State of the Art in the Treatment of Gastrointestinal Stromal Tumors

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Gastrointestinal stromal tumor · Risk classification · Surgery · Treatment standards · Tyrosine kinase inhibitors

Abstract
Background: Gastrointestinal stromal tumors (GISTs) are the most frequently diagnosed mesenchymal neoplasms of the gastrointestinal tract. Despite their biological and clinical heterogeneity, the majority of these tumors are positive for the receptor tyrosine kinase KIT and are driven by KIT- or platelet-derived growth factor receptor alpha (PDGFRα)-activating mutations. There are still uncertainties regarding their clinical and molecular characterization and the optimal treatment regimens, making it difficult to establish a universal treatment algorithm for these tumors. Summary: From a clinical perspective, the main difference between GISTs and other gastrointestinal neoplasms is that the benign or malignant behavior of GISTs cannot be predicted from histopathology, but instead relies on empirically established scoring systems. Clinical data suggest that malignant potential may be an inherent quality of some GISTs rather than a feature acquired by the tumor during disease progression. Thus, some patients may require prolonged anti-tumor treatment even after complete surgical removal of the tumor. Key Message: Although GISTs are the most frequently occurring mesenchymal neoplasms in the gastrointestinal tract, no universal treatment algorithms exist. This paper reviews the current evidence that guides the management of GISTs. Practical Implications: The management of localized GISTs involves the use of surgical resection, with the inclusion of preoperative tyrosine kinase inhibitor treatment for locally advanced, primarily unresectable tumors and for resectable cases requiring extensive surgery. Imatinib is also indicated as adjuvant therapy after complete surgical removal of GISTs with a high estimated risk of recurrence unless specific mutations conferring imatinib resistance are present. The optimal duration of adjuvant treatment is still controversial. For patients with metastatic imatinib-sensitive GISTs, imatinib constitutes the first-line standard treatment. Molecular characterization of the
tumor (with respect to the PDGFRA and KIT genes) is mandatory prior to imatinib therapy. Sunitinib and regorafenib are established as alternative treatments for patients demonstrating generalized disease progression on imatinib. New tyrosine kinase inhibitors such as ponatinib and crenolanib as well as drugs targeting alternative pathways are currently under investigation. Surgery and locally ablative treatments may be indicated in some metastatic patients.

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Introduction

Historically, the term 'gastrointestinal stromal tumor (GIST)' was used to describe gastrointestinal neoplasms classified as leiomyoma, leiomyosarcoma or leiomyoblastoma by light microscopy, but demonstrating ultrastructural and immunohistochemical features that suggested non-smooth muscular origin of these lesions [1]. When it was discovered in 1998 that virtually all of these tumors were immunohistochemically positive for the receptor tyrosine kinase KIT (CD117) and had mutations in the KIT gene that lead to ligand-independent, constitutive activation of that kinase [2, 3], these characteristics were soon recognized as their principal tumorigenic mechanism. 'GIST' has ever since been used to describe mesenchymal gastrointestinal neoplasms that are KIT-positive and driven by KIT- or platelet-derived growth factor receptor alpha (PDGFRA)-activating mutations, although there remains a small proportion of GISTs that do not demonstrate these properties and for which alternative pathogenetic mechanisms must be assumed. Expression of KIT is also essential for the development of the pacemaker system of gastrointestinal motility formed by the interstitial cells of Cajal, which is why GISTs are thought to derive from pluripotent precursor cells that normally differentiate into interstitial cells of Cajal. From a clinical perspective, GISTs are extremely heterogeneous. They may arise in the entire gastrointestinal tract between the lower esophagus and the anal canal. The principal difference to other gastrointestinal neoplasms is that benign or malignant behavior of GISTs is impossible to predict from histopathology. The spectrum extends between GISTs that remain indolent throughout life without ever requiring a therapeutic intervention and GISTs developing rapid multifocal dissemination in spite of intensified multidisciplinary treatment. So far, therapeutic decisions largely rely on empirically established scoring systems intended to predict the malignancy risk. The medical treatment of GISTs has been revolutionized by the introduction of the tyrosine kinase inhibitor (TKI) imatinib mesylate (Glivec®) [4]; however, most patients develop secondary drug resistance within 2 years after initiation of treatment [5, 6]. Moreover, the molecular characteristics of GISTs may confer differences in imatinib sensitivity. The clinical heterogeneity and complexity of GISTs make it difficult to establish universal treatment algorithms, and the management of these tumors is generally highly individualized, taking into account patient characteristics, morphological and molecular tumor features and clinical behavior of the disease on follow-up exams. This review summarizes the current status of GIST management, specifically focusing on controversial issues in the combined use of local and systemic treatment approaches in individual patients.

