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REVIEW ARTICLE

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Gastrointestinal stromal tumours (GIST) — 2018

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ABSTRACT

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of gastrointestinal tract. Advances in the understanding of the pathologic-molecular mechanisms of GIST pathogenesis have emerged GIST as a model of targeted therapy in oncology. The paper describes advances in diagnostics and therapy of these tumours based on new scientific basis. Radical surgery is still the mainstay treatment for primary, localized, resectable GISTs, although high percentages of the patients after potentially curative operations develop recurrent or metastatic disease; thus all GIST should be evaluated for potential adjuvant therapy with imatinib. In inoperable/metastatic lesions the treatment of choice is tyrosine kinase inhibitor — imatinib mesylate In case of disease progression the increase of imatinib dose to 800 mg daily is recommended and if further progression exists — sunitinib in the initial dose 50 mg daily should be introduced, thereafter sorafenib/regorafenib or clinical trial with new drugs (e.g. BLU-285 or DCC2618).

Key words: gastrointestinal stromal tumour, GIST, molecular diagnostics, imatinib, sunitinib, regorafenib, avapritinib, DCC2618

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Introduction

Gastrointestinal stromal tumours (GISTs) constitute a separate group of the most common mesenchymal gastrointestinal cancers. Clinically, GISTs represent a wide spectrum of lesions — from small benign tumours, found accidentally during endoscopic or surgical procedures, to very aggressive tumours that lead to massive metastatic disease. The incidence of GIST is estimated at 11–15 new cases/100,000 per year [1]; of which about 25% are overtly malignant tumours [2]. The basic and valid principle should be the treatment of non-operative and/or metastatic GIST by multidisciplinary teams experienced in the treatment of soft tissue sarcomas [3].

Pathomorphology and molecular diagnostics

GISTs are probably derived from the precursors of Cajal "pacemaker" cells (responsible for intestinal peristalsis), and characteristically the tumours express the immunohistochemical CD117 (*KIT*) marker, and in most cases they are associated with sporadic activating mutations in the *KIT* or *PDGFRA* genes (Table 1). Most commonly it occurs in older people, with the peak incidence in the age range 60–65 years, with a similar frequency in women and men. This cancer is rarely diagnosed in children and affects them almost exclusively in the stomach location. In adults, about 10–15% of GISTs do not show *KIT* or *PDGFRA* mutations. These cases may be associated with type 1 neurofibromatosis (then GISTs mainly occur in the small intestine) or may represent syndromes associated with succinate dehydrogenase deficiency (SDH) (refer to GISTs arising in the stomach) such as: the non-inherited Carney triad (GIST, pulmonary chondroma, and extra-adrenal paraganglioma) and autosomal dominant Carney-Stratakis syndrome (GIST, extra-adrenal paraganglioma, germinal mutation in one of the SDH subunit genes) [4, 5]. Most often GIST is found in the stomach (60–70%), followed by the duodenum and small intestine (20–25%), rectum and anus (5%), and oesophagus and colon (< 5%) [6].

Table 1. Molecular classification of gastrointestinal stromal tumours (GIST)

Mutations of the *KIT* gene	80–85% GISTs
Exon 11	The most common mutation in sporadic GIST (approximately 60%) with the best response to imatinib; also observed in the family GIST
Exon 9	A mutation that is more common in GISTs originating from the small intestine and the colon; worse response to imatinib, patients may benefit from a higher dose of imatinib (800 mg); good response to sunitinib
Exon 13 and 17	Clinical responses to imatinib have been observed; very rare mutations; described in the family GIST
***PDGFRA* gene mutations**	5–8% of GIST
Exon 12	Observed clinical response to imatinib
Exon 14	Only a few cases have been described, sensitive to imatinib
Exon 18	Most cases derived from the stomach or omentum; the D842V mutation is resistant to imatinib and sunitinib; other types of mutations are sensitive
"Wild-type"— or no *KIT* or PDGRA mutations	12–15% of cases; poor response to imatinib, sunitinib better; often in paediatric GISTs, typically for GISTs related to NF1 or Carney's triad (GIST of the stomach + pulmonary chondroma ± paraganglioma); often disorders of SDHB, sometimes a relationship with NF1, observed (1%) *BRAF* mutations

