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Current standards and progress in understanding and treatment of GIST

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Summary

Gastrointestinal stromal tumours (GIST), despite being rare, pose a relevant medical problem from the viewpoint of diagnosis and management. GIST are fragile, liable to metastasise and often located in delicate structures. Surgical options, therefore, are limited. In the last decade an improved understanding of the molecular mechanisms of the disease has resulted in novel modes of treatment. The introduction of systemic tyrosine kinase inhibitor therapy with imatinib has significantly improved the outcome of the disease and prolonged the survival of GIST patients. For many patients the acute threat of a deadly cancer has been transformed into a manageable chronic condition. Drug safety, tolerability and compliance, subjects of concern in all long-term therapies, have proven to be acceptable for the tyrosine kinase inhibitor imatinib. The present paper provides a compact overview of the epidemiology, pathophysiology and morphology of GIST, with special reference to the underlying molecular biology. Relevant aspects of diagnosis, therapy and monitoring of the disease are reviewed with particular emphasis on the available clinical evidence and recent guidelines.

Key words: review; GIST; gastrointestinal stromal tumour; cancer; metastasis; diagnosis; treatment; dosage; c-KIT; PDGFRα; mutation analysis; tyrosine kinase inhibitor; imatinib; sunitinib; surgery

Introduction

Historical aspects

While gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasm of the gastrointestinal tract, they have been known as an entity characterised by a specific histological and immunohistochemical pattern for only ten years [1, 2]. After 1998 diagnoses of GIST dramatically increased, most probably due to improved histopathological detection and greater awareness, but the true incidence may also be rising [3]. As GIST are highly resistant to conventional chemotherapy and radiotherapy [4–7], and carry a high risk of metastatic relapse after initial surgery [8], survival rates were poor until 2002 [9], when the FDA approved the tyrosine kinase inhibitor (TKI) imatinib mesylate (formerly STI571) for their treatment. Identification of KIT receptor tyrosine kinase (KIT, CD117) expression in GIST in 1998 [10] and its precursor cells, interstitial cells of Cajal, as well as the identification of gain-of-function mutations of KIT in the vast majority of GIST [1], resulted in the introduction in 2000 of imatinib mesylate as the first effective systemic therapy for patients with GIST [11]. Despite the substantial improvements in survival and quality of life of patients with GIST, primary and secondary resistance to imatinib may occur. Accordingly, further research has resulted in the introduction of an alternative kinase inhibitor, sunitinib (formerly SU011248), as second line therapy, and currently the efficacy of nilotinib (formerly AMN107) is under investigation. But although systemic tyrosine kinase inhibitor has become established as the treatment of GIST, it has not made surgery obsolete. Surgery continues to be the standard treatment of localised resectable GIST. At present imatinib treatment is under investigation in the adjuvant and neo-adjuvant setting [12, 13].

The clinical significance of oncogenic KIT and platelet derived growth factor alpha (PDGFRα) mutations in gastrointestinal stromal tumours has very recently been reviewed [14]. Another recent review discussed the pathogenesis of GIST, treatment strategies, mechanisms accounting for drug resistance and potential future perspectives [15].

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Epidemiology

In the past the incidence and prevalence GIST were underestimated [16], until recent population-based studies in Europe revealed annual incidences of 10–20 per million and the prevalence was estimated at 129 per million [17–21]. When stratified for risk according to tumour size and proliferative index [22], Swedish data [17] showed prevalence rates (per million) of 22 for very low risk, 52 for low risk, 24 for intermediate risk, 22 for high risk, and 9 for "overtly malignant" GIST. The latter group included all patients with proven metastases at initial diagnosis and accounted for 10% of the cohort (n = 288). Recent studies suggest that very small (0.2–10 mm) asymptomatic GIST are widespread in the population and that mutations of the KIT appear very early [23–25]. The majority of these micro-GIST, however, do not progress to major disease [23, 26].

GIST occur with about equal frequency in men (54%) and women (46%) [16] and over a wide age range, but about three quarters of symptomatic GIST are diagnosed in patients aged over 50, with a median at 58 years [8]. In population-based series, including cases diagnosed at autopsy, the median age was some ten years older (66–69 years) [17, 18].

Carney triad [27], familial gastrointestinal stromal tumour syndrome [28, 29], and von Recklinghausen syndrome are associated with an elevated risk of developing GIST [30]. Specific associations of GIST with other malignancies have not been determined, but GIST are not infrequently seen with other neoplasms [31]. No risk factors or causative factors have been identified.

GIST arise most commonly in the stomach (50–65%) or small bowel (20–30%), although they may occur anywhere along the gastrointestinal tract [26]. The colon and rectum host some 5%–10%, and the oesophagus 5%, of GIST [8, 32]. GIST rarely develop in the mesentery, omentum or retroperitoneum.

