

REVIEW

Gastrointestinal Stromal Tumors: Current Management

PETER W.T. PISTERS, MD^{1*} AND SHREYASKUMAR R. PATEL, MD²¹Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas²Department of Sarcoma Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Herein, we review the current management of localized and advanced gastrointestinal stromal tumors (GISTs). Although surgery remains the standard of care for patients with localized GIST, adjuvant imatinib can delay recurrence in some of these patients. In patients with advanced or metastatic disease, the standard of care is imatinib and surgery of residual masses is an option. Preoperative imatinib is an emerging treatment option for patients who require cytoreductive therapy. Sunitinib is a standard second-line therapy.

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KEY WORDS: gastrointestinal stromal tumors; GIST; imatinib; sunitinib; adjuvant; neoadjuvant

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and affect 5,000–6,000 individuals each year in the United States [1]. GISTs occur throughout the GI tract, from the lower esophagus to the anus but are found most commonly in the stomach (60%), followed by the jejunum and ileum (30%), duodenum (5%), and colorectum (<5%) [2]. Some GISTs are more malignant than others, but it is considered that all GISTs have some malignant potential. However, microscopic GISTs (micro-GISTs) usually found in upper regions of the stomach have little or no malignant potential [3,4].

Management strategies for patients with GISTs have evolved significantly in the past decade. Prior to 2002, surgical resection was the only known potentially curative treatment for patients with localized GISTs, and no adjuvant therapies were available. At that time, patients with metastatic disease had no effective therapeutic options. The availability of the first tyrosine kinase inhibitor, imatinib mesylate (STI-571; Glivec/Gleevec, Novartis Pharmaceuticals, Basel, Switzerland), revolutionized the management of GISTs.

GISTs are characterized by high immunoreactivity to the tyrosine kinase receptor KIT (CD117) [2]. Approximately 80–95% of GISTs harbor mutations in the *KIT* gene [5,6], and 5% have gain-of-function mutations in the *platelet-derived growth factor receptor-alpha* (*PDGFR-α*) gene [7]. Gain-of-function mutations in these activate downstream signaling pathways that result in increased proliferation and decreased apoptosis, ultimately resulting in aberrant growth and neoplasia [2].

Imatinib mesylate, a KIT and PDGFR- α inhibitor, is now the standard of care for patients with locally unresectable or metastatic GIST and was recently approved for its use in the adjuvant therapy setting in the United States and Europe [8,9]. Another tyrosine kinase inhibitor, sunitinib malate (SU11248; Sutent, Pfizer, Inc., New York, NY), has been approved as a second-line treatment for GIST patients who do not respond to or cannot tolerate imatinib. Newer agents are currently being evaluated in clinical trials. This review will discuss current treatment options for patients with locally resectable and locally advanced or metastatic GIST (Fig. 1).

PROGNOSTIC AND PREDICTIVE FACTORS

Surgical resection is the standard treatment for patients with localized, resectable GISTs. However, surgery does not always result in a cure, making evaluation of the risk of relapse essential in determining the future prognosis of patients and tailoring treatment regimens.

According to the 2002 U.S. National Institutes of Health (NIH) consensus criteria, the most relevant factors for risk stratification after resection of localized GISTs are tumor size and mitotic index [1]. More recently, evaluations of more than 1,600 patients from the Armed Forces Institute of Pathology expanded the prognostic criteria in patients with localized GIST to include tumor site, reflecting the fact that gastric GISTs are less aggressive than intestinal GISTs of the same size [2]. Another study confirmed these criteria and found that tumor size, mitotic rate, and tumor location were independent predictors of recurrence following complete resection of primary GIST [10]. Thus, it was suggested that the NIH consensus criteria be changed to include tumor location and tumor rupture during surgery as additional prognostic factors (Table I) [3].

Mutations in *KIT* and *PDGFR-α* have also been shown to have prognostic significance in GISTs. GISTs with mutations in the *KIT* or *PDGFR-α* genes have poorer prognoses than those with wild-type genes. GISTs harboring *KIT* mutations are more aggressive and have even a poorer prognosis than those with *PDGFR-α* mutations. Early

Abbreviations: GIST, gastrointestinal stromal tumor; PDGFR, platelet-derived growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival.