Epidemiology

While GISTs were formerly regarded as rare tumors, the definition of histomorphological and immunohistochemical criteria for their diagnosis has made it clear that many neoplasms once classified as smooth muscle cell or nerve sheath tumors by light microscopy are actually GISTs. Today, GISTs are the most frequently diagnosed mesenchymal gastrointestinal tumors,
with a reported annual incidence of 10–20 cases per million [7–9]. These figures probably underestimate the true incidence as subclinical, small gastric GISTs are found in up to 25% of patients in gastrectomy specimens and in autopsy series [10, 11]. Patients aged >50 years predominate among individuals diagnosed with GISTs (median age at diagnosis 60–65 years); however, GISTs may develop at any age. GISTs developing in patients <40 years frequently do not demonstrate activating KIT or PDGFRA mutations; instead, loss-of-function mutations in the succinate dehydrogenase (SDH) complex are found with increased frequency in this population [12, 13]. Clinically and morphologically, these tumors differ from GISTs with KIT or PDGFRA mutations in that they are generally restricted to the stomach, are less responsive to treatment with known TKIs and show a greater propensity for developing lymphovascular invasion and lymph node metastases [14]. Familial GIST syndrome caused by germline mutations in the KIT or PDGFRA gene has been reported [15–17]. Syndromal development of GISTs that are generally negative for KIT- or PDGFRA-activating mutations and preferentially located in the small intestine occurs in patients with neurofibromatosis type 1 (NF-1) [18, 19]. Similar to sporadic GISTs, the true incidence of NF-1-associated GISTs is probably underestimated as they are frequently found in autopsy studies. Clinically, these tumors are also characterized by their poor response to imatinib [18].

**Diagnosis**

The common clinical manifestations of GISTs include gastrointestinal bleeding, abdominal discomfort and ulcer-like symptoms. However, up to 30% of GISTs are asymptomatic and are diagnosed as an incidental finding during endoscopic screening or imaging procedures. In patients presenting with signs of chronic gastrointestinal hemorrhage, upper and lower gastrointestinal endoscopy are usually the initial diagnostic steps. However, small intestinal GISTs may not be amenable to standard endoscopic examination, and advanced endoscopic techniques (double-balloon enteroscopy and/or capsule endoscopy) may be required in these cases [20–23]. For treatment planning purposes, endoscopic assessment of GISTs should be complemented by cross-sectional imaging in all patients. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are both used to evaluate the extent of the primary tumor as well as its relation to adjacent organs and to detect gross metastatic disease. Moreover, CT and MRI imaging criteria have been described to help differentiate GISTs from other gastrointestinal tumors [24, 25] and to estimate their malignant potential [26, 27], although these need to be validated in larger trials.

Unguided endoscopic biopsy of subepithelial masses suspected to be GISTs is successful in yielding a definite diagnosis in only 20–30% of cases. For higher diagnostic accuracy, tissue acquisition for histopathological examination should be performed using endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) [28, 29]. In one study [30], endoscopic ultrasound-guided core needle biopsy was able to yield an accurate histomorphological and immunohistochemical diagnosis in 79 and 97% of cases, respectively, in patients in whom EUS-FNA had previously been unsuccessful. Moreover, obtaining a true tissue sample by core needle biopsy rather than a cluster of cells by FNA may facilitate further treatment planning because a mitotic count, which is crucial for metastatic risk assessment, may not be reliably performed on an FNA specimen. However, the smaller the suspicious lesion, the more difficult it will turn out to acquire adequate tissue for histological examination. For subepithelial gastric lesions <2 cm in diameter, it may therefore be acceptable to perform regular follow-up without a histological diagnosis and to postpone further diagnostic or therapeutic intervention until progression is observed. As discussed above, small, subclinical gastric GISTs are a common finding in gastrectomy specimens and in autopsy series and very likely have no prognostic
relevance. Alternatively, if the location of the lesion is favorable and complete surgical excision is feasible with low morbidity, it may be performed without having obtained a prior tissue diagnosis after discussing the risks and benefits with the patient. Obtaining a histological diagnosis is also not mandatory in larger lesions if upfront surgery is clearly indicated based on imaging findings. If a preoperative tissue diagnosis is required (e.g. if complete removal of the lesion necessitates extensive surgery, if a gastrointestinal lymphoma that should not be treated surgically is suspected, or if preoperative imatinib treatment is discussed), tissue acquisition should also be preferentially performed via the endoluminal route. For lesions not amenable to endoscopic ultrasound-guided biopsy, CT-, MRI- or ultrasound-guided percutaneous biopsy may be an alternative but must be executed with caution to prevent tumor spillage [31, 32].