Guidelines

In 2006 the National Comprehensive Cancer Network (NCCN) updated their clinical practice guidelines on the management of patients with GIST [33]. The ESMO Guidelines Working Group approved clinical guidelines for diagnosis, treatment and follow-up of GIST in 2006 [34] and 2008 [35]. The published guidelines partly diverge in their recommendations, and country-specific health regulations may interfere with their implementation, and so recommendations specifically addressing the diagnosis and treatment of GIST have recently been published in Switzerland [36].

Histopathology and molecular biology

Morphological variants

Gastrointestinal stromal tumours are assumed to derive from interstitial cells of Cajal or their stem cell-like precursors [1, 2] comprising KIT and KIT-ligand positive intermediates [37] between smooth muscle cells and the GI autonomic nervous system [38, 39]. Most GIST can be classified histologically as spindle cell type (70–80%), epithelioid type (20–30%) or mixed spindle and epithelioid cell type (10%) [22, 40]. It has been recognised that epithelioid cell type features occur more often in tumours that originate in the stomach, and further reports have already suggested that the frequency of PDGFRA mutations in epithelioid GIST may be higher than in spindle cell variants [43, 49]. Yet the relevance of these histological subtypes to underlying mutation, prognosis, response to kinase inhibitor treatment, progression-free and overall survival remains to be investigated. Before the identification of specific and sensitive diagnostic markers the morphological diversity added to the diagnostic challenge.

Immunohistochemical markers of GIST include KIT (positive in 95% of cases), CD34 (60–70%), and smooth muscle actin (30–40%, usually focal and weak staining). KIT is established as the most specific and sensitive diagnostic marker [10, 41].

Phenotypes

More than 95% of GIST express CD117, irrespective of histological appearance, site of origin or biological behaviour, and CD117 is therefore considered to be the best feature for definition of GIST [22, 42], though it is no longer considered an absolute requirement for diagnosis [43]. Usually at least 90% of cells in GIST show CD117 immunostaining, but occasionally as few as 5–20% have been reported [22].

The cell-cell adhesion glycoprotein CD34 is expressed by 60–80% of GIST [22, 40], slightly less by malignant [10] or small bowel GIST [44] but consistently by rectal GIST [43].

Focal reactivity for smooth muscle actin is ex-

hibited by 20–40% of GIST [22, 45], while positivity for the S100 protein and desmin are rare (<5% and <2%, respectively) [22].

A new promising marker was recently discovered on GIST, and was termed DOG-1. It appears to be virtually absent in non-GIST and is expressed independently of mutation type [46, 47]. Experience is still limited as sensitive monoclonal antibodies [47] are not yet universally available.

The expression of protein kinase C theta (PKC_θ) has been identified and found to be specific for GIST [48–52], but it has not been widely adopted for routine diagnosis.

Immunostaining for platelet derived growth factor alpha (PDGFRα) is not considered reliable and quantitative data are scarce, although some studies suggest its use as a diagnostic marker [53].

The KIT

Receptor tyrosine kinase

The c-KIT proto-oncogene located on chromosome 4q11-21 encodes the CD117 protein (c-KIT), a transmembrane receptor tyrosine kinase signalling molecule. The protein contains an extracellular receptor for a growth factor termed stem cell factor (SCF), mast cell growth factor or steel factor, and continues via a transmembrane domain to the intracellular tyrosine kinase moiety (table 1) [54]. Tyrosine kinase is activated (autophosphorylated) on dimerisation triggered by the binding of SCF to two CD117 molecules, and leads to the activation of further intracellular signalling cascades controlling cell proliferation, adhesion and differentiation [55]. The functionally important CD117 is expressed in mast cells, haematopoietic stem cells, germ cells, some epithelial cells and the interstitial cells of Cajal [56].

Expression in other tumour types

Some tumour types, e.g., adenoid cystic carcinoma, synovial sarcoma, rhabdomyosarcoma, glioma, germinoma/seminoma, melanoma, angiosarcoma, acute myeloid leukaemia and mastocytosis can also express CD117 [41, 44]. Not many of these occur within the gastrointestinal tract, and by their overall clinicopathologic features can hardly be mistaken for GIST [57]. Unusual CD117 staining is usually thought to be due to technical artefact [22].

Mutations

Of the four different regions of KIT that have been found to be mutated in GIST, the juxtamembrane part corresponding to exon 11 is most frequently affected (table 1). Missense mutations in KIT exon 11 are seen in 20–30% of GIST, and when occurring in gastric GIST they seem to be associated with a better prognosis [58, 59].