*Correspondence to: Dr. Peter W.T. Pisters, MD, Department of Surgical Oncology, Unit 444, The University of Texas M. D. Anderson Cancer Center, P.O. Box 301402, Houston, TX 77230-1402. Fax: 713-792-7829. E-mail: ppisters@mdanderson.org

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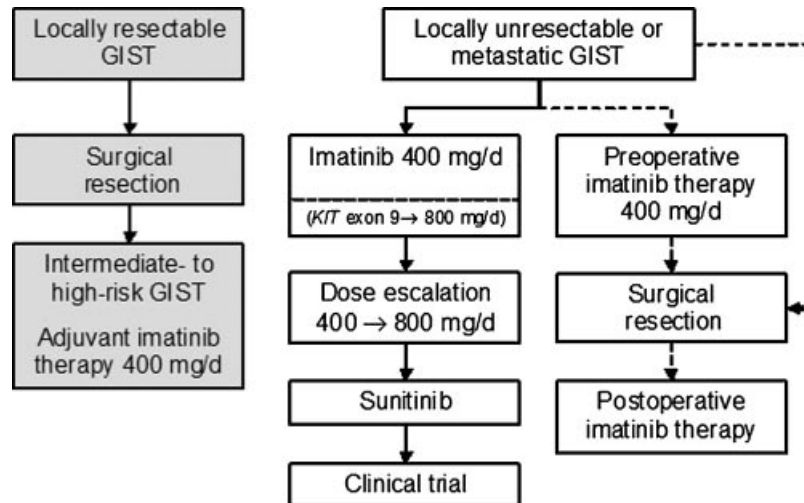


Fig. 1. Management of locally resectable versus advanced GISTs.

studies correlated *KIT* exon 11 mutations with malignancy [11–13], but other studies have shown that such ubiquitous mutations can be found in highly malignant and less malignant tumors [14,15]. Regardless, clinical outcome may correlate with certain types of *KIT* exon 11 mutations. For instance, *KIT* exon 11 deletions in gastric GISTs—but not GISTs of the small intestine—are associated with a more malignant behavior than those with single nucleotide substitutions [16–18]. Also, both gastric and small intestinal GISTs with homozygous *KIT* exon 11 mutations are almost always malignant [19]. *KIT* exon 9 mutations, originally associated with an aggressive phenotype, were subsequently found not to have a significantly different effect on clinical outcome than *KIT* exon 11 mutations in small intestine GISTs [11,18]. In contrast to gastric *KIT* exon 17 mutations, *KIT* exon 13 mutations, although relatively rare, appear to increase the aggressiveness of gastric GISTs. In addition, small intestine GISTs with *KIT* exon 13 or 17 mutation were not more aggressive than other mutations in that site [20].

Mutations in *KIT* and *PDGFR-α* are also predictive of response to imatinib treatment in GIST patients with locally advanced or metastatic disease. Patients with *KIT* exon 11 mutations (point mutations or deletions) had a greater likelihood of achieving a partial response (PR) to imatinib (83.5%) than did patients with *KIT* exon 9 mutations (47.8%; $P=0.0006$) or no detectable *KIT* or *PDGFR-α* mutations (0%; $P < 0.0001$) [7]. Furthermore, a logistical

regression analysis showed that *KIT* exon 11 mutations were the strongest predictor of response to imatinib (hazard ratio: 7.85; 95% confidence interval [CI]: 3.55–17.37) [7]. In another study, GIST patients with *KIT* exon 11 mutations had longer progression-free survival (PFS) and overall survival (OS) than did patients with *KIT* exon 9 mutations, with a relative risk increase of 190% and 171% for PFS and OS, respectively ($P < 0.0001$ for both endpoints); and 108% ($P < 0.0001$) and 76% ($P = 0.028$) for PFS and OS, respectively, when patients with exon 11 mutations are compared to those with no detectable mutations [21].

In unresectable or metastatic disease, prognostic factors that correlated with short PFS by multivariate analysis include performance status of 2–3 ($P < 0.0001$) and high baseline absolute neutrophil counts ($P = 0.0008$) [22]. Prognostic factors that correlated with short OS by multivariate analysis in unresectable or metastatic patients include *KIT* exon 9 genotype, wild-type genotype, performance status of 2–3, increased absolute neutrophil count, and low hemoglobin [23]. In locally advanced or metastatic GIST, parameters associated with initial resistance to imatinib (within 3 months of randomization) include presence of lung and absence of liver metastases, low hemoglobin level, and high granulocyte count; and factors that predict late resistance to imatinib (>3 months from randomization) include high baseline granulocyte count, primary tumor outside of the stomach, large tumor size, and low initial imatinib dose [24].

TABLE I. Modified Consensus Classification for Selecting Patients With GISTs for Adjuvant Therapy

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1–5.0	≤5	Any
Intermediate risk	2.1–5.0	>5	Gastric
	<5.0	6–10	Any
High risk	5.1–10.0	≤5	Gastric
	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1–5.0	>5	Non-gastric
	5.1–10.0	≤5	Non-gastric

HPFs, high-power fields. Adapted from Ref. [3], Table IV.