18 F-fluorodeoxyglucose positron emission tomography (FDG-PET) has a limited role in the primary diagnosis of GISTs. Tracer substances that are specific for GISTs (e.g. radiolabelled antibodies directed against KIT or other surface antigens of GIST cells) have been tested in preclinical models, but none of them has been introduced into clinical use yet [33, 34]. However, FDG-PET plays an important role in situations where early assessment of response to TKI treatment is necessary [35] (see below).

Management of Localized GISTs

Surgery

Complete surgical removal is the mainstay of treatment for localized gastric GISTs >2 cm and for extragastric GISTs of any size. Following surgery, 15-year disease-free survival is 59.9% according to a pooled analysis of 10 population-based series comprising 2,560 patients. Tumor recurrence later than 10 years is extremely rare. Thus, approximately 60% of patients with GISTs are cured by surgery [36]. Controversial data exist as to the issue of the prognostic relevance of surgical margins. While complete, margin-negative (R0) tumor excision remains the goal of GIST surgery and an increased recurrence rate might be expected following resection with tumor-involved margins, this was not confirmed in all studies [37, 38]. Therefore, if examination of the surgical specimen reveals microscopically tumor-positive margins, reoperation should only be attempted if the original site of the involved margin can be identified and its excision does not cause major functional sequelae and is not associated with undue operative risk; however, the paucity of data regarding this issue makes this decision a highly individual one.

Surgical procedures according to tumor site include local gastric wall excision, segmental gastric resection and gastrectomy for gastric GISTs, transhiatal or, rarely, transthoracic lower esophageal resection for esophageal GISTs, segmental resection for small intestinal GISTs, and transanal excision, anterior rectal resection or abdominoperineal rectal excision for rectal GISTs. Multivisceral resections may become necessary in case of involvement of adjacent organs, as can be the case with duodenal GISTs, which may require pancreatoduodenectomy; however, as in all patients requiring major functionally impairing surgery for complete tumor removal, tumor shrinkage through neoadjuvant imatinib treatment should be attempted in these cases to facilitate resection and possibly enable organ-preserving surgery (see below) [39, 40].

As GISTs rarely metastasize into regional lymph nodes [41, 42], systematic lymph node dissection is usually not required. Excision of regional lymph nodes may be considered in patients <40 years who often have SDH-deficient GISTs and are thus more prone to developing lymphovascular invasion and lymph node metastases [14]; however, lymphatic tumor spread was not identified as an adverse prognostic factor in retrospective studies [13]. The
benefit of systematic lymph node dissection in juvenile, SDH-deficient GISTs has never been prospectively evaluated, and lymphadenectomy should only be attempted if it does not lead to undue extension of the procedure with increased morbidity or functional impairment.

As limited resections are often adequate in localized GISTs, laparoscopic surgery may be a valuable alternative to open resection. The feasibility of laparoscopic surgery for GISTs has been demonstrated in numerous series [43–46]. In a recent retrospective analysis of patients treated by laparoscopic resection of GISTs between 2002 and 2012, the 5-year recurrence-free survival was 63% in high-risk patients whereas it was 100% at 10 years in the low- and very-low-risk groups, indicating that laparoscopic surgery may be performed with similar results as open resection [47]. A recent meta-analysis of 22 studies comparing laparoscopic versus open surgery for GISTs including 1,166 patients demonstrated improved short-term results (intraoperative blood loss, onset of gastrointestinal motility, time to oral intake, hospital stay and overall complications) in the laparoscopic group [48]. However, one of the major pitfalls of surgery for GISTs is the risk of intraoperative tumor rupture, conferring a recurrence rate of almost 100% [49]. Since the risk of tumor rupture increases with tumor size and may be elevated in tumors with an unfavorable location, laparoscopic surgery should be restricted to easily accessible lesions and is not recommended for large lesions (usually >5 cm), although this strongly depends on individual surgical expertise and laparoscopic resection has been demonstrated to be feasible even in large GISTs in single-center series [46, 50].