With a frequency of 5–13%, exon 9, encoding the extracellular domain of KIT, is the second most often mutated region of KIT and found almost exclusively in non-gastric intestinal GIST. Much less frequent mutations occur in KIT exon 13, encoding the tyrosine kinase 1 domain (<1–2%; Glu for Lys^{642}), and appear to be associated with higher malignancy of GIST [60, 61]. Mutations of KIT exon 17 were observed in approx. 1% of GIST where substitutions of Lys or Tyr for Asn^{822} interfere with the phosphotransferase domain (catalytic tyrosine kinase 2) [62]. There is also anecdotal evidence of a kindred with both familial GISTs and mastocytosis that express a germline KIT mutation in exon 8, resulting in deletion of codon Asp^{419} and affecting the extracellular, juxtamembrane domain of KIT [63].

The underlying mechanism responsible for the difference in dosing required from the mutational status of the tumour (see later) is not entirely understood. It is postulated that exon KIT 9 Ala^{501}-Tyr^{502} duplications/insertions inter-

Table 1

Frequency, location and type of mutations in GIST, ordered by frequency (del, deletion; ins, insertion; itc, internal tandem duplication; pm, point mutation) adapted from Lasota et al. 2008 [14].

	Frequency	(Functional) domain	Mutation type
c-KIT	80%		
Exon 11	67%	Juxtamembrane	del, pm, ins, itd
Exon 9	10%	Extracellular	ins Ala^{502}-Tyr^{503} ins Phe^{506}-Ala^{507}-Phe^{508}
Exon 13	1–2%	Intracellular tyrosine kinase 1 (P box, ATP and ADP binding sites, imatinib contact points)	Glu for Lys^{642} Lys for Glu^{635}
Exon 17	1%	Intracellular tyrosine kinase 2 (DFG motif, imatinib contact point)	Lys for Asn^{822} Tyr for Asn^{822} His for Asn^{822}
Exon 8	<1%	Extracellular, juxtamembrane	del Asp^{419}
PDGFRα	5–8%		
Exon 18	5%	Intracellular tyrosine kinase 2 (DFG motif, imatinib contact point)	Val for Asp^{842}, Val for Asp^{846} del
Exon 12	1%	Juxtamembrane	Val for $Aspl^{561}$, del, ins
Exon 14	<1%	Intracellular tyrosine kinase 1 (P box, ATP and ADP binding sites, imatinib contact points)	Lys for Asn^{659} Tyr for Asn^{659}

fere with an extracellular KIT antidimerisation motif, resulting in spontaneous receptor homodimerisation [64]. These mutations seem to activate diverse intracellular signalling compared with KIT exon 11 mutant tumours [65–67]. The *in vivo* imatinib dose dependency of tumours expressing KIT exon 9 compared to exon 11 isoforms is even more intriguing, bearing in mind that *in vitro* data show equal sensitivity to inhibition by imatinib [64]. The antitumour efficacy of imatinib may be dependent not only on KIT inhibition, but also on blockade of other kinases which play a role in tumour growth.

The PDGFRα

Receptor tyrosine kinase

A homologous receptor tyrosine kinase to KIT is platelet derived growth factor alpha (PDGFRα) which is involved in connective tissue growth and wound healing, but also expressed in GIST [54]. Of the 20–25% of GIST without KIT mutations, up to a third have mutations in PDGFRα (table 1) [1, 68]. Most frequently affected in 5% of cases is exon 18 with missense mutations (Val for Asp^{842}) or deletions [69]. This exon encodes the tyrosine kinase 2 moiety, and the mutations alter the activation loop that conformationally regulates the ATP-binding site [30]. Interestingly, PDGFRA mutations show a strong predilection for gastric GISTs with epithelioid morphology. These epithelioid GIST of the stomach harbouring PDGFRα mutations seem to have a favourable prognosis, whereas epithelioid GIST occasionally found in the duodenum have been associated with a malignant behaviour [43].

Mutations

Mutations in exons 12 and 14 of PDGFRα are rare (1% and <1%, respectively) and involve substitutions, insertions and deletions (table 1) [70, 71].

KIT und PDGFRα mutations are mutually exclusive.

Presenting symptoms and signs

About half of GIST are diagnosed in clinically symptomatic patients. Two thirds of patients with GIST present with often unspecific symptoms due to an abdominal mass or tumour disruption, such as dysphagia, obstruction, gastrointestinal bleeding (with ensuing anaemia and its sequelae), and/or abdominal pain. About a fifth of the tumours are found incidentally at endoscopy, radiological imaging or surgery for other reasons, and approx. one tenth are incidentally discovered at autopsy (table 2) [33].