GISTs arise in the muscular layer of the stomach or intestinal wall. Small GISTs usually form intramural or sub-ventricular nodules; in the small intestine they tend to form pedunculated lesions prominent to the peritoneal cavity. The growth of GIST has no specific direction; it can develop both into and out of the gastrointestinal tract as well as remain intra-articular. Malignant GISTs can reach significant sizes (over 20–30 cm in diameter) and infiltrate the spleen or pancreas, and determining their starting point can be difficult. Macroscopically, the GIST surface is usually pink, light brown or grey. Haemorrhagic changes, necrosis, or cystic degeneration are more common in larger tumours. In addition, in some cases, ulceration from the mucous side can be observed [7].

Histologically, GISTs have a wide variety of morphological pictures and may be either rich or poor cell, spindle or epithelioid cell (Figure 1A, B). Cancer cells form a variety of architectural patterns, including bundles (like smooth muscle cancers) or palisades (systems characteristic for neoplasms of nervous origin). The stroma usually has a prominent network of blood vessels, collagen bundles, or degenerative features. In smaller, indolent tumours, massive glazing and calcification are encountered, whereas in the GIST of the small intestine, extracellular collagen-like deposits in the shape of spheres and a material similar to the nerve felt are more often found. Almost all GISTs are immunohistochemically positive for CD117 (*KIT*) (Figure 1C); about 5% of cases, especially those involving gastric cancer with the *PDGFRA* mutation, may not show this staining. The marker independent of the status of the *KIT* and *PDGFRA* mutation and almost exclusively characteristic of GIST is staining with the DOG1 antibody (Figure 1D). In addition, histological examination and routine differential diagnosis most often include immunohistochemical staining with the following antibody panels: CD34, SMA, h-caldesmon, desmin, general cytokeratin or CK18, S100, HMB-45, and Melan A. The result of the histopathological examination should include the minimum parameters presented in Table 2, including the three most important prognostic factors of GIST: location, size, and mitotic activity of the tumour (Table 2) [8–10]. In simplified terms, gastric GIST with a diameter of more than 5 cm and more than five mitoses in 50 large fields of vision (5/50 HPF) are associated with a significant risk of progression; in the small intestine GIST greater than 5 cm and with mitotic activity below 5/50 HPF have a high risk of metastatic disease [11]. To perform histopathological assessment together with immunohistochemical and molecular tests to determine the status of *KIT* and *PDGFRA* genes, it is necessary to provide to the pathomorphology department with a paraffin block containing a representative tumour specimen.

Treatment

Primary surgical treatment

The most effective method of treating GIST is radical surgery with curative intent (35–65% five-year survival without relapse), which consists of an open resection of the stomach, small intestine, colon tumour, or intraperitoneal/retroperitoneal within borders of the macroscopically healthy tissue [3, 12, 13]. In the case of gastric GIST, local excision of the tumour with a fragment of the stomach wall (wedge resection) is most often performed, partial or total resection is less frequent (the extent of stomach resection is not