TREATMENT OF LOCALIZED DISEASE

Surgery

Table II summarizes the guidelines for the surgical management of localized GISTs at various locations. Successful surgical resection of GISTs should take into consideration tumor location and should be tailored accordingly [25]. Although surgery is the only known potentially curative treatment for primary resectable or marginally resectable GISTs [25,26], 40–90% of surgically treated patients experience disease recurrence [27]. In a study conducted by DeMatteo and colleagues, patients with completely resected primary GISTs had a disease-specific survival rate of 54% at 5 years and a median OS of 66 months. On multivariate analysis, only tumor size (>10cm) significantly influenced disease-specific survival, with a relative risk of 2.5 (CI: 1.2–5.5; $P = 0.01$) [28]. A more recent series of 127 patients with localized GISTs who underwent complete resection

TABLE II. Surgical Guidelines for the Management of GISTs

Location	Type of tumor	Surgical technique(s)	Considerations
Esophagus	<2 cm	Local resection if negative margins can be obtained	Surgical enucleation is inappropriate
	Large tumors and tumors close to the esophagogastric junction	Esophagectomy	Preoperative differentiation of GIST from leiomyoma
	High-risk tumors and distal lesions	Merendino procedure (vagotomiesparing segmental esophageal resection, jejunal interposition, and gastric preservation)	Biopsies obtained through endoscopic ultrasonography-guided fine-needle aspiration
Stomach	Gastric intramural tumors <2 cm	Active surveillance, laparoscopic wedge resection	Dual laparoscopic–endoscopic approach can facilitate tumor localization and circumferential dissection of both mucosal and submucosal layers around the lesion
	Small tumors of the esophagogastric junction	Limited resection using a “cut and sew” technique and reconstruction over an esophageal bougie	Obtain spiral computed tomogram and barium upper gastrointestinal X-ray prior to laparoscopy
	Locally advanced tumors of the esophagogastric junction	Esophagegastrectomy	Tumors <3 cm can be approached by combined endoscopy and laparoscopy using 2 or 3 intragastric trocars— <i>experimental</i>
	Tumors from the greater curvature and fundus	Laparoscopic wedge resection	Locally advanced patients might benefit from neoadjuvant imatinib therapy
Duodenum	Tumors of the antrum (prepyloric)	Distal gastrectomy	Staple line should be oriented longitudinally with the axis of the stomach to avoid luminal narrowing
	Tumors from the antrum >10 cm	Gastrectomy or local excision	GISTs located on the posterior wall of the stomach can be excised using a transgastric approach— <i>experimental</i>
	<1 cm located more than 2 cm away from ampulla of Vater >3 cm located on D3/D4	Wedge resection	Stapled wedge resection of tumors >3 cm has a risk of gastric outlet stenosis
Small bowel	Large tumors of D1/D2 and periampullary GISTs	Segmental duodenectomy Pancreaticoduodenectomy	—
	—	Sequential resection without node dissection	Laparoscopic resection may be feasible for small tumors
Colon	—	Segmental colectomy without lymph node dissection	Colonic GISTs must be distinguished from leiomyomas originating from the muscularis mucosae (benign)
Rectum	<3 cm with a limited extrarectal component	Transanal excision	Total mesorectal excision not needed
	>5 cm growing outside the rectum	Anterior or posterior resection	A transvaginal approach can be used in women with GISTs located on the anterior wall of the lower rectum

reported a 5-year RFS rate of 63%. By multivariate analysis, tumor size ≥ 10 cm, mitotic rate ≥ 5 per 50 high-power fields (HPF), and tumor location in the small intestine were all independently associated with an increased risk of recurrence [10].

Adjuvant Therapy

The remarkable efficacy of imatinib in treating metastatic GISTs prompted interest in the agent's deployment as an adjuvant after complete resection of GISTs. Preliminary results from the open-label phase II American College of Surgeons Oncology Group (ACOSOG) Z9000 study have been encouraging. Patients (n = 107) who underwent complete resection of high-risk primary GISTs (>10 cm, tumor rupture, or <5 peritoneal metastases) and were treated with adjuvant

imatinib (400 mg/day) for 1 year had 1-, 2-, and 3-year OS rates of 99%, 97%, and 97%, respectively. Moreover, the 1-, 2-, and 3-year recurrence-free survival (RFS) rates were 94%, 73%, and 61%, respectively. Both sets of survival rates compared favorably with data from historical controls [29].

Recent results from the ACOSOG Z9001 trial also provided encouraging data on imatinib as an adjuvant therapy. This phase III randomized trial involved 778 patients with localized GISTs who underwent complete surgical resection followed by 1 year of imatinib (400 mg/day) or placebo. Adjuvant imatinib significantly improved the 1-year RFS compared with the placebo (98% vs. 83%; $P < 0.0001$) [30]. Furthermore, adjuvant imatinib showed a significant improvement in RFS in all tumor size stratification groups; in fact, the greatest difference between the treatment and placebo arms was observed in

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high-risk patients (tumor size ≥ 10 cm) who obtain $>50\%$ benefit at 2 years with adjuvant therapy ($P < 0.0001$). However, OS rates in the imatinib and placebo groups were the same, possibly because of the relatively short patient follow-up period and a crossover design that permitted patients in the placebo arm who developed recurrence to be treated with imatinib (as it is the standard of care for recurrent disease). Imatinib at 400 mg/day was safe and well tolerated when administered in the adjuvant therapy setting and resulted in a low rate of serious adverse events (Fig. 1).

