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EDITORIAL

Current research and treatment for gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and have gained considerable research and treatment interest, especially in the last two decades. GISTs are driven by mutations commonly found in the *KIT* gene and less commonly in the platelet-derived growth factor receptor alpha gene, *BRAF* gene and succinate dehydrogenase gene. GISTs behave in a spectrum of malignant potential, and both the tumor size and mitotic index are the most commonly used prognostic criteria. Whilst surgical resection can offer the best cure, targeted therapy in the form of tyrosine kinase inhibitors (TKIs) has revolutionized the management options. As the first-line TKI, imatinib offers treatment for advanced and metastatic GISTs, adjuvant therapy in high-risk GISTs and as a neoadjuvant agent to downsize large tumors prior to resection. The emergence of drug resistance has altered some treatment options, including prolonging the first-line TKI from 1 to 3 years, increasing the dose of TKI or switching to second-line TKI. Other newer TKIs, such as sunitinib and regorafenib, may offer some treatment options for imatinib-resistant GISTs. New molecular targeted therapies are being evaluated, such as inhibitors of BRAF, heat shock protein 90, glutamine and mitogen-activated protein kinase signaling, as well as inhibitors of apoptosis proteins antagonist and even immunotherapy. This editorial review summarizes the recent research trials and potential treatment targets that may influence our future patient-specific management of GISTs. The current guidelines in GIST management from Europe, North America and Asia are highlighted.

Key words: Gastrointestinal stromal tumors; *KIT* gene; Platelet-derived growth factor receptor alpha gene; *BRAF* gene; Succinate dehydrogenase gene; CD117; Tyrosine kinase inhibitor; Molecular targeted therapy

Core tip: Research in the histogenesis of gastrointestinal stromal tumors (GISTs) identified gene mutations in *KIT*, platelet-derived growth factor receptor alpha and

BRAF. The discovery of tyrosine kinase inhibitors (TKIs) has allowed targeted therapy in metastatic and high-risk resected GISTs. However, the emergence of TKI-resistant GISTs has raised some important treatment issues. Newer TKIs and alternative targeted therapy within the domain of BRAF and the mitogen-activated protein kinase signaling pathway, heat shock protein 90 and succinate dehydrogenase inhibition are being investigated and appear promising. Many clinical trials have been undertaken and are still ongoing to define the best molecular targeted therapy for GISTs. The European, American and Asian guidelines on GISTs provide useful resources for specialists dealing with these interesting tumors.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) account for less than 1% of all gastrointestinal tumors, and the prevalence of histological type comes after adenocarcinoma and lymphoma. GISTs are, however, the most common mesenchymal tumors of the gastrointestinal tract[1]. Historically, GISTs were classified as leiomyomas or leiomyosarcomas due to smooth muscle features observed under light microscopy.

GISTs were first termed in 1983 by Mazur and Clark[2], who discovered that the majority of gastric wall tumors were not derived from smooth muscle and nerve sheath origin using immunohistochemistry. GISTs are believed to arise from the interstitial cells of Cajal or their precursors and are heterogeneous histologically, showing spindle cells (70%), epitheloid cells (20%) and mixed cells (10%)[3]. The histogenesis of GISTs has since gained considerable research and treatment interest.

A systematic review of population-based cohort studies on GISTs by Søreide *et al*[4] showed that incidence ranges from low 0.43 per 100000 per year in Shanxi Province, China to high 1.6-2.2 per 100000 per year in South Korea. The cohort of 13550 patients from 19 countries gave the reported age ranging from 10-100 years, with median age in the 60 s; both male and female populations had about equal distribution. The anatomical locations of GISTs are frequently the stomach (55.6%) and small bowel (31.8%), and are less commonly found in the colon and rectum (6%), other various locations (5.5%) and esophagus (0.7%)[4].

Primary GISTs are commonly symptomatic (in about 80% cases), presenting with gastrointestinal bleeding or obstructive symptoms and abdominal pain. Incidental asymptomatic GISTs are discovered in less than 20% of cases during other gastrointestinal endoscopy or imaging investigations.

The diagnostic tests for GISTs may include gastrointestinal endoscopy (Figure 1), computed tomography (CT) scan (Figure 2), magnetic resonance imaging (MRI) scan and ^{18}fluoro-deoxyglucose-positron emission tomography (^{18}FDG-PET) scan (Figure 3). Endoscopic ultrasound scan (Figure 4) with fine needle aspiration biopsy (Figure 5) may be useful in confirming GISTs histologically.