Transluminal endoscopic resection techniques have been described for small GISTs [51–53]. Since GISTs arise from the muscularis propria layer, established endoscopic resection techniques in the upper gastrointestinal tract (endoscopic mucosal resection, endoscopic submucosal dissection) can be expected to be associated with an increased risk of incomplete resection. Endoscopic full-thickness resection of the gastric wall has also been demonstrated to be feasible in single-center series [54, 55], but as long as methods for postinterventional gastric wall closure are not standardized, these techniques must be considered as experimental. In contrast to gastric GISTs, transanal excision via transanal endoscopic microsurgery may be a safe alternative to transabdominal resection in small rectal GISTs [56–58].

Preoperative Treatment

In patients with locally advanced, inoperable but non-metastatic GISTs as well as in patients with operable tumors that require extensive, functionally impairing surgery or a procedure associated with substantial morbidity for complete removal, preoperative treatment with the aim to shrink the tumor and enable less radical surgery is indicated. In contrast to other solid gastrointestinal malignancies such as rectal cancer or liver metastases from colorectal cancer, there are no data to indicate that neoadjuvant treatment reduces the local or distant recurrence rate in easily resectable GISTs, and these should be treated by upfront surgery.

The overwhelming success of treatment with imatinib in metastatic GISTs [4, 59], achieving response or disease stabilization in 80% of cases in a disease that had previously been considered largely chemotherapy-refractory, prompted investigation of this drug in a perioperative setting. In most patients a substantial reduction in tumor size can be observed within 2–8 months of treatment. In a Dutch multicentric retrospective study of 57 patients with locally advanced GISTs, neoadjuvant treatment with imatinib achieved almost 50% tumor size reduction, leading to successful R0 resection in 84% of patients [60]. In a prospective phase II study, imatinib was administered to 41 patients with locally advanced, non-metastatic GISTs. Less radical surgery was enabled by preoperative treatment in 26 patients and 3-year progression-free survival was 85.2% [61]. Similar results were demonstrated in a pooled analysis of 161 patients from 10 sarcoma centers treated with preoper-
ative imatinib for a median of 40 weeks, achieving R0 resection in 83% and 5-year disease-free survival in 65%. In a study evaluating combined neoadjuvant and adjuvant use of imatinib in patients with GISTs, R0 resection was achieved in 21 of 31 patients who had primary, locally advanced GISTS, with 23.8% of these developing recurrence at a median follow-up of 5.1 years. Taking these results together, it appears to be safe to perform less radical surgery if the tumor is downsized by preoperative treatment rather than upfront radical resection, although these two approaches have not been prospectively compared. GISTs of the rectum have a tendency to frequently require multivisceral resection or abdominoperineal excision, given the limited space within the pelvic cavity and the generally more aggressive course of this disease. Thus, preoperative downsizing to limit the extent of surgery may be particularly beneficial in these patients. In a study of 38 non-metastatic rectal GIST patients of whom 21 received preoperative imatinib, more patients in the preoperative imatinib group achieved R0 resection even though they had larger tumors at diagnosis than patients undergoing upfront surgery [62]. Given that most rectal GISTs also have a KIT exon 11 mutation that makes them sensitive to imatinib, some authors recommend preoperative imatinib treatment rather than upfront surgery for most patients with rectal GISTS.

Whenever neoadjuvant imatinib therapy is considered, the diagnosis of GIST must be clearly established and a mutation conferring primary imatinib resistance must be ruled out to avoid ineffective treatment and tumor progression, possibly leading to unresectability of a previously resectable lesion. In rare cases where a locally advanced GIST is suspected on imaging but obtaining a histopathological diagnosis including mutational analysis is not feasible or associated with considerable risk, a possible alternative may be to start imatinib treatment using early assessment of treatment response by FDG-PET imaging. Metabolic response seen on FDG-PET as early as 1–2 weeks after initiation of treatment has been demonstrated to accurately predict CT morphological response occurring at 8-week follow-up [63–65]. Thus, patients with lesions that do not demonstrate major reduction in FDG uptake after 1–2 weeks of imatinib treatment should not continue to receive the drug and undergo definite histopathological assessment or upfront surgery.