Based on results from the ACOSOG Z9001 trial, imatinib was recently approved as adjuvant therapy for GISTs by the U.S. Federal Drug Administration (FDA) and by the European Medicines Agency (EMA). The most recent management guidelines in the United States (National Comprehensive Cancer Network [NCCN]) and Europe (European Society for Medical Oncology [ESMO]) recommend adjuvant imatinib for at least 1 year following complete resection in patients with intermediate- to high-risk GIST (Table III) [31,32]. However, the optimal duration of adjuvant therapy has not been

TABLE III. Management Recommendations for Patients With GISTs: NCCN and ESMO 2009 Guidelines

Type of disease	Management	Management guidelines	
		NCCN [31]	ESMO [32]
Locally resectable GIST	Surgical resection	GISTs should be handled with care to avoid tumor rupture. The goal is to achieve complete gross resection with an intact pseudo-capsule	Standard treatment of localized GIST is complete surgical excision, without dissection of clinically negative lymph nodes A laparoscopic approach is discouraged in patients who have large tumors R0 excision is the goal. If R1 excision, re-excision may be a choice provided no major sequelae are foreseen
	Pathologic assessment	Pathologic assessment of biopsies and resection specimens should include size, location, and mitotic rate Consider <i>KIT</i> and <i>PDGFR-α</i> mutation assay for CD117-negative tumors	Pathologic diagnosis relies on morphology and CD117 positivity Mutational analysis is strongly recommended in the diagnostic work-up of all GIST
	Adjuvant imatinib therapy	Adjuvant imatinib (400 mg/day) therapy for at least 12 months should be considered in patients with intermediate- to high-risk GIST The optimal duration has not yet been determined Patients at higher risk for disease may justify a longer course of therapy	Adjuvant imatinib therapy is an option for those patients with a substantial risk of relapse Therapy should be given for 1 year
Locally unresectable or metastatic GIST	Pathologic assessment	Pathologic assessment of biopsies and resection specimens should include size, location, and mitotic rate Consider <i>KIT</i> and <i>PDGFR-α</i> mutation assay for CD117-negative tumors	Biopsy of the metastatic focus is sufficient and laparotomy for diagnostic purposes is not required Pathologic diagnosis relies on morphology and CD117 positivity Mutational analysis is strongly recommended in the diagnostic work-up of all GIST
	Surgical resection	—	Surgery of metastatic responding patients is considered investigational
	First-line treatment	Suggested starting dose is 400 mg/day If <i>KIT</i> exon 9 positive start at 800 mg/day	Imatinib 400 mg/day is standard treatment Imatinib 800 mg/day is the standard treatment in patients with <i>KIT</i> exon 9 mutations Treatment should be continued indefinitely
	Second-line treatment	If limited progression and resection is feasible, consider resection of progressing lesion(s) Imatinib dose increase up to 800 mg/day may be considered, as clinically tolerated If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then sunitinib should be considered	In case of tumor progression with imatinib 400 mg/day, dose escalation to 800 mg/day is the standard approach In case of progression or intolerance on imatinib, second-line standard treatment is sunitinib
	Third-line treatment	If patient is no longer receiving clinical benefit from sunitinib or imatinib, strongly consider clinical trial, or other options, or discontinuation of anticancer therapy	After failing on sunitinib, the patient should be considered for participation in a clinical trial of new therapies or new combinations Surgical excision may be a palliative option if limited progression
	Neoadjuvant therapy	Recommended if surgical morbidity would be improved by reducing the size of the tumor preoperatively Biopsy is necessary when planning neoadjuvant therapy	Recommended in the case that R0 surgery is not feasible, or that it might be achieved through less mutilating surgery in the case of cytoreduction, or that it might reduce the risk of bleeding and tumor rupture Generally given for 6–12 months Mutational analysis may help to exclude imatinib-resistant mutations from therapy

determined. Ongoing phase III clinical trials in Europe, namely SSGXVIII/AIO by the Scandinavian Sarcoma Group and Sarcoma Group of the AIO multicenter, and European Organization for Research and Treatment of Cancer (EORTC) 62024, will address questions such as duration of adjuvant imatinib treatment in patients with high-risk disease, and whether adjuvant imatinib therapy improves OS [33].

MANAGEMENT OF LOCALIZED UNRESECTABLE OR METASTATIC GISTS

Surgery

Prior to the introduction of imatinib, all GIST patients, including those with metastases, were considered candidates for surgery. However, patients with metastases were less likely to undergo complete resection and consequently had earlier recurrences than patients with localized disease [28]. In a study of 200 patients with localized and metastatic GISTs, complete resection was achieved in 30% of patients with metastasis compared with 86% of patients with localized disease. Moreover, the median disease-specific survival was 19 and 60 months in patients with metastatic and localized disease, respectively [28].