Open or laparoscopic complete surgical R_0 resection of GISTs (Figure 6) represent the only potentially curative treatment, but certain high risk features of the resected GISTs give rise to recurrence of the disease. DeMatteo *et al*[5] reviewed 200 patients with GISTs treated and followed-up at a single institution and found that 46% had primary disease, 47% had metastasis and 7% had isolated local recurrence. Eighty patients with primary disease who underwent complete resection had 5-year survival rate of 54%. Survival was predicted by tumor size, but not by microscopic resection margin. However, tumor recurrence was noted to occur at the original primary tumor site, peritoneum and liver. These data predated the use of tyrosine kinase inhibitors (TKIs). In later years, the treatment options for residual or progressive liver metastases of GISTs included hepatic artery embolization, radiofrequency ablation or liver resection[6-8].

Historical assessment of the malignant potential in GISTs were based on the criteria of tumor size, mitotic count, proliferating cell nuclear antigen and proliferation index, which allowed classification into low- and high-risk subgroups[9]. Subsequently, different risk stratification systems for GISTs were proposed, such as the National Institutes of Health (NIH) consensus criteria (Fletcher's criteria based on size and mitotic count) and the Armed Forces Institute of Pathology criteria (Mittinen's criteria based on size, mitotic count and tumor site) and the 8th edition of the International Union Against Cancer utilizing TNM classification in addition to a grade category based on mitotic count[10-12].

According to the NIH criteria for primary GISTs, the distribution of risk is categorized as very low risk (15%), low risk (30%), intermediate risk (22%) and high risk (33%)[10]. Table 1 shows the commonly used criteria for assessing malignant risk of GISTs. Other factors associated with a higher malignant risk of GISTs are the presence of necrosis, high cellularity, invasion to serosa or adjacent structure and rich vascularity. In addition, factors associated with a higher risk of recurrence of GISTs are now recognized to be incomplete R_1 or R_2 resection margin, tumor rupture and spillage during surgery.

GENETIC MUTATIONS IN GISTs

The landmark article by Hirota *et al*[13] discovered that GISTs express the proto-oncogene KIT and that

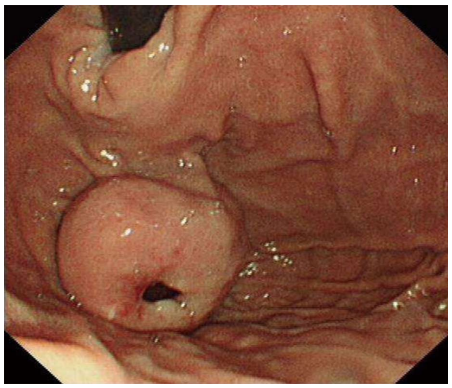

Figure 1 Gastroscopy view of a gastric gastrointestinal stromal tumors. A 4 cm × 4 cm in diameter gastric fundal submucosal tumor with a central ulceration associated with a recent bleed is shown.

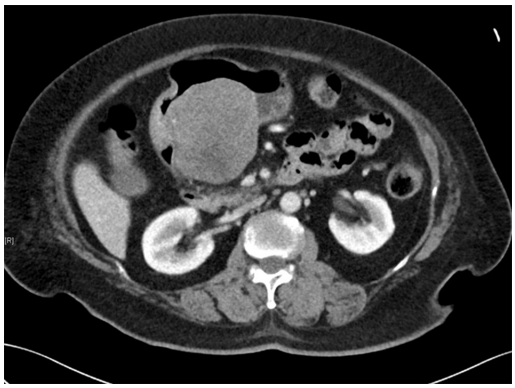

Figure 2 Computed tomography scan image of a gastric gastrointestinal stromal tumors. A submucosal tumor measuring 7.7 cm × 7.6 cm × 7.2 cm in dimension was located on the posterior wall of gastric antrum. An ill-defined hypodensity within the mass could represent an area of necrosis.

