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REVIEW

A gist of gastrointestinal stromal tumors: A review

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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.

REFERENCES

1 **Joensuu H**. Gastrointestinal stromal tumor (GIST). *Ann Oncol* 2006; **17** Suppl 10: x280-x286 [PMID: 17018739 DOI: 10.1093/annonc/mdl274]

2 **Walker P**, Dvorak AM. Gastrointestinal autonomic nerve (GAN) tumor. Ultrastructural evidence for a newly recognized entity. *Arch Pathol Lab Med* 1986; **110**: 309-316 [PMID: 3006627]

3 **Mazur MT**, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol* 1983; **7**: 507-519 [PMID: 6625048 DOI: 10.1097/00000478-198309000-00001]

4 **Hirota S**, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577-580 [PMID: 9438854 DOI: 10.1126/science.279.5350.577]

5 **Kim KM**, Kang DW, Moon WS, Park JB, Park CK, Sohn JH, Jeong JS, Cho MY, Jin SY, Choi JS, Kang DY. Gastrointestinal stromal tumors in Koreans: it's incidence and the clinical, pathologic and immunohistochemical findings. *J Korean Med Sci* 2005; **20**: 977-984 [PMID: 16361808 DOI: 10.3346/jkms.2005.20.6.977]

6 **Goettsch WG**, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. *Eur J Cancer* 2005; **41**: 2868-2872 [PMID: 16293410 DOI: 10.1016/j.ejca.2005.09.009]

7 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. *Pol J Pathol* 2003; **54**: 3-24 [PMID: 12817876]

8 **Miettinen M**, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. *Am J Surg Pathol* 2005; **29**: 1373-1381 [PMID: 16160481 DOI: 10.1097/01.pas.0000172190.79552.8b]

9 **Beham AW**, Schaefer IM, Schüler P, Cameron S, Ghadimi BM. Gastrointestinal stromal tumors. *Int J Colorectal Dis* 2012; **27**: 689-700 [PMID: 22124674 DOI: 10.1007/s00384-011-1353-y]

10 **Chabot B**, Stephenson DA, Chapman VM, Besmer P, Bernstein A. The proto-oncogene c-kit encoding a transmembrane tyrosine kinase receptor maps to the mouse W locus. *Nature* 1988; **335**: 88-89 [PMID: 2457811 DOI: 10.1038/335088a0]

11 **Huizinga JD**, Thuneberg L, Klüppel M, Malysz J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. *Nature* 1995; **373**: 347-349 [PMID: 7530333 DOI: 10.1038/373347a0]

12 **Nishida T**, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, Kanakura Y, Tanaka T, Takabayashi A, Matsuda H, Kitamura Y. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. *Nat Genet* 1998; **19**: 323-324 [PMID: 9697690 DOI: 10.1038/1209]

13 **Miettinen M**, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; **30**: 1213-1220 [PMID: 10534170 DOI: 10.1016/S0046-8177(99)90040-0]

14 **Hatch KF**, Blanchard DK, Hatch GF, Wertheimer-Hatch L, Davis GB, Foster RS, Skandalakis JE. Tumors of the rectum and anal canal. *World J Surg* 2000; **24**: 437-443 [PMID: 10706916 DOI: 10.1007/s002689910069]

15 **Pidhorecky I**, Cheney RT, Kraybill WG, Gibbs JF. Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. *Ann Surg Oncol* 2000; **7**: 705-712 [PMID: 11034250 DOI: 10.1007/s10434-000-0705-6]

16 **Yan BM**, Kaplan GG, Urbanski S, Nash CL, Beck PL. Epidemiology of gastrointestinal stromal tumors in a defined Canadian Health Region: a population-based study. *Int J Surg Pathol* 2008; **16**: 241-250 [PMID: 18573781 DOI: 10.1177/1066896907306967]

17 **Corless CL**, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004; **22**: 3813-3825 [PMID: 15365079 DOI: 10.1200/JCO.2004.05.140]