**Adjuvant Treatment**

ACOSOG Z9001 was the landmark trial establishing the use of imatinib as adjuvant therapy in patients following complete surgical removal of GISTS [66]. 713 patients were randomly assigned to receive imatinib 400 mg daily or placebo for 1 year following complete resection of primary GISTS >3 cm in size. Patients developing recurrence in the placebo arm were offered crossover to imatinib. Recurrence-free survival was significantly improved in the imatinib arm (hazard ratio 0.35) whereas overall survival was not different between the two arms. This trial led to regulatory approval of adjuvant imatinib by the US and European authorities in 2008 and 2009, respectively. Given the potential toxicity associated with imatinib as well as the considerable cost of this treatment, identification of patients deriving benefit from adjuvant imatinib therapy remains a crucial issue. Data from retrospective studies were able to identify three clinical factors associated with the risk to develop tumor recurrence following resection of primary GISTS: anatomic site (GISTS of the stomach generally have a lower recurrence risk than extragastric GISTS), tumor size and mitotic rate. The Armed Forces Institute of Pathology (AFIP) classification of recurrence risk based on these criteria has since been used to select patients for adjuvant treatment [67] (table 1). Modified National Institutes of Health (NIH) criteria also acknowledge the AFIP criteria and incorporate tumor rupture as an independent feature placing a patient at high risk for tumor recurrence regardless of tumor size, anatomic site or mitotic count [68].

Despite significant improvement of recurrence-free survival with adjuvant imatinib in ACOSOG Z9001, that study also demonstrated that withdrawal of imatinib in the experi-
mental arm was generally followed by a marked increase in recurrences after approximately 6 months. 12 months after imatinib was stopped (24 months after study entry), recurrence rates were largely similar in the imatinib and placebo arms, raising the question whether adjuvant imatinib should be given for a longer period. This was the rationale for the Scandinavian Sarcoma Group trial of adjuvant imatinib in resected GISTs (NCT00116935), randomizing patients with any high-risk feature (tumor diameter >10 cm, mitotic count >10/50 high-power fields, tumor diameter >5 cm and mitotic count >5/50 high-power fields, or tumor rupture) to receive 1 vs. 3 years of adjuvant imatinib. The study demonstrated superior 5-year recurrence-free survival in the 3-year arm (65.6 vs. 47.9%, hazard ratio 0.46). At a relatively short follow-up of 54 months, 5-year overall survival was also significantly improved with 3 vs. 1 year of imatinib (92.0 vs. 81.7%, hazard ratio 0.45) [69]. Following these results, 3 years of adjuvant imatinib has become the treatment standard in patients with a high estimated risk of relapse following resection of a primary GIST as per current European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines [70, 71]. Again, a marked increase in recurrences was observed in both arms approximately 6 months after imatinib withdrawal, raising the question whether postoperative imatinib really decreases the probability of tumor recurrence in the long run (as would be expected from a truly adjuvant treatment) or rather postpones overt manifestation of a relapse that will occur anyway, being a palliative rather than an adjuvant treatment. Postoperative imatinib administration for 5 years is currently being evaluated in a phase II study (PERSIST-5, NCT00867113) and results are expected in 2016. However, in light of the observations from ACOSOG Z9001 and the Scandinavian study, indefinite continuation of treatment may be warranted for some patients. Further extension of postoperative imatinib treatment, however, requires more precise criteria for patient selection. Molecular tumor characteristics will likely play an important role in patient selection for adjuvant treatment in the future. While there is a consensus that patients demonstrating a PDGFRA exon 18 mutation that confers resistance to imatinib in the palliative setting (D842V) [72] should not receive adjuvant imatinib either, things are less clear for other molecular subtypes. A subgroup analysis of patients on the Scandinavian trial revealed no benefit of longer imatinib administration in patients demonstrating KIT exon 9 or any PDGFRA mutation, although these groups were small [69]. A recently published