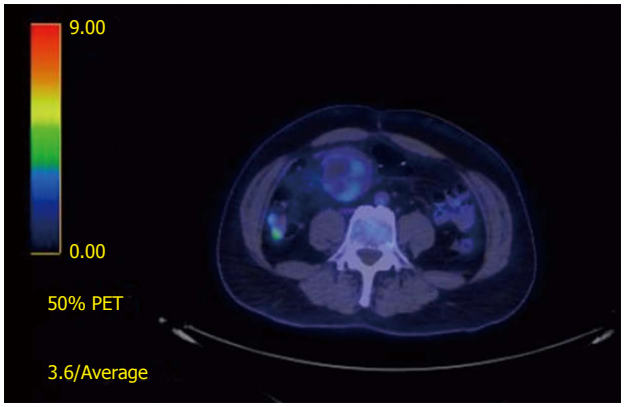

Figure 3 ^{18}Fluoro-deoxyglucose-positron emission tomography scan views of a small bowel gastrointestinal stromal tumors. There is a mildly fluoro-deoxyglucose avid mass adjacent to the jejunal anastomosis with SUVmax 3.4 suggestive of a local recurrence.

this *KIT* gene mutation provides growth stimulation of GISTs. c-KIT, also known as CD117, is a protein and a type of a receptor tyrosine kinase found on the surface of a variety of cell types; it is also a type of tumor marker. The binding of stem cell factor to

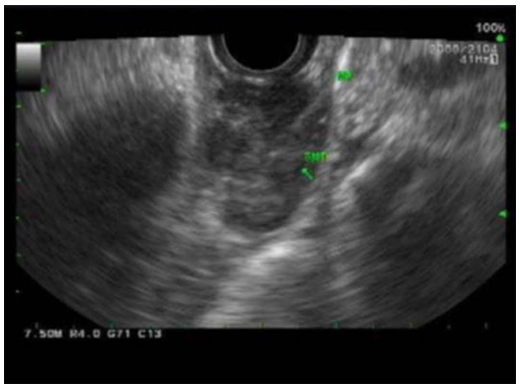

Figure 4 Endoscopic ultrasonography images of esophageal gastrointestinal stromal tumors. A distal esophageal submucosal lesion measuring 2.6 cm × 1.3 cm in diameter was noted to be well circumscribed, heterogeneous with hypoechoic echotexture without disruption of wall architecture and with no perilesional lymph node.

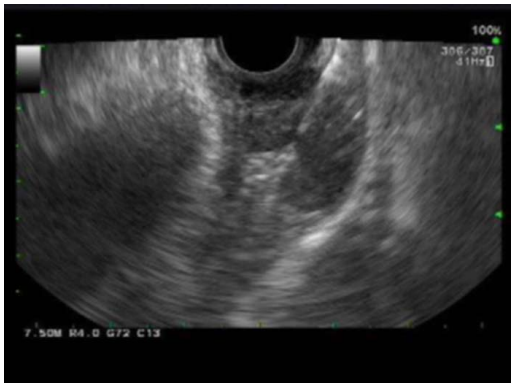

Figure 5 Endoscopic ultrasound scan and fine needle aspiration image of an esophageal gastrointestinal stromal tumors. The procedure was performed using a 22F procore needle with on-site cytotech.

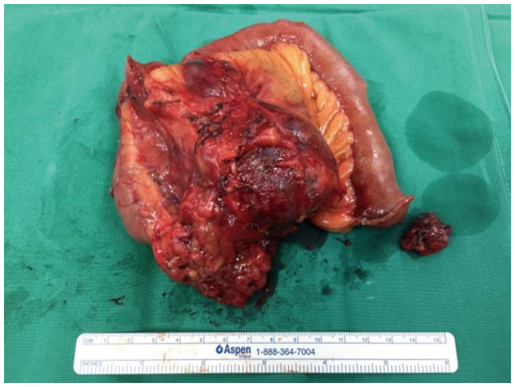

Figure 6 Macroscopic image of a recurrent small bowel gastrointestinal stromal tumors. A picture of a large enbloc resection specimen of a small bowel mesentery and jejunum was taken along a separate smaller metastatic mesenteric nodule.

the extracellular domain of c-KIT induces receptor dimerization and activation of downstream signaling pathways responsible for pro-growth signals within the cells.

Table 1 National Institutes of Health *vs* Armed Forces Institute of Pathology criteria for assessing malignant risk of gastrointestinal stromal tumors

Degree of risk	NIH criteria	AFIP criteria
Unknown	-	< 2 cm and ⩽ 5 mitotic index
Very low	< 2 cm and < 5 mitotic index	⩽ 5 cm and ⩽ 5 mitotic index
Low	2-5 cm and < 5 mitotic index	Gastric: > 5 cm and ⩽ 5 mitotic index Others: 2-5 cm and ⩽ 5 mitotic index
Intermediate or moderate	5-10 cm and < 5 mitotic index > 5 cm and 6-10 mitotic index	Gastric: > 10 cm and ⩽ 5 mitotic index or > 2-5 cm and > 5 mitotic index Others: 5-10 cm and ⩽ 5 mitotic index
High	> 5 cm and > 5 mitotic index > 10 cm and any mitotic index Any size and > 10 mitotic index	Gastric: > 5 cm and > 5 mitotic index Others: > 10 cm and > 5 mitotic index

Mitotic index = number of mitoses per 50 high-power field. AFIP: Armed Forces Institute of Pathology; NIH: National Institutes of Health.