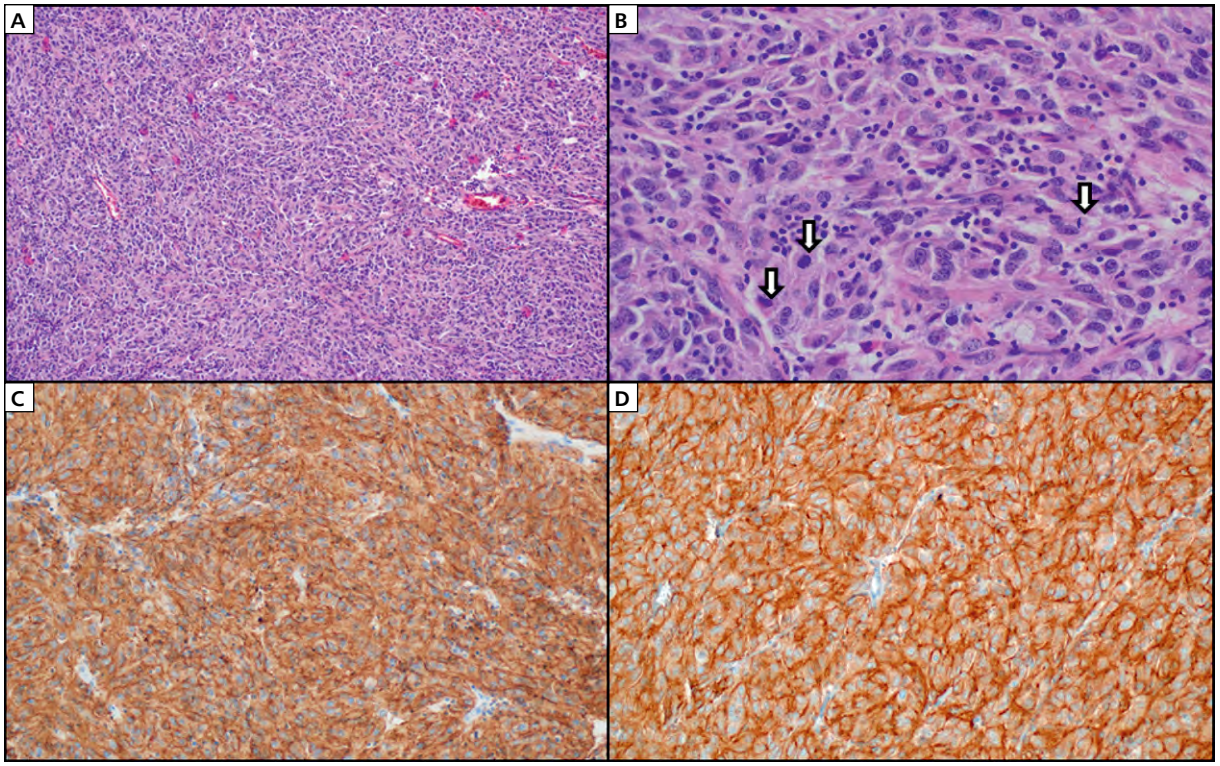

Figure 1. Microscopic evaluation of GIST. **A.** Picture of rich cell, spindle cell GIST (HE 40 ×); **B.** Showed mitotic activity (arrows; HE 400 ×); **C.** Positive immunohistochemistry for CD117 (KIT 100 ×); **D.** Positive staining for DOG1 (200 ×)

Table 2. The data, which should be included in a report from the histological examination of gastrointestinal stromal tumours (GIST)

Macroscopic examination
Tumour location: stomach, small intestine, large intestine, different
Tumour size
Description of the tumour
Surgical margins
Microscopic examination
Histological type
A subtype depending on the cell type
Mitotic index for 50 large fields of view
Pathomorphic staging according to the 8th edition of TNM AJCC/UICC (pTNM)
Assessment by Miettinen & Lasota criteria
Surgical margins
Changes after treatment
Immunohistochemistry
CD117
DOG1
Molecular research
KIT mutation
PDGFRA mutation

significant for the risk of tumour recurrence), and subsequent relapses of GIST recurrence do not lead to curing the patients. In other locations, segmental resection of the small intestine or hemicolectomy is performed. In contrast to cancers of the digestive system, there is no need to remove the locoregional lymphatic system, because metastases to the lymph nodes occur sporadically in the case of GIST (< 3% of patients). In the case of R1 resection (microscopic non-radical resection) performing a reoperation may be considered, provided there is a possibility to determine the location of the primary tumour and that it is not connected with serious consequences for the functioning of the gastrointestinal tract (in other cases, only observation after surgery is recommended). Laparoscopy is an effective surgical procedure for GISTs localised in the stomach; however, laparoscopic resection in primary GISTs of larger sizes (> 5–8 cm) is not recommended. During the operation, it is of importance to prevent the tumour from being damaged or ruptured because it is an unfavourable prognosis factor. In patients with locally advanced GIST (borderline resectable) extensive multi-organ resections should be avoided, and particularly undesirable are reoperations of recurrences (GIST diagnosis is already known after the first operation). In these cases, pre-operative treatment with imatinib (daily dose: 400 mg) should be considered under strict CT monitoring performed every two months, with the possibility of surgical management

Table 3. Scale of Miettinen and Lasota (2006) defining the risk assessment of GIST aggressiveness (frequency of metastases or cancer-related death) depending on the location, size, and mitotic activity of GIST; accepted by the ESMO guidelines (2012)