18 **Stamatakos M**, Douzinas E, Stefanaki C, Safioleas P, Polyzou E, Levidou G, Safioleas M. Gastrointestinal stromal tumor. *World J Surg Oncol* 2009; **7**: 61 [PMID: 19646278 DOI: 10.1186/1477-7819-7-61]

19 **Nishida T**, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. *Histol Histopathol* 2000; **15**: 1293-1301 [PMID: 11005253]

20 **Fletcher CD**, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; **33**: 459-465 [PMID: 12094370 DOI: 10.1053/hupa.2002.123545]

21 **Miettinen M**, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. *Am J Surg Pathol* 2009; **33**: 1401-1408 [PMID: 19606013 DOI: 10.1097/PAS.0b013e3181a90e1a]

22 **Choi H**, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 2007; **25**: 1753-1759 [PMID: 17470865 DOI: 10.1200/JCO.2006.07.3049]

23 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney

M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

24 **Akahoshi K**, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, Motomura Y, Honda K, Watanabe M, Nagaie T. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. *World J Gastroenterol* 2007; **13**: 2077-2082 [PMID: 17465451]

25 **Shah P**, Gao F, Edmundowicz SA, Azar RR, Early DS. Predicting malignant potential of gastrointestinal stromal tumors using endoscopic ultrasound. *Dig Dis Sci* 2009; **54**: 1265-1269 [PMID: 18758957 DOI: 10.1007/s10620-008-0484-7]

26 **Young H**, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Pruim J, Price P. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 1999; **35**: 1773-1782 [PMID: 10673991 DOI: 10.1016/S0959-8049(99)00229-4]

27 **Sepe PS**, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 363-371 [PMID: 19365407 DOI: 10.1038/nrgastro.2009.43]

28 **Sepe PS**, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. *Gastrointest Endosc* 2009; **70**: 254-261 [PMID: 19482280 DOI: 10.1016/j.gie.2008.11.038]

29 **Demetri GD**, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, Sundar HM, Trent JC, Wayne JD. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 2010; **8** Suppl 2: S1-S41; quiz S42-S44 [PMID: 20457867]

30 **Shim CS**, Jung IS. Endoscopic removal of submucosal tumors: preprocedure diagnosis, technical options, and results. *Endoscopy* 2005; **37**: 646-654 [PMID: 16010609 DOI: 10.1055/s-2005-861477]

31 **Chu YY**, Lien JM, Tsai MH, Chiu CT, Chen TC, Yang KC, Ng SC. Modified endoscopic submucosal dissection with enucleation for treatment of gastric subepithelial tumors originating from the muscularis propria layer. *BMC Gastroenterol* 2012; **12**: 124 [PMID: 22978826 DOI: 10.1186/1471-230X-12-124]

32 **Park YS**, Park SW, Kim TI, Song SY, Choi EH, Chung JB, Kang JK. Endoscopic enucleation of upper-GI submucosal tumors by using an insulated-tip electrosurgical knife. *Gastrointest Endosc* 2004; **59**: 409-415 [PMID: 14997145 DOI: 10.1016/S0016-5107(03)02717-2]

33 **Sun S**, Ge N, Wang S, Liu X, Lü Q. EUS-assisted band ligation of small duodenal stromal tumors and follow-up by EUS. *Gastrointest Endosc* 2009; **69**: 492-496 [PMID: 19136107 DOI: 10.1016/j.gie.2008.05.025]

34 **Wilhelm D**, von Delius S, Burian M, Schneider A, Frimberger E, Meining A, Feussner H. Simultaneous use of laparoscopy and endoscopy for minimally invasive resection of gastric subepithelial masses - analysis of 93 interventions. *World J Surg* 2008; **32**: 1021-1028 [PMID: 18338207 DOI: 10.1007/s00268-008-9492-1]

35 **Hiki N**, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Miki A, Ohyama S, Seto Y. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc* 2008; **22**: 1729-1735 [PMID: 18074180 DOI: 10.1007/s00464-007-9696-8]