Table 2 Frequency of genetic mutations in gastrointestinal stromal tumors

KIT mutation (about 85%)	*PDGFRA* mutation (about 5%)	*BRAF* mutation (< 1%)	*SDH* mutation (12%-15% adult, 90% pediatric GIST)
Exon 11 (about 70%)	Exon 18 (about 5%)	Exon 15 V600E	Subunit B, C and D
Exon 9 (10%-15%)	Exon 12 (1%)		
Exon 13 (1%-3%)	Exon 14 (< 0.5%)		
Exon 17 (1%)	Exon 18 D842V (about 0%)		

PDGFRA: Platelet-derived growth factor receptor alpha; SDH: Succinate dehydrogenase.

Another landmark article by Heinrich *et al*[14] later discovered GISTs lacking KIT expression have mutations related to platelet-derived growth factor receptor alpha (PDGFRA). Overall, *KIT* or *PDGFRA* mutations are found in 85% and 5% of GISTs respectively.

Agaram *et al*[15] later discovered *BRAF* mutation in imatinib-naïve and imatinib-resistant GISTs. This *BRAF* mutation in GISTs is quite rare, accounting < 1% of cases[16]. It is noted that these *KIT*, *PDGFRA* and *BRAF* gene mutations are mutually exclusive.

"Wild-type" GISTs were previously referred to GISTs lacking any mutation in *KIT* and *PDGFRA*. This "wild-type" terminology should be avoided now that new mutations have been discovered in *BRAF* genes and in genes encoding the protein succinate dehydrogenase (SDH). About 12%-15% of adult GISTs and 90% of pediatric GISTs lacking *KIT*, *PDGFRA* or *BRAF* mutations are classified into SDH-deficient and non-SDH-deficient groups. The SDH-deficient group includes Carney triad (GISTs, pulmonary chondroma and extra-adrenal paraganglioma) and Carney-Stratakis syndrome (GISTs and paraganglioma)[17].

The vast majority of *KIT* mutations are localized in exon 11 (juxtamembrane domain; about 70%), exon 9 (extracellular dimerization motif; 10%-15%), exon 13 (tyrosine kinase 1 domain; 1%-3%), and exon 17 (tyrosine kinase 2 domain and activation loop; 1%-3%)[18]. Secondary *KIT* mutations in exons 13, 14, 17 and 18 are commonly identified in post-imatinib biopsy specimens, after the patients have developed the acquired resistance. The mutations of *PDGFRA* are noted to be localized in exon 12, 14 and 18, and more specifically as 18 D842V. The mutation of *BRAF* is identified and localized to exon 15 V600E[15]. Mutations of the *SDH* gene are found to be localized to subunit B, C and D[17]. Table 2 summarizes the frequency of different genetic mutations in GISTs.

TKIs AND BIOLOGICAL THERAPY IN GISTs

Whilst complete surgical resection of GISTs can offer the best cure, targeted therapy in the form of TKIs has altered our management options. A landmark case report by Joensuu *et al*[18] described the effect of a TKI called STI571 in a patient with a metastatic GIST, for which the evaluation of MRI and ^{18}FDG-PET scans showed a very dramatic reduction of the GIST.

STI571 was the first TKI, also called imatinib, approved by the United States Food and Drug Administration (FDA) in 2002 for the treatment of unresected or metastatic GISTs. In 2008, imatinib was approved for adjuvant use in high-risk resected GISTs patients to prevent recurrence[19]. In 2012, the FDA granted the extension of standard 1 year imatinib therapy to 3 years, due to increase in overall patient survival[20,21]. An important study demonstrated that imatinib when used as a neoadjuvant therapy decreased the tumor volume and was associated with improved complete surgical resection in the locally advanced primary GISTs[22].