### Table 1. Prognosis of GISTs according to the AFIP criteria (from [67])

| Tumor parameters | Patients with progressive disease during follow-up and characterization of malignant potential, % |
|-------------------|---------------------------------------------------------------------------------------------------|
|                   | gastric GISTs                                                                                   |
|                   | small intestinal GISTs                                                                          |
| group size, cm    | mitotic rate per 50 HPFs                                                                        |
|                   |                                                                                                 |
| 1                 | ≤2                                                | ≤5                                               | 0 / very low if any | 0 / very low |
| 2                 | >2 to ≤5                                         | ≤5                                               | 1.9 / low          | 4.3 / low    |
| 3a                | >5 to ≤10                                        | ≤5                                               | 3.6 / low          | 2.4 / intermediate |
| 3b                | >10                                               | ≤5                                               | 12 / intermediate  | 52 / high    |
| 4                 | ≤2                                                | >5                                               | 0 / low*           | 50 / high*  |
| 5                 | >2 to ≤5                                         | >5                                               | 16 / intermediate  | 73 / high    |
| 6a                | >5 to ≤10                                        | >5                                               | 55 / high          | 85 / high    |
| 6b                | >10                                               | >5                                               | 86 / high          | 90 / high    |

HPFs = High-power fields.

* Based on very small numbers insufficient for prediction of malignant potential.
long-term follow-up analysis of patients on ACOSOG Z9001 [73] found that benefit from adjuvant imatinib in that study was basically accounted for by patients demonstrating deletions in KIT exon 11, whereas patients with insertions or point mutations in KIT exon 11, patients with KIT exon 9 mutations and patients with KIT/PDGFRA wild-type GISTs did not seem to derive benefit from adjuvant imatinib. In the absence of prospectively collected data, most oncologists will likely continue to offer adjuvant imatinib treatment to patients following resection of high-risk GISTs, except for those with a D842V mutation until more data become available; however, in light of this post hoc analysis, the decision has to be discussed in more detail with the patient if no KIT exon 11 mutation is present. For patients with a KIT exon 9 mutation, the above-mentioned analysis has to be interpreted with caution as patients in both the Z9001 and the Scandinavian trial uniformly received 400 mg of imatinib daily, whereas a higher dose (800 mg) has been proven to be more effective in this cohort in the palliative setting [74]. While data in the adjuvant setting are lacking, offering 800 mg per day as adjuvant treatment to patients with a KIT exon 9 mutation may be considered by extrapolation of these data.

Management of Advanced/Metastatic GISTs

Medical Treatment

Until the beginning of this century, GIST was generally regarded as a chemotherapy-resistant disease, with response rates in the order of 0–5% and little to no improvement in survival with the use of conventional therapy [75]. The introduction of imatinib mesylate, a TKI that binds in a reversible manner to the adenosine triphosphate-binding pocket of KIT, PDGFRA and PDGFRB, has revolutionized the medical treatment of metastatic GISTs, achieving objective response in more than half of the patients and disease stabilization in over 80% [59]. Tumor response was likely underestimated in this initial trial as response was evaluated solely according to size-based criteria, whereas measurement of lesion density on CT is considered an essential component of response evaluation in GISTs by today's standards as it yields increased sensitivity compared to size-based criteria alone [76]. 400 mg of imatinib per day constitutes the current first-line standard treatment for patients with metastatic GISTs unless they have a specific mutation in exon 18 of the PDGFRA gene (D842V) that has been demonstrated to confer resistance to imatinib [72]. In patients with a KIT exon 9 mutation, increasing the imatinib dose to 800 mg per day has demonstrated a significant improvement in progression-free survival [74]. Hence, the higher dose should be given to patients with a proven exon 9 mutation who can tolerate it.