A study at the National Cancer Center Hospital in Japan evaluated the outcome of surgical resection in 18 patients with liver metastases from GISTs [34]. Complete resection of liver metastases was achieved in 15 patients (83%), and the 3- and 5-year posthepatectomy OS rates were 64% and 34%, respectively. However, following hepatectomy, a high proportion of patients experienced recurrence (94%) in the remnant liver and in other organs. Therefore, surgical intervention for metastatic GISTs is only palliative [34].

Although complete resection of residual metastatic GISTs has been related to good prognosis in patients responding to imatinib, the ESMO guidelines establish that surgery of metastatic disease remains investigational (Table III) [32].

Imatinib

Several studies have demonstrated unprecedented increases in survival achieved with imatinib in patients with advanced GISTs compared with historical controls. Before imatinib was introduced, the median disease-specific survival of GIST patients with metastatic disease was approximately 20 months [28]. In contrast, a large clinical study of imatinib for unresectable or metastatic GISTs have reported a median OS of up to 57 months, representing an almost threefold increase in OS [35]. Nowadays, imatinib 400 mg/day is the standard of care for patients with locally advanced, recurrent, or metastatic disease (Fig. 1) [31,32].

In the randomized, open-label U.S.–Finland B2222 study, more than half of the patients with advanced disease had a sustained response to imatinib at doses of 400 or 600 mg/day [36]. Although no patient had a complete response (CR) with a follow-up of more than 9 months, 79 (53.7%) of 147 patients had a PR. In addition, treatment with imatinib resulted in a reduction of tumor size by 50–96% in patients who experienced a PR. With a longer follow-up of up to 71 months, 2 patients (1.4%) achieved a CR and 98 patients (66.7%) had a PR, for an overall objective response rate of 68.1% (95% CI: 59.8–75.5%) [35]. The median time to progression was 24 months, and the estimated median OS was 57 months. However, the response rates were not affected by the doses of imatinib tested.

The effectiveness of imatinib was confirmed in two large phase III trials involving patients who were randomized to receive either standard- (400 mg/day) or high-dose (800 mg/day) imatinib [22,37]. The North American S0033 trial enrolled 746 patients with unresectable or metastatic GISTs. With a median follow-up of

4.5 years, the median PFS was 18 months for patients receiving standard-dose imatinib and 20 months for those receiving high-dose imatinib ($P = 0.13$). The median OS was 55 and 51 months in patients receiving 400 and 800 mg/day, respectively [22]. Both treatment regimens were well tolerated, but more grade 3 or higher adverse events were observed in the high-dose arm.

The EORTC 62005 study enrolled 946 patients with advanced or metastatic KIT-positive GISTs [37]. With a median follow-up of approximately 25 months, patients in the high-dose arm experienced a significantly longer PFS than those in the standard-dose arm. However, with a longer median follow-up (40 months), no difference in PFS was seen between the dose levels, and the two groups combined had a median PFS of 22 months and a 3-year PFS rate of 33% [38].

In both the S0033 and EORTC 62005 studies, patients who were initially assigned to the 400 mg/day arm were permitted to cross over to high-dose imatinib if disease progression occurred. In the S0033 study, of the 117 assessable patients who crossed over, 3 (2.5%) achieved a CR and 33 (28%) had stable disease (SD) [22]. Results among the 133 crossover patients in the EORTC 62005 study were similar, with 3 patients (2%) experiencing PR and 36 (27%) having SD [39]. These data suggest that patients with progressive disease (PD) may derive a clinical benefit from dose escalation.

Mutational analysis of GISTs in the S0033 and EORTC 62005 studies showed that patients who received standard-dose imatinib and whose tumors harbored *KIT* exon 11 mutations had a higher response rate and longer median OS duration than patients with other mutations [21,23]. Conversely, patients with *KIT* exon 9 mutations had a better response to high-dose imatinib than did those with other mutations [21]. MetaGIST, a meta-analysis that combined data of 1,640 patients from these studies (S0033 and 62005), showed that high-dose imatinib was associated with a small but statistically significant improvement in PFS compared with the standard dose (median PFS, 19 months vs. 23 months for 400 and 800 mg/day, respectively), especially among patients with *KIT* exon 9 mutations (median PFS, 6 months vs. 19 months for 400 and 800 mg/day, respectively) [40].

In fact, these results spurred the NCCN and ESMO guidelines to recommend imatinib dose escalation to 800 mg/day in patients with advanced GIST who experience disease progression while receiving 400 mg/day of imatinib [31,32]. The NCCN and ESMO guidelines emphasize confirming adherence to treatment before increasing the dose in response to apparent disease progression. Based on mutational analysis data, both sets of guidelines recommend that patients with *KIT* exon 9 mutations begin imatinib treatment at 800 mg/day (Table III) [21,31,32,40].