In a trial examining the relationship between kinase genotype and treatment outcome for 428 patients treated with either 400 mg or 800 mg daily doses of imatinib confirmed the favorable impact of *KIT* exon 11 genotype, when compared with KIT exon 9 and wild-

Table 3 Implication of gastrointestinal stromal tumors mutations and response to targeted therapy

	Imatinib[23]	Sunitinib[25]	Regorafenib[28]
KIT mutation			
Exon 11	OR 63%	CB 34%	Increased sensitivity
Exon 9	OR 37%. Intermediate sensitivity. Higher dose 800 mg more effective in metastatic disease than 400 mg daily	CB 34%	Unknown
Exon 13	OR 40%. Sensitivity as primary mutation. Resistance as secondary mutation	CB 100%	Unknown
Exon 14	Resistance as secondary mutation	Unknown	Unknown
Exon 17	OR 25%. Primary mutation sensitive *in vitro*. Resistance as secondary mutation	CB 0%	Unknown
PDGFRA mutation			
Exon 18	OR 50%	CB 0%	Unknown
Exon 12	Increased sensitivity	CB 0%	Unknown
Exon 14	Increased sensitivity *in vitro*	Unknown	Unknown
Exon 18 D842V	Decreased sensitivity	Decreased sensitivity	Unknown
BRAF mutation	Resistance	Resistance	Unknown
SDH mutation	Decreased sensitivity	Unknown	Increased sensitivity
No *KIT*, *PDGFRA* or *BRAF* mutation	OR 28%	CB 56%	Some activity

Objective response (OR) is defined as a complete or partial response by Response Evaluation Criteria for Solid Tumors (RECIST) criteria, excludes non-evaluable patients. Clinical benefit (CB) is defined as response or stable disease for 6 mo or more according to RECIST. PDGFRA: Platelet-derived growth factor receptor alpha; SDH: Succinate dehydrogenase.

type genotype for patients with advanced GISTs[23].

The American College of Surgeons Oncology Group led a trial studying the long-term outcome of patients categorized as high risk of recurrence who underwent complete gross GISTs resection followed by adjuvant imatinib at 400 mg/d for 1 year. After a median follow-up of 7.7 years, the 1-, 3- and 5-year overall survival rates were 99%, 97% and 83% respectively, which compared favorably with a historical 5-year overall survival rate of 35%. The 1-, 3- and 5-year recurrence-free survival rates were 96%, 60% and 40% respectively. On univariate analysis, age and mitotic rate were associated with overall survival. On multivariate analysis, the recurrence-free survival rate was lower with increasing tumor size, small bowel site, *KIT* exon 9 mutation, high mitotic rate, and older age[24].

TKIs other than imatinib are considered as second-generation TKIs, and include sunitinib, regorafenib, sorafenib, nilotinib, dasatinib and pazopanib. Table 3 summarizes the implication of different mutations in GISTs and their response to TKI therapy.

Sunitinib was approved by the FDA for the treatment of imatinib-resistant GISTs in 2006 and is considered as second-line TKI[25]. Heinrich *et al*[26] discovered clinical activity of sunitinib after imatinib failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases that implicate the optimum treatment of patients with GISTs.

Regorafenib was approved by the FDA in 2013 to treat advanced GISTs that cannot be surgically removed and are resistant to other TKIs, and it is considered as third-line TKI[27]. The long-term follow-up results of the multicenter phase Ⅱ trial of regorafenib in patients with metastatic or unresectable GISTs after failure of imatinib and sunitinib showed benefit in patients with primary *KIT* exon 11 mutations and SDH-deficient GISTs[28].

The use of other TKIs, apart from imatinib, sunitinib and regorafenib, is still being evaluated and remains debated. In a Korean clinical trial in 2012, sorafenib was shown to maintain disease control in one-third of the patients with metastatic GISTs who had otherwise failed with two or more TKIs[29].

In a phase Ⅰ study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant GISTs showed some partial clinical response but required phase Ⅱ doses for further evaluation[30].

In a phase Ⅱ study of imatinib-resistant GISTs treated with dasatinib, there was a significant activity by objective response rate but it did not meet the predefined 6 mo progression-free survival rate of 30%[31]. There is an American phase Ⅱ clinical trial of dasatinib in advanced sarcoma including GISTs patients and a European phase Ⅱ trial of dasatinib as first-line therapy in GISTs patients[32,33]. Both trials have stopped recruiting participants and the conclusion of the study is expected in the future.

In a phase Ⅱ French trial, Mir *et al*[34] showed that pazopanib plus best supportive care improves progression-free survival compared with best supportive care alone in patients with advanced GISTs resistant to imatinib and sunitinib. This trial provides reference outcome data for future studies of targeted inhibitors in the third-line setting for this group of patients.