36 **Wong DC**, Wong SK, Leung AL, Chung CC, Li MK. Combined endolaparoscopic intragastric excision for gastric neoplasms. *J Laparoendosc Adv Surg Tech A* 2009; **19**: 765-770 [PMID: 19645605 DOI: 10.1089/lap.2009.0067]

37 **Ridwelski K**, Pross M, Schubert S, Wolff S, Günther T, Kahl S, Lippert H. Combined endoscopic intragastral resection of a posterior stromal gastric tumor using an original technique. *Surg Endosc* 2002; **16**: 537 [PMID: 11928044 DOI: 10.1007/s004640042014]

38 **Kato M**, Nakajima K, Nishida T, Yamasaki M, Nishida T, Tsutsui S, Ogiyama H, Yamamoto S, Yamada T, Mori M, Doki Y, Hayashi N. Local resection by combined laparoendoscopic surgery for duodenal gastrointestinal stromal tumor. *Diagn Ther Endosc* 2011; **2011**: 645609 [PMID: 21808595 DOI: 10.1155/2011/645609]

39 **Heinrich MC**, Owzar K, Corless CL, Hollis D, Borden EC, Fletcher CD, Ryan CW, von Mehren M, Blanke CD, Rankin C, Benjamin RS, Bramwell VH, Demetri GD, Bertagnolli MM, Fletcher JA. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol* 2008; **26**: 5360-5367 [PMID: 18955451 DOI: 10.1200/JCO.2008.17.4284]

40 **Debiec-Rychter M**, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, Blay JY, Leyvraz S, Stul M, Casali PG, Zalcberg J, Verweij J, Van Glabbeke M, Hagemeijer A, Judson I. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer* 2006; **42**: 1093-1103 [PMID: 16624552 DOI: 10.1016/j.ejca.2006.01.030]

41 **Heinrich MC**, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003; **21**: 4342-4349 [PMID: 14645423 DOI: 10.1200/JCO.2003.04.190]

42 **Debiec-Rychter M**, Dumez H, Judson I, Wasag B, Verweij J, Brown M, Dimitrijevic S, Sciot R, Stul M, Vranck H, Scurr M, Hagemeijer A, van Glabbeke M, van Oosterom AT. Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2004; **40**: 689-695 [PMID: 15010069 DOI: 10.1016/j.ejca.2003.11.025]

43 **Lasota J**, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology* 2008; **53**: 245-266 [PMID: 18312355 DOI: 10.1111/j.1365-2559.2008.02977.x]

44 **Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST)**. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. *J Clin Oncol* 2010; **28**: 1247-1253 [PMID: 20124181 DOI: 10.1200/JCO.2009.24.2099]

45 **Zalcberg JR**, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay JY, Schlemmer M, Van Glabbeke M, Brown M, Judson IR. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer* 2005; **41**: 1751-1757 [PMID: 16098458 DOI: 10.1016/j.ejca.2005.04.034]

46 **Wang D**, Zhang Q, Blanke CD, Demetri GD, Heinrich MC, Watson JC, Hoffman JP, Okuno S, Kane JM, von Mehren M, Eisenberg BL. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. *Ann Surg Oncol* 2012; **19**: 1074-1080 [PMID: 22203182 DOI: 10.1245/s10434-011-2190-5]

47 **Eisenberg BL**, Harris J, Blanke CD, Demetri GD, Heinrich

MC, Watson JC, Hoffman JP, Okuno S, Kane JM, von Mehren M. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol* 2009; **99**: 42-47 [PMID: 18942073 DOI: 10.1002/jso.21160]

48 **Blesius A**, Cassier PA, Bertucci F, Fayette J, Ray-Coquard I, Bui B, Adenis A, Rios M, Cupissol D, Pérol D, Blay JY, Le Cesne A. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. *BMC Cancer* 2011; **11**: 72 [PMID: 21324142 DOI: 10.1186/1471-2407-11-72]

49 **Fiore M**, Palassini E, Fumagalli E, Pilotti S, Tamborini E, Stacchiotti S, Pennacchioli E, Casali PG, Gronchi A. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). *Eur J Surg Oncol* 2009; **35**: 739-745 [PMID: 19110398 DOI: 10.1016/j.ejso.2008.11.005]