Despite initial treatment response, most patients develop secondary resistance to imatinib after a median of 2 years on treatment, essentially due to secondary mutations in the KIT or PDGFRA gene that interfere with drug binding [5, 77, 78]. Escalating the imatinib dose to 800 mg per day in this progressing population was demonstrated to achieve response or disease stabilization in one third of patients in a recent systematic review of published data [79], and this approach is considered as the treatment standard by many oncologists, although all of the available evidence is based on retrospective, observational studies. Sunitinib, a multi-TKI active against KIT, platelet-derived growth factor receptors and vascular endothelial growth factor receptors, is the standard treatment for patients progressing on or intolerant to imatinib. In a study that randomized patients to receive either sunitinib 50 mg daily on a 4 weeks on-/2 weeks off schedule or placebo, progression-free survival was 6.3 months in the sunitinib arm vs. 1.9 months in the placebo arm [80]. A recently published randomized controlled trial compared a novel TKI, masitinib, to standard-dose sunitinib in imatinib-refractory patients. Progression-free survival was
3.71 months in the masitinib arm. Patients receiving sunitinib after progression on masitinib had longer overall survival compared to patients switching directly to sunitinib after imatinib failure in a secondary efficacy analysis [81], indicating that introducing a further line of therapy between imatinib and sunitinib may become an option as more data become available.

In patients progressing on both imatinib and sunitinib, imatinib rechallenge has been compared to best supportive care plus placebo in a randomized phase III trial. Progression-free survival was doubled in the imatinib rechallenge arm, although the absolute progression-free survival difference was only 0.9 months. There was no difference in overall survival, possibly due to the fact that 93% of patients on the placebo arm crossed over to imatinib upon progression [82]. Regorafenib, another orally available inhibitor of several tyrosine kinases approved in many countries for patients with metastatic colorectal cancer refractory to standard chemotherapy, was compared to placebo in patients with metastatic GISTs who were resistant to at least imatinib and sunitinib in the randomized phase III GRID trial [83]. Progression-free survival in the placebo arm was identical to the corresponding arm in the imatinib rechallenge trial (0.9 months), however, it was significantly prolonged to 4.8 months in the regorafenib arm. Overall survival was not different but, again, 85% of patients on the placebo arm crossed over to regorafenib upon progression, likely accounting for the lack in overall survival difference. This study led to regulatory approval of regorafenib for third-line treatment of metastatic GISTs and the drug can now be considered standard treatment for appropriate patients in this setting.

In all patients with metastatic GISTs, treatment should be continued indefinitely until disease progression or intolerance, even in the presence of sustained disease control. Interruption of imatinib treatment in patients with controlled disease invariably resulted in rapid progression, regardless of whether imatinib was withheld after 1, 3 or 5 years in the French Sarcoma Group BFR14 trial [84–86]. When imatinib was reintroduced in progressing patients, the vast majority responded again, but most patients did not achieve the remission status observed before imatinib interruption [87].

**Novel Agents**

A number of novel agents for the treatment of GISTs are currently under investigation, including TKIs, immunomodulating agents, heat shock protein inhibitors, a phosphoinositide 3-kinase inhibitor and an insulin-like growth factor 1 inhibitor. Among novel multikinase inhibitors, ponatinib might have the potential to become a new treatment option for patients refractory to all known TKIs. Ponatinib has demonstrated in vitro activity against a number of clinically relevant KIT mutants [88]. In a phase II study of 35 patients with refractory metastatic GISTs, roughly 50% of whom had progressed on all three established TKIs, ponatinib achieved response or disease stabilization in 55% of patients with and 22% of patients without a primary KIT exon 11 mutation [89]. This study is still ongoing to enroll a total of 45 patients.

The management of metastatic patients demonstrating a PDGFRA exon 18 D842V mutation remains a particular challenge. In a preclinical model, more than 100-fold enhanced activity against this specific mutation was demonstrated for crenolanib, an inhibitor of PDGFRA [90], compared to imatinib. A clinical trial to investigate crenolanib in D842V-mutant patients is currently ongoing.

KIT/PDGFRA wild-type GISTs constitute another entity that generally responds poorly to treatment with known TKIs. As these patients often have high expression of insulin-like growth factor 1 receptor (IGF-1R) due to deficient SDH function, linsitinib, a TKI with specific activity against IGF-1R, was investigated in a phase II study in this population [91]. No objective responses were observed, but 9-month progression-free survival was 52% with
linsitinib. However, wild-type GISTs are heterogeneous and benefit from an anti-IGF-1R kinase inhibitor can only be expected for patients with deficient SDH function. Inclusion of patients with a normally functioning SDH complex (i.e., without hyperexpression of IGF-1R) could be an explanation for these rather disappointing results.