Other TKIs identified in clinical trials include masitinib (AB1010), crenolanib (CP-868,596), AZD2171, vatalanib (PTK787), OSI-930, TKI258 and DCC-2618 (Table 4). A biologics inhibitor of KIT and PDGFRA called olaratumab (IMC-3G3) was trialed (NCT01316263) but the development was put on hold and the stage 2 of this study was not completed.

Table 4 Potential treatment targets for gastrointestinal stromal tumors

Category	Name	ClinicalTrials.gov Identifier
TKI of KIT and PDGFRA	Masitinib (AB1010)	NCT00998751 (U)[57]
	Crenolanib (CP-868,596)	NCT02847429 (R), NCT01243346 (C)[58]
	AZD2171	NCT00385203 (C)[59]
	Vatalanib (PTK787)	NCT00117299 (C), NCT00655655 (A)
	OSI-930	NCT00513851 (C)
	TKI258	NCT01478373 (C), NCT01440959 (C)
	DCC-2618	NCT02571036 (R)
Biologic inhibitors of KIT and PDGFRA	Olaratumab (IMC-3G3)	NCT01316263 (C)
HSP90 inhibitors	Retaspimycin (IPI-5040)	NCT00276302 (C), NCT00688766 (T)
	BIIB021 (CNF2024)	NCT00618319 (C)
	Ganetespib (STA-9090)	NCT01039519 (C)
	AUY922	NCT01389583 (R), NCT01404650 (C)
	AT13387	NCT01294202 (C)
Inhibitors of pathways downstream of KIT and PDGFRA	RAS/RAF/MEK/ERK/MAPK inhibitors: MEK162	NCT01991379
	AKT inhibitors: perifosine	NCT00455559 (C)[60]
	mTOR inhibitors: everolimus (RAD001)	NCT01275222 (C), NCT00510354 (C), NCT02071862 (R)
	mTOR inhibitors: temsirolimus (Torisel)	NCT00700258 (R)
Cell cycle inhibitors	Alvocidib (Flavopiridol)	NCT00098579 (C)
Insulin-like growth factor pathway inhibitors	OSI-906	NCT01560260 (C)[61]

R: Recruiting; T: Terminated; C: Completed; A: Active, not recruiting; U: Unknown. PDGFRA: Platelet-derived growth factor receptor alpha.

CURRENT RESEARCH IN GISTs

The emergence of TKI-resistant GISTs has led to further research in understanding of this treatment failure and the alternative signaling mechanism conferring GIST survival. The research to find new drugs, particularly targeted therapy, is being evaluated.

Agaram *et al*[15] found that *BRAF* mutations appear to be associated with a higher malignant risk and resistance to TKI compared to *KIT* and *PDGFRA* mutations. Kinase inhibitors targeting BRAF may be considered as an effective therapeutic option in this GISTs subset. Falchook *et al*[35] published the first report on BRAF inhibitor, dabrafenib (GSK2118436), which showed prolonged anti-tumor activity in V600E *BRAF*-mutated GIST patients. There is presently no trial in GISTs looking at BRAF inhibitors.

In a phase Ⅱ trial study of heat shock protein (HSP)90 inhibitor, BIIB021, given to patients with GISTs refractory to imatinib and sunitinib, promising response was shown[36]. This result encourages future development of HSP90 inhibitors in TKI-resistant GISTs. A next phase study evaluating BIIB021 in GISTs is therefore warranted.

Testing for germline mutations in *SDH* is presently recommended for patients with GISTs lacking mutations in *KIT*, *PDGFRA* and *BRAF*[37]. There is an ongoing phase Ⅱ trial of vandetanib in children and adults with "wild-type" GISTs but it is currently not recruiting participants and the estimated study conclusion will be available in 2023[38]. Another study currently recruiting participants is the glutamine inhibitor CB-839 trial in solid tumors including SDH-deficient GISTs[39].

Ran *et al*[40] recently reported the combined inhibition of mitogen activated kinase (MAPK) and KIT signaling synergistically destabilizes the transcription factor called ETV1 and suppresses GIST growth. The combination of MAPK inhibitors and TKIs to target ETV1 may provide an effective therapeutic strategy in GISTs clinical management. There is currently a trial recruiting participants to study MEK162 in combination with imatinib in patients with untreated advanced GISTs[41].

In another emerging target category, Falkenhorst *et al*[42] discovered inhibitor of apoptosis proteins (IAPs) such as XIAP and survivin are commonly dysregulated in GISTs. Future study to assess the combination of imatinib with an IAP antagonist such as YM155 to enhance the pro-apoptotic activity in GISTs is therefore needed.