50 **McAuliffe JC**, Hunt KK, Lazar AJ, Choi H, Qiao W, Thall P, Pollock RE, Benjamin RS, Trent JC. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. *Ann Surg Oncol* 2009; **16**: 910-919 [PMID: 18953611 DOI: 10.1245/s10434-008-0177-7]

51 **Dematteo RP**, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **373**: 1097-1104 [PMID: 19303137 DOI: 10.1016/S0140-6736(09)60500-6]

52 **Joensuu H**, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, Ramadori G, Hohenberger P, Duyster J, Al-Batran SE, Schlemmer M, Bauer S, Wardelmann E, Sarlomo-Rikala M, Nilsson B, Sihto H, Monge OR, Bono P, Kallio R, Vehtari A, Leinonen M, Alvegård T, Reichardt P. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA* 2012; **307**: 1265-1272 [PMID: 22453568 DOI: 10.1001/jama.2012.347]

53 **Guilhot F**. Indications for imatinib mesylate therapy and clinical management. *Oncologist* 2004; **9**: 271-281 [PMID: 15169982 DOI: 10.1634/theoncologist.9-3-271]

54 **Miettinen M**, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol* 2006; **30**: 477-489 [PMID: 16625094 DOI: 10.1097/00000478-200604000-00008]

55 **Mussi C**, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, Casali PG, Fiore M, Hohenberger P, Gronchi A. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? *Ann Oncol* 2010; **21**: 403-408 [PMID: 19628568 DOI: 10.1093/annonc/mdp310]

56 **Raut CP**, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnolli MM. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006; **24**: 2325-2331 [PMID: 16710031 DOI: 10.1200/JCO.2005.05.3439]

57 **Rutkowski P**, Nowecki Z, Nyckowski P, Dziewirski W, Grzesiakowska U, Nasierowska-Guttmejer A, Krawczyk M, Ruka W. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol* 2006; **93**: 304-311 [PMID: 16496358 DOI: 10.1002/jso.20466]

58 **Andtbacka RH**, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PW, Pollock RE, Benjamin RS, Burgess MA, Chen LL, Trent J, Patel SR, Raymond K, Feig BW. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol* 2007; **14**: 14-24 [PMID: 17072676 DOI: 10.1245/s10434-006-9034-8]

59 **DeMatteo RP**, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg* 2007; **245**: 347-352 [PMID: 17435539 DOI: 10.1097/01.sla.0000236630.93587.59]

60 **Gronchi A**, Fiore M, Miselli F, Lagonigro MS, Coco P, Messina A, Pilotti S, Casali PG. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg* 2007; **245**: 341-346 [PMID: 17435538 DOI: 10.1097/01.sla.0000242710.36384.1b]

61 **Sym SJ**, Ryu MH, Lee JL, Chang HM, Kim TW, Kim HC, Kim KH, Yook JH, Kim BS, Kang YK. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). *J Surg Oncol* 2008; **98**: 27-33 [PMID: 18452195 DOI: 10.1002/jso.21065]

62 **Yeh CN**, Chen TW, Tseng JH, Liu YY, Wang SY, Tsai CY, Chiang KC, Hwang TL, Jan YY, Chen MF. Surgical management in metastatic gastrointestinal stromal tumor (GIST) patients after imatinib mesylate treatment. *J Surg Oncol* 2010; **102**: 599-603 [PMID: 20976730 DOI: 10.1002/jso.21630]

63 **Trent JC**, Patel SS, Zhang J, Araujo DM, Plana JC, Lenihan DJ, Fan D, Patel SR, Benjamin RS, Khakoo AY. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. *Cancer* 2010; **116**: 184-192 [PMID: 19885836 DOI: 10.1002/cncr.24683]

64 **Maleddu A**, Pantaleo MA, Nannini M, Di Battista M, Saponara M, Lolli C, Biasco G. Mechanisms of secondary resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumours (Review). *Oncol Rep* 2009; **21**: 1359-1366 [PMID: 19424610 DOI: 10.3892/or_00000361]