Imatinib Combined With Surgery

Some patients with localized unresectable or metastatic GISTs may be candidates for surgery after response to imatinib treatment or a period of disease stabilization (Fig. 1). Surgical resection has been achieved in cases of previously unresectable disease following 3–12 months of imatinib therapy [41–44]. The timing of the surgical procedure is critical; resection should be performed once the maximum benefit from imatinib has been achieved but before tumor progression occurs.

Raut et al. [45] assessed outcomes in 69 patients who underwent surgery for unresectable primary disease or metastatic disease following treatment with kinase inhibitors. The outcome of resection was significantly associated with disease status at the time of surgery ($P < 0.0001$). The 1-year PFS rates were 80%, 33%, and 0% for patients with SD, limited PD (majority of disease stable or responding, and in which all sites of disease progression could be resected), and generalized PD (metastatic GIST in which complete resection of all progressing sites would not be possible), respectively ($P < 0.0001$). The 1-year OS rates were 95% and 86% for patients with SD and

limited PD, respectively ($P < 0.0001$), while all patients with generalized PD died within 1 year of surgery. This study showed that although surgery may extend the benefits of first-line therapy with imatinib in patients with SD or limited PD, surgery has no benefit in patients with generalized PD [45].

DeMatteo and colleagues found that 39 of 40 patients with metastatic GISTs achieved a PR or SD after imatinib therapy enabling those patients to undergo surgical resection after a median of 15 months. After resection, 20 patients with imatinib-responsive disease had a 2-year OS rate of 100%, compared with 36% in 13 patients with focal resistance to imatinib (one tumor growing) [46]. Similarly, Gronchi and colleagues showed that advanced and/or metastatic patients responsive to imatinib had a postsurgery 2-year disease-specific survival rate of 100% and a 1-year PFS rate of 96%, compared with a 2-year disease-specific survival rate of 60% and 1-year PFS rate of 0% in patients with PD (median follow-up, 29 and 12 months, respectively). Furthermore, all patients with bulky primary GIST who received cytoreductive treatment were alive and without evidence of disease at a median follow-up of 21 months [47].

Various studies have sought to combine the benefit of neoadjuvant imatinib with that of adjuvant imatinib. The French Sarcoma Group's BFR14 study included a subgroup of 36 patients with advanced GIST who underwent surgery of residual masses after starting imatinib therapy, with all patients continuing therapy after surgery. Patients with an objective response or SD experienced fewer recurrences postsurgery (5 of 25 patients) than those with PD (10 of 10). In addition, the 2-year PFS rate was 93% among responding patients who had resection with microscopically negative margins or microscopically positive but grossly negative margins, 45% in patients who had resection with grossly positive margins, and 50% in patients who did not undergo surgery [48].

Two other studies recently evaluated the use of imatinib (600 mg/day) as neoadjuvant and adjuvant therapy in patients with primary or metastatic GISTs [49,50]. The Radiation Therapy Oncology Group 0132/ACRIN 6665 trial allocated patients to receive neoadjuvant imatinib in patients with primary GIST or preoperative imatinib in patients with operable metastatic GIST for 8–12 weeks, followed by surgical resection and postoperative imatinib for a prospective 2 years. Early results showed that the 2-year PFS rates were 82.7% and 77.3%, and the 2-year OS rates were 93.3% and 90.9% in patients with primary and metastatic disease, respectively, with a median follow-up of 3 years [49]. The other study, by McAuliffe et al., allocated 19 patients (13 with primary GIST and no metastasis, 2 with primary GIST and metastasis, 1 with local recurrence with metastasis, and 3 with metastatic recurrence) to receive preoperative (neoadjuvant) imatinib for 3, 5, or 7 days and postoperative (adjuvant) imatinib for 2 years. Although cytoreduction was not observed in such short period

of neoadjuvant therapy, imatinib decreased tumor blood flow (dCT) and increased apoptosis within 3–7 days of starting therapy as evidenced by pre- and postimatinib tumor tissue. On the other hand, postoperative imatinib improved disease-free survival (DFS): the 1- and 2-year DFS rates were 94% and 87%, respectively. In addition, patients with larger tumors had shorter DFS ($P = 0.02$); therefore, these patients are likely to benefit from longer adjuvant therapy [50].

The NCCN guidelines state that patients with marginally resectable GISTs, as well as patients with resectable GISTs who have a high risk of surgical morbidity, should first receive treatment with imatinib. These patients should be monitored closely for rapid progression, which may lead to unresectability. A patient who is stable and responding should continue to receive imatinib until the maximum response is achieved (3–6 months), and then undergo surgery if it is safe. If there is evidence of disease progression, imatinib should be discontinued and surgery performed; imatinib can be restarted following surgery once the patient is able to tolerate oral medications [31]. The ESMO guidelines recommend neoadjuvant imatinib in patients with locally advanced GISTs when resection with microscopically negative margins is not possible or would be too “mutilating” but might become possible or less mutilating following cytoreduction. In addition, a surgeon may recommend neoadjuvant imatinib to reduce the risks of surgery. Once maximum response is achieved (6–12 months), surgery can be performed (Table III) [32].