There was a clinical trial study looking at the role of immunotherapy by combining pegylated-interferon α-2b with imatinib for treatment of stage Ⅲ/Ⅳ GISTs that yielded highly promising clinical outcomes. The trial was terminated early in 2012 in preparation for a larger future trial[43]. Table 4 summarizes the potential treatment targets in GISTs under clinical trials. The trials' information was obtained from https://clinicaltrials.gov/ct2/home online.

CURRENT TREATMENT GUIDELINES FOR GISTs

Most countries have their own clinical practice guidelines for GISTs, such as the American National Comprehensive Cancer Network (NCCN) (2010 update), the European Society of Medical Oncology (ESMO) (2012), the French National Federation of Cancer Centers consensus guidelines (in French) (2005),

the Japan Society of Clinical Oncology (2008), the Korean GISTs guidelines (2012 Update), the Canadian Advisory Committee on GISTs statement (2006) and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) (2009)[44-50]. Most recently, the Asian Consensus Guidelines (2016) for the Diagnosis and Management of GISTs was published to promote optimal care for Asian populations[51].

The NCCN task force report update on GISTs management is quite comprehensive and detailed, and covers over 41 pages. It described the epidemiology from the Surveillance, Epidemiology and End Results data from the National Cancer Institute, the clinical presentation, the pathology and differential diagnosis using immunohistochemistry and gene expression profiling, the recommendations for diagnosing GISTs, the significance of *KIT* and *PDGFRA* mutation status, the recommendations for mutational analysis, the management of adult *vs* pediatric patients with GISTs, the principles of surgery for GISTs, the need for multidisciplinary management for primary, recurrent or metastatic GISTs and the imaging of GISTs[44].

The ESMO clinical practice guidelines on GISTs describes the incidence of GISTs in Europe, the strategy to diagnose GISTs, the stage classification and risk assessment (does not recommend TNM classification), the staging procedure using CT, MRI and FDG-PET scan, the treatment planning involving multidisciplinary team for localized and metastatic disease, the response evaluation and optimal follow-up for different risk categories[45].

In the Asian consensus guidelines for diagnosis and management of GISTs, some points were highlighted. Firstly, it recommends the minimal 3-year treatment with imatinib before and after surgery for high-risk GISTs. Secondly, it recommends early evaluation of tumor response after 1 mo of neoadjuvant imatinib treatment, when genotyping is not feasible for primary gastric GISTs. Thirdly, it suggested a prospective study on the feasibility and efficacy of high-dose imatinib therapy in Asian patients. Lastly, it recommends imatinib rechallenge instead of discontinuing TKI treatment if third-line regorafenib is not available or failed[51].

In summary of these published treatment guidelines, the general consensus is complete surgical resection of GISTs as the first step when possible. Surgery is potentially curative for primary GISTs that have not metastasized and the probability of recurrence will depend on the malignant potential risk stratification criteria.

GIST cases that are initially inoperable may be given neoadjuvant therapy with the first-line TKI imatinib to improve resectability. Following complete removal of primary GISTs, patients with a higher risk of tumor recurrence may consider adjuvant therapy with first-line TKI. Patients with metastatic GIST disease, even if removed, will benefit from TKI to maintain disease control.

For patients with imatinib-resistant GISTs, sunitinib is a second-line drug treatment whilst regorafenib is the third-line drug for imatinib- or sunitinib-resistant GISTs. Some drugs approved for other conditions may be prescribed off-label for GISTs at a physician's discretion but with a caveat, and clinicians are advised to follow the local guidelines. New molecular targeted drugs are being tested in many clinical trials and some are still under development. An algorithm for the management of GISTs based on the summary of current guidelines is included (Figure 7).

PROGNOSIS

Data from pooled analysis of 2560 patients diagnosed with operable GISTs who were not given adjuvant therapy gave the estimated 15-year recurrence-free survival after surgery at 59.9%[52]. Whilst in a trial previously alluded to with resected GISTs deemed high risk were subsequently treated with imatinib showed the 5-year overall survival rate of 83%[24]. In a different follow-up study to assess the long-term survival of 695 patients with metastatic GISTs who were treated with imatinib, the estimated 10-year overall survival is 23%[53].

There was an interesting Dutch study which highlighted that severe fatigue occurred in 30% of patients with GISTs and in 33% of patients with GISTs who took TKIs. The disabling fatigue was associated with psychological distress and physical function[54]. In another survey study, the long term functional outcomes of laparoscopic resection of gastric GISTs were investigated by utilizing the Gastrointestinal Quality of Life Index (GIQLI). Most patients reported no change in symptoms and the GIQLI scores were within the normal range, with minimal effect on long-term quality of life[55].