65 **Heinrich MC**, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, Eisenberg BL, von Mehren M, Fletcher CD, Sandau K, McDougall K, Ou WB, Chen CJ, Fletcher JA. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. *J Clin Oncol* 2006; **24**: 4764-4774 [PMID: 16954519 DOI: 10.1200/JCO.2006.06.2265]

66 **Demetri GD**, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368**: 1329-1338 [PMID: 17046465 DOI: 10.1016/S0140-6736(06)69446-4]

67 **Heinrich MC**, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, Town A, McKinley A, Ou WB, Fletcher JA, Fletcher CD, Huang X, Cohen DP, Baum CM, Demetri GD. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol* 2008; **26**: 5352-5359 [PMID: 18955458 DOI: 10.1200/JCO.2007.15.7461]

68 **Chu D**, Lacouture ME, Weiner E, Wu S. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. *Clin Genitourin Cancer* 2009; **7**: 11-19 [PMID: 19213662 DOI: 10.3816/CGC.2009.n.002]

69 **Chu TF**, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, Woulfe K, Pravda E, Cassiola F, Desai J, George S, Morgan JA, Harris DM, Ismail NS, Chen JH, Schoen FJ, Van den Abbeele AD, Demetri GD, Force T, Chen MH. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; **370**: 2011-2019 [PMID: 18083403 DOI: 10.1016/S0140-6736(07)61865-0]

70 **Raut CP**, Wang Q, Manola J, Morgan JA, George S, Wagner AJ, Butrynski JE, Fletcher CD, Demetri GD, Bertagnolli MM. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. *Ann*