Parameters of the primary tumour			Recurrence rate after surgery							
Prognostic group	Size [cm]	Mitotic count	Stomach		Duodenum		Small intestine		Rectum	
1	≤ 2	≤ 5/50 HPF	0%	Very low	0%	Very low	0%	Very low	0%	Very low
2	> 2, ≤ 5		1.9%	Low	8.3%	Low	4.3%	Low	8.5%	Low
3a	> 5, ≤ 10		3.6%	Low	No data; at least intermediate		24%	Intermediate	No data; at least intermediate	
3b	> 10		12%	Intermediate	34%	High	52%	High	57%	High
4	≤ 2	> 5/50 HPF	0%	Very low	No data		50%	High	54%	High
5	> 2, ≤ 5		16%	Intermediate	50%	High	73%	High	52%	High
6a	> 5, ≤ 10		55%	High			85%	High	High	
6b	> 10		86%	High	90%	High	90%	High	71%	High

when maximum response to imatinib is achieved. In each patient after the primary GIST surgery, when the final histological result is ready, the risk of recurrence according to the NCCN-AFIP-AJCC classification should be assessed, which forms the basis for the classification of the AJCC 2010 staging. The most important risk factors for recurrence after excision of the primary tumour include the value of the mitotic index, size and location of the tumour, and the state of surgical margins (especially intraoperative tumour rupture) (Table 3) [14]. In GIST derived from the stomach, prognosis is better when compared to tumours located in the small or large intestine. The patient should be informed about the possibility of relapse after a long period of time from the excision of the primary lesion and subjected to follow-up.

Adjuvant and neoadjuvant therapy

Adjuvant treatment with imatinib for three years in the group of patients with a high risk of relapse extends relapse-free survival (RFS) and overall survival as compared to the one-year treatment regimen (SSGXVIII, five-year-old RFS) 65.6% *vs.* 47.9% for 36-month and 12-month imatinib, respectively, and five-year OS, respectively, 92% *vs*. 81.7% [15]. Previous results of the study ACOSOG Z9001, in which adjuvant imatinib was used for a year, led to the registration in the treatment of postoperative imatinib in GIST patients with a significant risk of recurrence. In light of current knowledge, patients with very low or low risk of relapse should not receive adjuvant therapy with imatinib. Adjuvant therapy in the group with high risk of recurrence after resection of the primary lesion should last for three years (Table 4). At the same time, when qualifying patients for adjuvant therapy, it is obligatory to determine the status of the GIST mutation — it is not advisable to use adjuvant therapy with imatinib in GIST genotypes with low sensitivity to imatinib (*PDGFRA D842V* or wild-type) [17].

The greatest benefits from adjuvant therapy are seen in patients with the highest risk of recurrence of the disease (> five mitoses/50 fields of view at high magnification and/or size of tumours > 5 cm, the location of the primary tumour in other parts of the digestive tract other than the stomach, resection in confirmed microscopically infiltrated surgical margins — R1 or tumour rupture during surgery) and the confirmed mutation in exon 11 of the *KIT* gene [17].

Based on the current results of studies in patients with GIST with borderline operability an attempt to treat with neoadjuvant imatinib is recommended. Neoadjuvant treatment with imatinib is a safe therapeutic option, which should always be considered in the case of inability to perform radical resection R0 or "unfavourable" GIST location with a high risk of postoperative complications (mutilating surgeries should not be performed). The combination of neoadjuvant treatment with surgery is particularly indicated in the locations of the primary GIST being a priori technically challenging (rectum, duodenum, gastroesophageal junction). Pre-operative therapy with imatinib should be used until the maximum response is obtained (usually 6–12 months from the beginning of treatment), and the response must be strictly controlled in imaging studies (in order not to omit the onset of resistance to therapy, there may be place for positron emission tomography — PET-CT). Probably after neoadjuvant treatment, adjuvant therapy should be used for a total duration of therapy of three years. So far, only small formal phase II trials have been performed on initially advanced GISTs treated with neoadjuvant imatinib, and several studies of groups of patients have been published [16, 18]. The largest group includes 161 patients from 10 EORTC

Table 4. Main clinical trials of adjuvant imatinib in gastrointestinal stromal tumours (GIST) (by [16])