FUTURE GIST TREATMENT TRENDS

About 5 years ago, Dematteo[56] proposed a concept of personalized therapy for GISTs. With accumulating research data in biology, such as genetic mutations and adjuvant or neoadjuvant therapy with systemic drugs, it is considered true that personalized assessment and therapy may appear to be the future trend for GIST management.

Complete surgical resection of GISTs is the gold standard of primary treatment when possible, with or without the adjunct of molecular targeted drug therapy. Through the understanding of the mutations of GISTs and addressing treatment resistance with TKIs, new treatment ideas such as combination trials of TKI plus other drugs, TKI plus surgery in specified sequences, newer line TKIs, inhibitors of BRAF, HSP inhibitors, inhibitors of downstream pathways such as MAPK, IAP inhibitors and immunotherapy may play

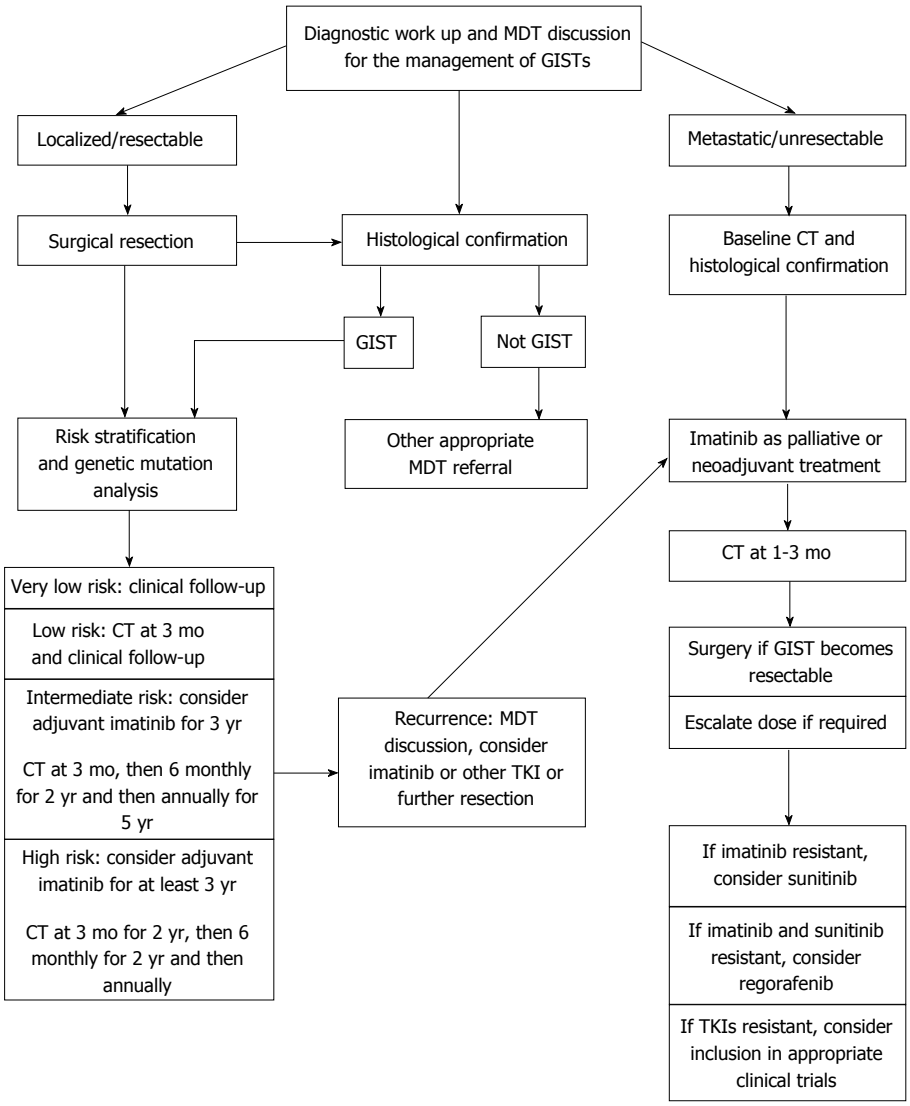

Figure 7 Algorithm for the management of gastrointestinal stromal tumors. GIST: Gastrointestinal stromal tumor; CT: Computed tomography; TKI: Tyrosine kinase inhibitor.

important roles as molecular targeted therapy in the future.

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