Surg Oncol 2010; **17**: 407-415 [PMID: 19898902 DOI: 10.1245/s10434-009-0784-y]
71 **George S**, Blay JY, Casali PG, Le Cesne A, Stephenson P, Deprimo SE, Harmon CS, Law CN, Morgan JA, Ray-Coquard I, Tassell V, Cohen DP, Demetri GD. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. *Eur J Cancer* 2009; **45**: 1959-1968 [PMID: 19282169 DOI: 10.1016/j.ejca.2009.02.011]
72 **Zhu X**, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. *Acta Oncol* 2009; **48**: 9-17 [PMID: 18752081 DOI: 10.1080/02841860802314720]
73 **Torino F**, Corsello SM, Longo R, Barnabei A, Gasparini G. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. *Nat Rev Clin Oncol* 2009; **6**: 219-228 [PMID: 19333228 DOI: 10.1038/nrclinonc.2009.4]
74 **Prior JO**, Montemurro M, Orcurto MV, Michielin O, Luthi F, Benhattar J, Guillou L, Elsig V, Stupp R, Delaloye AB, Leyvraz S. Early prediction of response to sunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission tomography in patients with gastrointestinal stromal tumor. *J Clin Oncol* 2009; **27**: 439-445 [PMID: 19064982 DOI: 10.1200/JCO.2008.17.2742]
75 **Demetri GD**, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 295-302 [PMID: 23177515 DOI: 10.1016/S0140-6736(12)61857-1]
76 **Demetri GD**, Casali PG, Blay JY, von Mehren M, Morgan JA, Bertulli R, Ray-Coquard I, Cassier P, Davey M, Borghaei H, Pink D, Debiec-Rychter M, Cheung W, Bailey SM, Veronese ML, Reichardt A, Fumagalli E, Reichardt P. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. *Clin Cancer Res* 2009; **15**: 5910-5916 [PMID: 19723647 DOI: 10.1158/1078-0432.CCR-09-0542]
77 **Reichardt P**, Montemurro M, Gelderblom H, Blay J, Rutkowski P, Bui B, Hartmann JT, Pink D, Leyvraz S, Schütte J. Sorafenib fourth-line treatment in imatinib-, sunitinib-, and nilotinib-resistant metastatic GIST: A retrospective analysis. *J Clin Oncol* 2009; **27**: Abstract 10564
78 **Kindler HL**, Campbell NP, Wroblewski K. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial. *J Clin Oncol* 2011; **29**: Abstract 10009
79 **Park SH**, Ryu MH, Ryoo BY, Im SA, Kwon HC, Lee SS, Park SR, Kang BY, Kang YK. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. *Invest New Drugs* 2012; **30**: 2377-2383 [PMID: 22270258 DOI: 10.1007/s10637-012-9795-9]
80 **Montemurro M**, Schöffski P, Reichardt P, Gelderblom H, Schütte J, Hartmann JT, von Moos R, Seddon B, Joensuu H, Wendtner CM, Weber E, Grünwald V, Roth A, Leyvraz S. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. *Eur J Cancer* 2009; **45**: 2293-2297 [PMID: 19467857 DOI: 10.1016/j.ejca.2009.04.030]
81 **Sawaki A**, Nishida T, Doi T, Yamada Y, Komatsu Y, Kanda T, Kakeji Y, Onozawa Y, Yamasaki M, Ohtsu A. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. *Cancer* 2011; **117**: 4633-4641 [PMID: 21456006 DOI: 10.1002/cncr.26120]
82 **Demetri GD**, Lo Russo P, MacPherson IR, Wang D, Morgan JA, Brunton VG, Paliwal P, Agrawal S, Voi M, Evans TR. Phase I dose-escalation and pharmacokinetic study of dasatinib in patients with advanced solid tumors. *Clin Cancer Res* 2009; **15**: 6232-6240 [PMID: 19789325 DOI: 10.1158/1078-0432.CCR-09-0224]
83 **Trent JC**, Wathen K, von Mehren M. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). *J Clin Oncol* 2011; **29**: Abstract 10006
84 **George S**, Wang Q, Heinrich MC, Corless CL, Zhu M, Butrynski JE, Morgan JA, Wagner AJ, Choy E, Tap WD, Yap JT, Van den Abbeele AD, Manola JB, Solomon SM, Fletcher JA, von Mehren M, Demetri GD. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *J Clin Oncol* 2012; **30**: 2401-2407 [PMID: 22614970 DOI: 10.1200/JCO.2011.39.9394]
85 **Demetri GD**, Reichardt P, Kang Y-K. Randomized phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial. *J Clin Oncol* 2012; **30**: Abstract LBA10008
86 **Fumagalli E**, Coco P, Morosi C. Rechallenge with Imatinib in GIST patients resistant to second or third line therapy. Connective Tissue Oncology Society (CTOS) 15th Annual Meeting, 2009: Abstract 39404
87 **Guo T**, Agaram NP, Wong GC, Hom G, D'Adamo D, Maki RG, Schwartz GK, Veach D, Clarkson BD, Singer S, DeMatteo RP, Besmer P, Antonescu CR. Sorafenib inhibits the imatinib-resistant KITT670I gatekeeper mutation in gastrointestinal stromal tumor. *Clin Cancer Res* 2007; **13**: 4874-4881 [PMID: 17699867 DOI: 10.1158/1078-0432.CCR-07-0484]
88 **Huynh H**, Lee JW, Chow PK, Ngo VC, Lew GB, Lam IW, Ong HS, Chung A, Soo KC. Sorafenib induces growth suppression in mouse models of gastrointestinal stromal tumor. *Mol Cancer Ther* 2009; **8**: 152-159 [PMID: 19139124 DOI: 10.1158/1535-7163.MCT-08-0553]
89 **Kee D**, Zalcberg JR. Current and emerging strategies for the management of imatinib-refractory advanced gastrointestinal stromal tumors. *Ther Adv Med Oncol* 2012; **4**: 255-270 [PMID: 22942908 DOI: 10.1177/1758834012450935]
90 **Bonvalot S**, Eldweny H, Péchoux CL, Vanel D, Terrier P, Cavalcanti A, Robert C, Lassau N, Cesne AL. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol* 2006; **13**: 1596-1603 [PMID: 16957966 DOI: 10.1245/s10434-006-9047-3]
91 **Hasegawa J**, Kanda T, Hirota S, Fukuda M, Nishitani A, Takahashi T, Kurosaki I, Tsutsui S, Hatakeyama K, Nishida T. Surgical interventions for focal progression of advanced gastrointestinal stromal tumors during imatinib therapy. *Int J Clin Oncol* 2007; **12**: 212-217 [PMID: 17566845 DOI: 10.1007/s10147-007-0657-y]
92 **Parikh PM**, Gupta S. Management of gastrointestinal stromal tumor: The Imatinib era and beyond. *Indian J Cancer* 2013; **50**: 31-40 [PMID: 23713042 DOI: 10.4103/0019-509X.112289]
93 **Dagher R**, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, Rahman A, Chen G, Staten A, Griebel D, Pazdur R. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res* 2002; **8**: 3034-3038 [PMID: 12374669]
94 **Reichardt P**, Blay JY, Mehren Mv. Towards global consensus in the treatment of gastrointestinal stromal tumor. *Expert Rev Anticancer Ther* 2010; **10**: 221-232 [PMID: 20131998 DOI: 10.1586/era.09.171]
95 **Maurel J**, Martins AS, Poveda A, López-Guerrero JA, Cubedo R, Casado A, Martínez-Trufero J, Ramón Ayuso J, Lopez-