Role of Surgery in Metastatic Patients

In the French BFR14 trial, interruption of imatinib treatment in patients with metastatic GISTs was generally followed by rapid disease progression, even in patients who had complete tumor remission at the time when imatinib was stopped. Notably, some of these had achieved complete remission by surgical removal of all tumors (primary and metastatic) and presented with new lesions soon after imatinib withdrawal [84, 85]. These observations indicate that resection of metastatic disease in GISTs, in contrast to metastatic colorectal cancer, is generally not curative and must rather be considered as a debulking procedure. Primary surgery of metastatic GISTs is therefore not recommended and patients should undergo upfront TKI therapy [92], even if the disease is technically resectable. However, as the vast majority of metastatic GIST patients eventually develop secondary mutations making them resistant to imatinib, there may be a rationale for surgery in resectable patients who achieve disease stabilization, the aim being to decrease the likelihood that secondary mutations occur anywhere in the tumor. Moreover, as secondary resistance often develops in a focal manner, resulting in some lesions progressing while the majority is still under control with imatinib, another possible approach is to selectively remove the progressing lesions, which would ideally be able to postpone the need for second-line treatment if only lesions still responding to imatinib are left behind. While these approaches clearly appear to make sense, they have so far not been underscored by sufficient data. A prospective trial randomizing patients with metastatic GISTs who responded to imatinib to either continuation of imatinib therapy or debulking surgery at the time of best response (EORTC Soft Tissue and Bone Sarcoma Group 62063) was initiated in 2009 but had to be closed due to poor accrual in 2011. In a retrospective study, 80 patients treated with imatinib who either underwent debulking surgery at the time of best imatinib response or selective removal of progressing lesions in the case of focal progression were analyzed [93]. In the latter group, median progression-free survival following surgery (while imatinib was continued) was 8 months, meaning that surgery was able to postpone the need for second-line therapy by this period. In patients in whom focally progressing lesions are easily resectable, surgery may therefore be considered, as has also been acknowledged by current ESMO guidelines [70]. In the aforementioned study, progression-free survival was still substantially better in patients who underwent surgery of all residual disease before progression occurred (median progression-free survival not reached at median follow-up of 31 months); however, as these were retrospective data, these results are likely biased. However, if responding lesions can be removed without major functional impairment and with low risk of morbidity, surgery may be considered in this situation after shared decision-making with the patient.

Other Treatments

Since surgery for metastatic GISTs usually does not cure the patients and the evidence demonstrating its benefit is limited, maximum emphasis must be put on the safety of any intervention that these patients are submitted to. Locally ablative or locoregional therapies are in use in a variety of tumors, including primary and secondary liver neoplasms, and may constitute a less invasive modality for tumor debulking in this disease. Radiofrequency ablation [94, 95], transarterial chemoembolization [96, 97] and transarterial yttrium-90 radioembolization [98, 99] have all been used in patients with metastatic GISTs. As with
surgery, data regarding local interventional treatments are retrospective and based on limited patient numbers. So far, any local treatment (including surgery) in metastatic GISTs must be considered as experimental and the appropriate modality must be chosen on an individual basis, taking into account both efficacy and safety concerns.

Conclusions

Although a relatively rare tumor entity, GISTs are the most frequently diagnosed mesenchymal neoplasm of the gastrointestinal tract. Their clinical and molecular characterization continues to evolve, extending the data foundation on which treatment decisions are made and new drugs are developed. Still, prediction of benign or malignant behavior of an individual GIST relies on empirically established scoring systems. Since data accumulated in the imatinib era suggest that malignant potential may be a constitutive quality of some GISTs rather than a feature acquired by the tumor during disease progression, some patients may require prolonged anti-tumor treatment even after complete surgical removal of their disease. Therefore, more accurate differentiation between benign and malignant GISTs is needed.

Development of new targeted drugs for use in patients whose GISTs are either primarily resistant to established TKIs or acquire resistance during treatment is an ongoing process, with several new targets currently under investigation. As progression in metastatic GISTs often occurs in a focal manner, local (surgical or interventional) treatment approaches in metastatic GISTs are expected to yield substantial benefit; however, creating solid evidence supporting their use has proved challenging. In a time where the distinction between curative and palliative treatment approaches is becoming less dogmatic in many fields of oncology, local therapies will continue to be used on an individual basis in metastatic GISTs. As long as their benefit is not formally proven, however, these treatments must be employed with extreme caution and a clear focus on patient safety.

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