival benefit of cytoreductive surgery following preoperative imatinib in patients responding to preoperative imatinib[51,55-62]. The lesion is assessed within 3 mo of initiating therapy to determine if it has become resectable. In cases where the tumor remains unresectable, imatinib is continued indefinitely until there is evi-

dence of tumor progression. Continuation of TKI therapy life-long for palliation of symptoms forms an essential component of best supportive care[9,18,27,29,51,56-62]. Options for patients with progressive disease or with widespread systemic disease and good performance status (0-2) include continuation of imatinib at the same dose, dose escalation up to 800 mg in the absence of severe adverse drug reactions or switching to sunitinib[29,44-46,51,53,55].

TOXICITY OF IMATINIB

The more common side effects include fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain and rash. The adverse-effect profile improves with prolonged therapy. The more serious side effects include liver function abnormalities, lung toxicity, low blood counts and GI bleeding[29,44-47]. Congestive heart failure has been noted in 8.2% of patients, manageable with medical therapy. Arrhythmias and acute coronary syndromes have also been reported[63]. All the toxicities abate if imatinib is withheld. Sunitinib should be considered, after discontinuing imatinib[29,44-47].

RESISTANCE TO IMATINIB

Non achievement of stable disease or progression of disease within 6 mo of an initial clinical response (KIT exon 9 mutation or no detectable kinase mutation – wild-type tumors, PDGFRA exon 18) is defined as primary resistance, occurs in 10%-20% patients and relates to the mutational profile of the tumor. The majority of wild-type GISTs [pediatric GISTs (Carney Triad), NF1 GISTs, adult WT-GISTs] show primary resistance[29,52]. When there is disease progression after more than 6 mo of clinical response (new acquired kinase mutation in KIT or PDGFR that interferes with imatinib activity, secondary mutations in KIT exon 11), it is termed as secondary resistance. This has been attributed to genomic amplification and overexpression of KIT/PDGFRA without new point mutations and to loss of KIT expression, accompanied by activation of an alternative tyrosine kinase or other oncogenes. Secondary resistance is also related to the acquisition of new kinase mutations[29,44,52,64,65]. Dose escalation of imatinib is the first step in overcoming drug resistance. If there is continued resistance, the use of other kinase inhibitors (sunitinib) is recommended[29,44,52,64,65].

SUNITINIB MALATE

Sunitinib malate is an orally administered multi-targeted receptor tyrosine kinase inhibitor which has shown significant and sustained clinical benefit in patients with imatinib-resistant or imatinib-intolerant GIST. Sunitinib has been associated with a significant improvement in median time to progression (27.3 wk *vs* 6.4 wk) and significantly greater estimated OS[66,67]. The clinical activity of sunitinib in imatinib-resistant GISTs is significantly influenced by both primary and secondary mutations in the KIT kinase domain. Sunitinib induces higher response rates in patients with primary KIT exon 9 mutations than in those with KIT exon 11 mutations (58% *vs* 34% respectively)[27,29,66-72]. The recommended dosage of sunitinib is 50 mg orally once daily on a schedule of 4 wk on treatment followed by 2 wk off. Common adverse effects which are also dose-limiting include fatigue, nausea and vomiting. Other toxicities include hematological toxicities (anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia and skin discoloration. Patients on sunitinib have a significant risk of developing hand-foot skin reaction, the incidence of which can be reduced by routine application of emollient lotions[27,29,68]. Hypertension is common because sunitinib targets the vascular endothelial growth factor receptor (VEGFR). Other significant toxicities involve cardiotoxicity and hypothyroidism. Close monitoring of blood pressure and left ventricular ejection fraction is essential, especially in patients with a history of heart disease or cardiac risk[72]. Routine monitoring (every 3-6 mo) of thyroid stimulating hormone levels is indicated. All of sunitinib-related toxicities can managed with dose interruptions or reductions[68,69,72,73].

Second-generation TKIs like sorafenib, nilotinib, dasatinib and regorafenib have shown activity in patients resistant to imatinib and sunitinib[75-88]. Results with regorafenib are most encouraging. Regorafenib is a multikinase inhibitor with activity against KIT, PDGFR and VEGFR and is well tolerated, with common adverse effects being hypertension (23%), hand-foot skin reaction (20%) and diarrhea (5%)[29,75,76].

PERITONEAL AND LIVER METASTASES

Patients who are medically fit with surgically accessible focally progressive disease should be considered for resection. The rationale behind this approach is the elimination of drug-resistant clones that will allow ongoing therapy with imatinib[89-94]. Debulking in the form of removal of the gross tumor followed by intraperitoneal chemotherapy with cisplatin and doxorubicin or mitoxantrone have been attempted; the median time to recurrence was increased from 8 to 21 mo with the addition of intraperitoneal chemotherapy[94-97]. Surgery in metastatic patients is a case based decision. Residual tumor resection is safe but multifocal resection is not recommended without considering the patient's performance status and personal situation[29,89-91]. When surgery may not be possible, limited evidence exists that similar benefits could be obtained with nonsurgical ablative techniques such as radiofrequency ablation or embolization[98-100]. In carefully selected patients with GIST liver metastases, radiofrequency ablation has been shown to be a safe and useful therapeutic option[100]. Liver transplantation for patients with metastatic GIST has been attempted with guarded results. Serralta *et al*[101] performed a transplant in three patients for tumors which on histopathology turned out to be GIST; all their patients had a recurrence after a median period of 3 years and survival was extended by starting them on imatinib.

SURVEILLANCE

GISTs have unpredictable behavior and long term follow up is essential for all patients, independent of their benign or malignant characteristics. As the majority of GISTs tend to recur within the first 3-5 years, intense follow up is required during this period[18,27,29]. It is recommended both for persistent gross residual disease and for completely resected disease. Clinical examination with abdominopelvic CECT scan every 3-6 mo is the recommended surveillance protocol[18,29].

CONCLUSION

GISTs are the most common mesenchymal tumors of the GI system. Improved knowledge of the oncogenic drivers and resistance mechanism operant in GIST has acted as a foundation for the general understanding of the role of targeted therapies in human cancers. Surgery is the primary treatment of choice in localized or potentially resectable GIST. Surgery and imatinib form the first-line therapy and their effectiveness for the majority of patients has been revolutionary. Sunitinib is an approved second-line agent which is effective in many non-responders to imatinib therapy. Personalizing the treatment of GISTs and tailoring treatments to tumor genotype using combination therapies in order to prevent emergence of resistance is essential to optimize patient outcomes.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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