Study	Imatinib dose and treatment duration	Inclusion criteria	Results	
			Primary endpoints	Secondary endpoints
ACOSOG Z9001 Randomised, phase III, placebo-controlled	400 mg per day (n = 359) *vs.* placebo (n = 354) for 1 year	• KIT + primary GIST • Tumour size ≥ 3 cm • R0 — resection • Low, intermediate, and high risk of relapse	1-year RFS: 98% with imatinib *vs.* 83% placebo (83%) FU median: 19.7 months HR 0.35, p < 0.0001	No differences in the 1-year OS FU median: 19.7 months HR 0.66, p = 0.47
ACOSOG Z9000 Single arm, open-label, phase II	400 mg per day (n = 107) for 1 year	• KIT + primary GIST • R0 — resection • High risk of relapse — Tumour size ≥ 10 cm OR — Tumour rapture OR — Intraperitoneal metastases < 5	1-year OS: 99% 2-year OS: 97% 3-year OS: 97% FU median: 4 years	1-year RFS: 94% 2-year RFS: 73% 3-year RFS: 61% FU median: 4 years
SSGXVIII/AIO Randomised, open-label, phase III	400 mg a day for a year (n = 200) *vs.* 3 years (n = 200)	• KIT + GIST primary • High risk of relapse*: — Tumour size > 10 cm OR — Mitotic index > 10/50 HPFs OR — Mitotic index > 5/50 and tumour size > 5 cm OR — Rupture of the tumour	5-year RFS: 65.6% after 3 years *vs*. 47.9% after 1 year of imatinib (71.1% *vs.* 52.3% in the population with the intention of treatment) FU median: 54 months HR 0.46, 95% CI 0.32–0.65; p < 0.0001	5-year OS: 92% after 3 years *vs*. 81.7% after one year of imatinib median 54 months of follow-up HR 0.45, 95% CI 0.22–0.89; p = 0.019 93.4% *vs*. 86.8% (with an 8-year observation period)
EORTC 62024 Randomised, phase III	400 mg a day *vs.* observation (n = 908) for 2 years	• KIT + primary GIST • R0 — resection • The intermediate or high risk of recurrence**: — Tumour size > 5 cm I/OR — Mitotic index > 5/50 HPF	5-year survival without treatment failure with imatinib; imatinib failure-free survival (IFFS): 87% in the arm with imatinib *vs.* 84% in the control arm HR = 0.80, p = 0.23 Five-year IFFS in high risk GIST: 89% *vs.* 73% p = 0.11	RFS (after 3 years): 84% after 2 years of therapy with 2-years *vs.* imatinib 66% in the control arm FU median: 4.7 years HR 0.45, 95% CI 0.22–0.89; p = 0.019 OS: no significant differences
Kang et al. Single arm, prospective, II phase	400 mg per day (n = 47) for 2 years	• Primary GIST with exon 11 *KIT* mutation • R0 — resection • High risk of recurrence: — Tumour size ≥ 10 cm OR — Mitotic index ≥ 10/50 HPFs OR — Tumour size ≥ 5 cm and mitotic index ≥ 5/50 HPF	1-year RFS: 97.7% 2-year RFS: 92.7% FU median: 26.9 months	
Li et al. Open label, non-randomized, phase II	400 mg daily (n = 56) *vs.* no treatment (n = 49) for 3 years	• KIT + primary GIST • R0 — resection • The intermediate or high risk of recurrence**: — Tumour size > 5 cm and/or — mitotic index > 5/50 HPF	RFS with imatinib vs no treatment: 1-year RFS: 100% *vs*. 90% 2 years old RFS: 96% *vs.* 57% 3-year-old RFS: 89% *vs.* 48% FU median: 45 months HR 0.188, 95% CI 0.085–0.417; p < 0.001	Significantly reduced risk of death with imatinib treatment FU median: 45 months HR 0.254, 95% CI 0.070–0.931; p = 0.025

ACOSOG — American College of Surgeons Oncology Group; EORTC — European Organization for Research and Treatment of Cancer; HPF — high-power microscope field; HR — hazard ratio; OS — overall survival; RFS — recurrence-free survival; CI — confidence interval; NIH — National Institutes of Health; *NIH-classification modified; **NIH-classification

Table 5. Drugs registered for systemic gastrointestinal stromal tumours (GIST) in advanced GIST