RESPONSE ASSESSMENT IN GIST

Imaging examination is essential to detect recurrence or progression of patients who have undergone surgical resection of localized GIST or metastatic GIST patients who have been treated with imatinib therapy, in addition to patients who have undergone cytoreductive therapy with imatinib. Radiologic monitoring is aimed at gauging changes in the size, appearance, and density of tumors as an indicator of tumor response to therapy. While tumor shrinkage is evident in a majority of responding patients, some tumors respond to treatment without any measurable decrease in size; such tumors do, however, have a measurable decrease in density [32]. Lack of disease progression following months of therapy should, in fact, be considered evidence of tumor response. Conversely, tumors may progress without a measurable increase in size; in such cases, increased tumor density indicates progression [32].

The Response Evaluation Criteria in Solid Tumors (RECIST) commonly used to assess responses to chemotherapy are based solely on changes in tumor size and thus have been shown to underestimate the response to tyrosine kinase inhibitor treatment [51–53]. Choi and colleagues proposed modified response criteria that consider both tumor size and density to assess response (Table IV). This

TABLE IV. Modified Computed Tomography Response Evaluation Criteria

Response	Definition
Complete response (CR)	Disappearance of all lesions No new lesions
Partial response (PR)	Decrease in size ^a of $\geq 10\%$ or a decrease in tumor density (HU) $\geq 15\%$ on CT No new lesions
Stable disease (SD)	No obvious progression of non-measurable disease Does not meet the criteria for CR, PR, or PD
Progressive disease (PD)	No symptomatic deterioration attributed to tumor progression Increase in tumor size of $\geq 10\%$ and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

HU, Hounsfield unit; CT, computed tomography.

Adapted from Ref. [52], Table III.

^aThe sum of longest diameters of target lesions as defined in RECIST [54].

modified criterion has been shown to predict response more accurately than RECIST and has a better correlation with time to progression [51,52].

The ESMO guidelines indicate that both tumor size and density by CT scan or MRI should be considered as criteria for tumor response [32]. The NCCN guidelines establish that in patients with marginally resectable GIST, as well as resectable GIST with significant risk of morbidity, the therapeutic effect should be assessed after 2–4 weeks of therapy, taking into consideration the use of positron emission tomography (PET). In patients with unresectable, recurrent, or metastatic GIST, response assessment should be performed within 3 months of initiating therapy using CT and PET, but in some patients, imaging prior to 3 months might be required [31].

DISEASE PROGRESSION AND ALTERNATIVE TREATMENTS FOR GISTS

Although treatment with imatinib results in a clinical response in the majority of advanced GIST patients, some patients are initially resistant or develop resistance to imatinib. Primary resistance to imatinib (progression within the first 6 months of therapy) is uncommon but occurs in approximately 10% of patients, mostly those with mutations in *KIT* exon 9 or *PDGFR- α* exon 18. Primary resistance is infrequently associated with secondary mutations. Approximately 67% of GIST patients develop secondary resistance to imatinib (progression after a minimum of 6 months of partial remission or SD) due to the appearance of secondary mutations, mainly in *KIT* exon 11 [55].

Patients who exhibit disease progression while receiving standard-dose imatinib should have their doses escalated to 800 mg/day. If progression recurs after dose escalation, sunitinib is an approved second-line treatment. In situations of focal disease progression, surgical resection may be an option (Fig. 1) [31,32].

Sunitinib

Presently, sunitinib is the only tyrosine kinase inhibitor approved for the treatment of patients with locally advanced or metastatic GISTs who have not responded to prior imatinib therapy. Sunitinib inhibits a number of receptor tyrosine kinases including *KIT*, *PDGFR- α* and $-\beta$, vascular endothelial growth factor receptors 1–3 (*VEGFR₁₋₃*), Fms-like tyrosine kinase-3 (*FLT3*), colony-stimulating factor receptor type 1 (*CSF-1R*), and *RET*. Moreover, sunitinib has activity against some *KIT* mutations that are imatinib resistant [56].

In a pivotal phase III trial, patients with imatinib-resistant GISTs were randomized to receive sunitinib at 50 mg/day or a placebo in 6-week cycles (intermittently 4 weeks on and 2 weeks off). The study was unblinded early, following a planned interim analysis that revealed that patients treated with sunitinib had a significantly longer time to progression than those treated with placebo (27.3 weeks vs. 6.4 weeks, respectively; $P < 0.0001$) [57]. However, this and other studies of sunitinib have shown that sunitinib can cause serious, life-threatening adverse events, including hypertension, cardiotoxicity, and hypothyroidism [58–60].