Pousa A, Garcia-Albeniz X, Garcia del Muro X, de Alava E. Imatinib plus low-dose doxorubicin in patients with advanced gastrointestinal stromal tumors refractory to high-dose imatinib: a phase I-II study by the Spanish Group for Research on Sarcomas. *Cancer* 2010; **116**: 3692-3701 [PMID: 20564079 DOI: 10.1002/cncr.25111]

96 **Joensuu H**, De Braud F, Coco P, De Pas T, Putzu C, Spreafico C, Bono P, Bosselli S, Jalava T, Laurent D, Casali PG. Phase II, open-label study of PTK787/ZK222584 for the treatment of metastatic gastrointestinal stromal tumors resistant to imatinib mesylate. *Ann Oncol* 2008; **19**: 173-177 [PMID: 17698976 DOI: 10.1093/annonc/mdm419]

97 **Schöffski P**, Reichardt P, Blay JY, Dumez H, Morgan JA, Ray-Coquard I, Hollaender N, Jappe A, Demetri GD. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. *Ann Oncol* 2010; **21**: 1990-1998 [PMID: 20507881 DOI: 10.1093/annonc/mdq076]

98 **Kobayashi K**, Szklaruk J, Trent JC, Ensor J, Ahrar K, Wallace MJ, Madoff DC, Murthy R, Hicks ME, Gupta S. Hepatic arterial embolization and chemoembolization for imatinib-resistant gastrointestinal stromal tumors. *Am J Clin Oncol* 2009; **32**: 574-581 [PMID: 19636238 DOI: 10.1097/COC.0b013e31819cca35]

99 **Dileo P**, Randhawa R, Vansonnenberg E. Safety and efficacy of percutaneous radio-frequency ablation (RFA) in patients (Pts) with metastatic gastrointestinal stromal tumor (GIST) with clonal evolution of lesions refractory to imatinib mesylate (IM). *J Clin Oncol* 2004; **22**: Abstract 9024

100 **Yamanaka T**, Takaki H, Nakatsuka A, Uraki J, Fujimori M, Hasegawa T, Sakuma H, Yamakado K. Radiofrequency ablation for liver metastasis from gastrointestinal stromal tumor. *J Vasc Interv Radiol* 2013; **24**: 341-346 [PMID: 23352855 DOI: 10.1016/j.jvir.2012.11.021]

101 **Serralta AS**, Sanjuan FR, Moya AH, Orbis FC, López-Andújar R, Pareja EI, Vila JC, Rayón M, Juan MB, Mir JP. Combined liver transplantation plus imatinib for unresectable metastases of gastrointestinal stromal tumours. *Eur J Gastroenterol Hepatol* 2004; **16**: 1237-1239 [PMID: 15489588 DOI: 10.1097/00042737-200411000-00025]

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