Name of the drug	Registration/indications	Efficacy	Toxicity/remarks
Imatinib	Registered in Europe and the US in patients with advanced GIST first-line treatment and as adjuvant therapy after resection of GIST with a high risk of recurrence	In metastatic/unresectable cases: objective responses 54–70%, disease stabilization 16–30%; median overall survival 57 months–6 years; median survival free from disease progression 2–3 years In adjuvant treatment, a significant improvement in relapse-free survival with imatinib treatment for 3 years compared to a year with a median follow-up of 54 months (HR 0.46, 95% CI 0.32–0.65, p < 0.0001) 5 years: 65.6 *vs.* 47.9%; significant improvement in OS for imatinib treatment for 3 years compared to a year with a median follow-up of 54 months (HR 0.45, 95% CI 0.22–0.89, p = 0.019): 5-year OS: 92.0% *vs.* 81.7%	Oedema, nausea, diarrhoea, musculoskeletal pain, muscle cramps, fatigue, skin reactions, anaemia
Sunitinib	Registered in Europe and the USA in patients with advanced (metastatic or unresectable) GIST for the treatment of patients after failure of imatinib therapy	Objective responses 8–19%, disease stabilisation 58–70%; median total survival of 1.5 years; median survival free from disease progression 6–8 months	Fatigue, hypertension, hand-foot syndrome, hypothyroidism, hair discoloration, skin Lesions, diarrhoea, mucositis, anaemia, neutropoenia
Regorafenib	Registered in Europe and the USA in patients with advanced (metastatic or unresectable) GIST for the treatment of patients after failure of therapy with imatinib (understood as progression or intolerance of treatment) and previously treated with sunitinib with failure (understood only as the progression of the disease)	Percentage of disease control around 50% (single objective responses); median survival free from disease progression 4.8–10 months	Hypertension, hand–foot syndrome, diarrhoea, fatigue

centres, where excellent five-year relapse-free survival and overall survival were achieved after pre-operative treatment — 65% and 87%, respectively [19]. In summary, current indications for pre-operative treatment with imatinib in GIST include [16]:

— locally advanced tumour that is not eligible *a priori* for a non-mutilating (e.g. abdominoperineal excision, pelvic exenteration);
— it is problematic to achieve negative margins of primary resection (R0) or there is a risk of tumour perforation;
— after reducing the primary tumour, it is possible to perform a saving operation (e.g. gastric wedge resection instead of gastrectomy, local excision instead of pancreatoduodenectomy, thoracoabdominal resection).

Treatment of advanced stage

Advanced GISTs (unresectable or metastatic) are resistant to conventional chemotherapy. The value of radiotherapy is not definitively determined, although palliative irradiation of local unresectable lesions (pelvis minor) or bone metastases are encouraging. Until recently, prognosis in patients with unresectable, relapsed, or metastatic lesions was poor (median survival < 12 months).

Imatinib. The breakthrough was the introduction to clinical practice of imatinib mesylate, which is a small molecule inhibitor of tyrosine kinase (including KIT, PDGFR [platelet-derived growth factor]).

The results of available prospective phase I–III studies in imatinib treatment of inoperable or metastatic GISTs showed that total responses are rarely observed (about 5–7%) and most often there are partial remissions (about 40%) and disease stabilisation (about 36%), sporadic primary and early resistance (about 10–15%) is noted, and the number of metastases is not significant for the response (Table 5) [3, 20, 21]. Longer use of imatinib in advanced GIST increases the proportion of partial responses in patients with stabilisation found in the first months of treatment, but at the same time is associated with a higher rate of progression. Long-term results of the phase II trial (observation > 4 years) showed

that the median overall survival in the group of patients with advanced GIST was about five years, which is about a four-fold increase compared to historical data (median survival: 12–15 months). The median progression-free survival of patients treated with imatinib is 2–3 years. Similar results were published by the Polish multicentre group as part of the GIST Clinical Registry [22]. It is now widely accepted that treatment with imatinib should be continued until tumour progression (even for several years) because discontinuation of treatment may cause rapid progression of the disease. Treatment starts with a dose of 400 mg of imatinib taken orally once per day. It is now recommended to increase the dose to 800 mg (2 × 400 mg/day) if the disease progresses. There are available results of studies that indicate the need to begin the treatment with a daily dose of 800 mg in the case of a specific mutation in exon 9 of the *KIT* gene due to better progression survival.