Both the NCCN and ESMO guidelines recommend sunitinib as a second-line option in patients who experience disease progression while receiving high-dose imatinib or who have life-threatening side effects. If further progression occurs with sunitinib, patients should be considered for enrollment in clinical trials of new agents or new combinations or discontinuation of anti-cancer therapy (Table III) [31,32].

Investigational Therapies

Following the success of imatinib, research has increased substantially to identify other agents with potential efficacy against

GISTs. Nilotinib (AMN107; Tassigna, Novartis Pharmaceuticals) is a second-generation tyrosine kinase inhibitor that targets *KIT*, *PDGFR*, and *BCR-ABL*. In addition, nilotinib has demonstrated activity against imatinib-resistant GIST cell lines [61]. Data from a phase I study in patients with imatinib-resistant GISTs demonstrated promising activity when nilotinib was given alone or in combination with imatinib (mean PFS, 168 and 203 days, respectively) [62]. A retrospective analysis of nilotinib given outside clinical trials (compassionate use) in patients who had not responded to prior imatinib and sunitinib therapy demonstrated objective response in 10% of patients and disease control in 37% of patients. The median PFS was 12 weeks and the median OS was 34 weeks [63].

Sorafenib, a multitargeted tyrosine kinase inhibitor active against *KIT*, *PDGFR- β* , *VEGFR*, and *Raf*, has been shown to inhibit imatinib-resistant *KIT* mutations in vitro [64]. In a phase II trial, 3 of 24 patients resistant to imatinib and sunitinib achieved a PR, and 14 had SD, resulting in a disease control rate (PR + SD) of 71%. The mean PFS was 5.3 months, and the median OS was 13 months. The most common grade 3 and 4 toxicities were hand–foot syndrome (28%), hypertension (24%), rash (20%), and diarrhea (12%) [65].

A number of other agents are at various stages of clinical investigation for efficacy against GISTs. Motesanib (AMG-706), an anti-angiogenic multikinase inhibitor, has shown activity in a phase II study in Japanese patients with advanced GISTs who experienced disease progression or relapsed while receiving imatinib. A preliminary analysis showed PR or SD in 8 of 33 patients, for a clinical benefit rate of 24%. All patients had some treatment-related adverse events [66].

Masitinib (AB1010), a tyrosine kinase inhibitor with activity against *PDGFR* and fibroblast growth factor receptor 3 (*FGFR3*), has greater activity than imatinib against wild-type *KIT*. Preliminary results of a phase II study showed that of 30 imatinib-naïve patients, 7% achieved CR, 43% had PR, and 47% exhibited SD after a median follow-up of approximately 24 months. The median PFS was 27.2 months [67].

A wide number of drugs are currently being evaluated for the treatment of GIST; these include dasatinib (phase II), sorafenib (phase II), vatalanib (phase II), cediranib (phase II), XL820 (phase II), semaxanib (phase II), BIIB021 (phase II), temozolomide (phase II), everolimus (phase II), temsirolimus (phase II), gemcitabine and docetaxel combination (phase II), carboplatin, cisplatin and floxuridine combination (phase II), imatinib plus bevacizumab (phase III), dasatinib plus bevacizumab (phase I), trabectedin (phase II), brostallicin (phase II), alvocidib and doxorubicin combination (phase I), romidepsin (phase II), rubitecan (phase II), sargramostim and 540–548 peptide vaccine combination (phase I), imatinib plus oblimersen (phase II), and octreotide acetate (phase II) [33].

CONCLUSIONS

The management of GISTs has evolved rapidly since imatinib was introduced. Prognostic assessment is a critical part of developing a treatment strategy, which should be planned by a multidisciplinary team of healthcare professionals with expertise in sarcoma. Surgery remains the first-line treatment for patients with resectable primary disease. In patients with locally unresectable, recurrent, or metastatic GISTs, imatinib is the standard of care. Because some GISTs have a high rate of recurrence following surgical resection, adjuvant therapy with imatinib is appropriate after complete surgical resection for high-risk patients, as well as for some intermediate-risk patients. Recently, imatinib was approved as adjuvant therapy for GISTs in the United States and Europe. For patients with locally advanced or metastatic GISTs, in whom complete resection is not possible, the use of neoadjuvant imatinib may contribute to improved outcomes by inducing tumor shrinkage prior to surgery. However, more studies

are required before the clinical benefits of this approach can be clearly determined.

Despite unprecedented results observed with imatinib for metastatic GISTs, disease progression typically occurs within 2 years of treatment initiation, a phenomenon likely due to the development of secondary resistance. In some cases, higher doses of imatinib may be able to overcome resistance. About 15% of patients with metastatic GISTs have primary resistance to imatinib and never respond to imatinib therapy. For patients who have PD or life-threatening adverse events while receiving imatinib, second-line therapy with sunitinib can induce a response. In addition, several promising new agents are currently under investigation for the treatment of GISTs. Evolving treatment strategies and novel agents thus provide a promise for the future of safer agents and improved treatment outcomes.

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