In some patients, clinical benefits are slow (median time to response: four months), and the first full assessment of the response to treatment should be made after four months and (at least) two CT follow-up examinations. The main parameters to be assessed are the size of neoplastic lesions according to the criteria for the evaluation of tumour responses RECIST (response to criteria in solid tumours) — assessment of the sum of the longest dimensions of measurable changes — and determining the density of changes (so-called Choi criteria). The response should be assessed very carefully, which is of importance in differentiating between stabilisation (inhibition of progression) and actual progression because patients with disease stabilisation assessed according to the classic RECIST criteria have a significant benefit from treatment (an effect similar to that observed in patients with partial response to treatment). Caution is due to the fact that in the initial period of treatment, a decrease in the density of neoplastic lesions (e.g. multiple metastases in the liver) may cause a false picture of "new" changes or an apparent increase in the already existing size, which does not correspond to the progression of the disease and is the response to treatment. The quickest evaluation of the response to treatment can be obtained by means of PET-CT examinations.

Resistance to imatinib. During treatment with imatinib, some patients have progression of disease associated with drug resistance. A small proportion of patients (about 10–15%) among those correctly qualified for treatment (GIST CD117+) show primary and early resistance during the initial six months of treatment. In patients responding to treatment, along with the prolonged duration of therapy, secondary (acquired) resistance to imatinib may appear. It is estimated that, in 2–3 years of treatment with imatinib, approximately 40–50% of patients show signs of disease progression. In imaging studies, there may be a limited form of progression (e.g. progression of 1–2 lesions with persistent regression of other metastases or the emergence of a growing nodule within the necrotic metastasis — the so-called "nodule in tumour" symptom). However, images of multifocal progression are usually observed. It has been found that probably different mechanisms accompany the primary and secondary resistance that occurs during treatment with imatinib. Most often, secondary resistance is the result of the tumour acquiring additional mutation or additional mutations in the *KIT* or *PDGFRA* genes, which lead to a change in the conformation of the receptor and the inability to bind to imatinib. Considering the primary molecular characteristics of GIST, the best responses to imatinib are observed when the most frequent mutation in exon 11 is found (coding for the intracellular epithelial region of the transmembrane KIT receptor), whereas much worse results are in exon 9 or no mutation in the *KIT* gene (sometimes related to the presence of mutations in the *PDGFRA* gene, especially D842V) [23].

In cases of progression after the increase of imatinib up to a maximum dose of 800 mg, the use of second-line tyrosine kinase inhibitors should be considered. The use of other inhibitors, operating on different points in the pathway handle than a mutation associated with *KIT* exon 11, can help overcome resistance to imatinib. Currently, the only registered drug in the second line, in the case of resistance to imatinib or drug intolerance, is **sunitinib** malate, which is a tyrosine inhibitor of KIT receptor tyrosine kinases, PDGFR, vascular endothelial growth factor (VEGFR, vascular-endothelial growth factor receptor), and FLT3. The available data suggest that long-term responses may be obtained in approximately 40% of GIST-resistant patients, especially in the presence of the primary mutation in exon 9 or in the absence of mutation in the *KIT* gene "wild type" (e.g. GIST in children). The median time to progression in GIST patients treated with sunitinib is 6–8 months [24, 25]. The published results of the Phase III double-blind, randomised, placebo-controlled study for 312 patients showed that the median time to disease progression during treatment with sunitinib (at a starting dose of 50 mg in the four weeks of treatment schedule, two weeks of break) is four times longer than for placebo (27.3 *vs*. 6.4 weeks, $p < 0.0001$, respectively). For treatment with sunitinib, therapy should start with a daily dose of 50 mg in a six-week regimen (four weeks of active treatment and two weeks of break). If toxicity occurs, it is possible to reduce the daily dose of sunitinib to 37.5 or 25 mg, and to prolong the interruption in the treatment schedule. An alternative continuous dosing regimen (37.5 mg daily without interruption) is more commonly accepted, which seems more justified for tyrosine kinase inhibitors. Grade III–IV treatment toxicities are more frequent than with imatinib and mainly include the occurrence of hand-foot syndrome, fatigue, neutropoenia, thrombocytopaenia, diarrhoea, nausea, mucositis, hypertension, and hypothyroidism.

Table 6. New drugs showing promising activity in advanced GISTs

Substance name	Manufacturer	Molecular target	Examples of known *KIT*/*PDGFRA* muta ions sensitive to a given drug	Examples of known drug-resistant *KIT*/*PDGFRA* mutations	Phase of clinical trials (ClinicalTrial.gov ID)
Inhibitors of receptor tyrosine kinases					
Sorafenib (BAY43-9006)	Bayer	VEGFR2/3, PDGFRB, KIT, BRAF, FLT-3, RET	KIT: W557_K558del/T670I; V560del/V654A; V559D/D820Y	KIT: T670I V654A D816G N882K Y832D	Phase II (NCT01091207)
Crenolanib	Arog Pharmaceuticals	PDGFRA		PDGFRA: D842V	Phase II (NCT01243346)
Ponatinib (AP24534)	ARIAD	KIT, PDGFRA	KIT: D816A/G/H/V D820A/E/G/Y N822H/K Y823D A829P T670I	KIT: V654A	Phase II (NCT01874665)
Kabozantynib	Exelixis/Ipsen Pharma	KIT, MET, VEGFRS			Phase II NCT02216578
BLU-285 (avapritinib)	Blueprint Medicines	KIT, PDGFRA	Most KIT, PDGFRA (also D842V)		Phase I/II (NCT02508532) and III (NCT03465722)
DCC-2618	Deciphera	KIT, PDGFRA	Most KIT, PDGFRA		Phase III (NCT03353753)
PLX-9486 (in combination with PLX-3397)	Plexxicon	KIT (especially 17)			Phase I (NCT02401815)

VEGFR — vascular endothelial cell growth factor receptor; EGFR — endothelial cell growth factor receptor; PDGFRA/B — platelet-derived growth factor receptor, alpha/beta polypeptide; FLT3 — FMS-like tyrosine kinase 3; HSP-90 — heat shock protein 90

A prospective clinical trial, randomised and placebo-controlled, showed prolonged progression-free survival with **regorafenib** (at a starting dose of 160 g per day in three-week treatment cycles with one-week intervals) in GIST patients resistant to imatinib and sunitinib (median 4.8 *vs.* 0.9 months for regorafenib compared with placebo, hazard ratio 0.27, $p < 0.0001$), and this drug was registered as the recommended therapeutic option in the third line [26, 27] (Table 5). The most important adverse events during regorafenib treatment included hypertension, hand-foot syndrome, and diarrhoea. In Poland, it is now possible to treat patients after progression during imatinib and sunitinib therapy with **sorafenib** in addition to registration indications (off label) under the drug program based on the positive results of the phase II study and cohort studies [28, 29]. In the case of further progression, it is recommended that the patient be included in clinical trials with new drugs (e.g. BLU-285, DCC-2618, crenolanib) [30, 31], which in phase I studies showed promising activity also in the case of the *PDGFRA D842V* mutation (Table 6).

In the case of symptomatic or rarely limited progression of disease, the use of interventional procedures can be considered (thermoablation of lesions in radio waves, surgical resection, chemoembolisation of the hepatic artery branches). In the rare case of bone metastases palliative radiotherapy should be considered. In elected cases, one may also consider going back to continuing treatment with imatinib at a daily dose of 400 mg, which can significantly slow down the progression of the disease (some of the lesions remain sensitive to treatment with imatinib).

A small percentage of total remissions observed in imaging studies during treatment with imatinib, along with a progressively increasing percentage of patients with progression due to the occurrence of secondary mutations and clinically late resistances, encourage individualised use of surgical methods to improve the results of treatment with imatinib. Complementary surgery during use tyrosine kinase inhibitors to be planned in patients with oligometastatic disease, with initially clear partial response and subsequent stabilisation of the changes in two subsequent CT scans (i.e. for

4–6 months) and provided resection is possible; it can improve progression-free survival and overall survival [32–34]. At the same time, it is necessary to continue treatment with imatinib and/or sunitinib after excision (including — complete) of residual changes. Surgical treatment should not be used in cases of multifocal GIST progression when imatinib or sunitinib is used.

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