GIST are most frequent in the elderly (median age at diagnosis in 288 Swedish patients: 69 years (table 2 and [17]), with only 25% diagnosed at age 50 years or younger. Cases in patients under 30, including paediatric, are extremely rare (see below). There is no predilection for either gender. The tumours may form polypoid mucosal- or serosal-based masses, but generally they are centred on the intestinal wall. GIST usually present as single, well-circumscribed nodules (table 2 and [30, 33]). The usual clinical manifestations of GIST malignancy are liver metastases and/or metastatic dissemination in the abdominal cavity as innumerable serosal-based nodules. Metastasis to lymph nodes, lung, bones and other extra-abdominal sites, however, is extremely uncommon [33].

Primary GIST range in size from less than 1 cm diameter, usually found incidentally, to more than 35 cm, with a median at 50 mm [23, 33].

Paediatric GIST are very rare, occurring predominantly in female patients and associated with gastric localisation and epithelioid morphology. In general these tumours lack KIT and PDGFRα mutations, suggesting an unrelated oncogenic pathway. Recently, however, different mutations (KIT exon 9 or PDGFRα exon 18) have been described in paediatric GIST, but these mutations may represent random mutagenic events [14].

Table 2

Clinical presentation of GIST in the pre-imatinib era according to a population-based study in Sweden [data from 17] (G, stomach; D, duodenum; J, jejunum-ileum; C, colon; R, rectum; M, mesenterium; O, omentum).

	Patients	Gender	Age	Tumour size	Tumour site				
	no. (%)	M/F ratio	median (range) (years)	median (range) (cm)	G	D	J	C, R	M, O
All	288 (100%)	1.0	69 (10–92)	7.0 (0.5–35.0)	170	13	84	18	3
Clinical-symptomatic	199 (69%)	1.14	67 (10–92)	8.9 (1.0–35.0)	120	12	50	6 (C) 10 (R)	1 (M)
Clinical-incidental	60 (21%)	0.67	74 (42–89)	2.7 (0.5–10.0)	23	1	32	2	2 (O)
Autopsy-incidental	29 (10%)	0.93	78 (48–90)	3.4 (0.5–10.0)	27	0	2	0	0

Prognostic factors and risk assessment

Long known and well established factors affecting overall survival (OS) and progression- (or disease-) free survival (PFS or DSF) of GIST patients are mitotic activity, measured in number of mitoses per 50 high power fields (i.e., per 5 mm^2, mitotic index), and size of primary tumour. Apart from these histological parameters, further clinicopathological factors have recently been shown also to affect OS and/or PFS, such as tumour location [72], male sex, R1 resection or tumour rupture, and, to a lesser degree, epithelioid cell or mixed cell pathological subtype, also depending on their localisation [73]. Analysis of two imatinib trials (SWOG S0033 and EORTC 62005) by the GIST Meta-Analysis Group (MetaGIST) involving data of 1640 patients followed up for a median 45 months has identified more prognostic parameters. Poor performance status (PS), high absolute neutrophil count (ANC), absent exon-11 mutation and low baseline haemoglobin level were significantly correlated with a lower PFS [74].

There is no specific staging or grading system for GIST. Assessment of prognosis, i.e. the risk of relapse or progression, is most commonly based on tumour size and mitotic index of the primary tumour (table 3) [22]. Extensions or adaptations of this scheme have recently been published [75, 76]. Patients in the high risk strata have generally been shown to be associated with increased disease recurrence and decreased survival [21, 75, 76] despite complete surgical resection [77].

Another important risk factor in GIST is the location of the tumour. It was shown in the pre-imatinib era that small bowel stromal tumours carry a higher risk of progression than gastric stromal tumours of similar size and mitotic activity. Accordingly, risk assessment has recently been refined by including the anatomic site of the resected primary tumour (table 4) [33, 72]. In general, GIST not exceeding 2 cm behave biologically in a non-aggressive manner (unless located in the duodenum or rectum and showing more than 5 mitoses per 50 high power fields), whereas tumours larger than 2 cm have an increased risk of recurrence. Other clinicopathologic factors, such as PS, ANC, haemoglobin level and mutational status should also be considered [74].

Table 3

Risk stratification of primary GIST according to tumour size and mitotic activity, a consensus approach 2002 [22] (HPF, high power field corresponding to 5 mm^2).

Risk group	Mitotic index (counts per 50 HPF)	Tumour size (cm)
Very low	<5	<2
Low	<5	2–5
Intermediate	6–10	<5
	<5	5–10
High	>5	>5
	Any	>10
	>10	Any
	Resected metastases at diagnosis	

Table 4

Risk assessment of primary GIST considering anatomic site in addition to size and mitotic activity [33]. Data based on long-term follow-up observation of 1939 patients [72] (HPF, high power field corresponding to 5 mm^2).

Tumour parameter		Risk of progressive disease*			
Mitotic index (counts per 50 HPF)	Size (cm)	Gastric	Duodenum	Jejunum or Ileum	Rectum
≤5	≤2	None	None	None	None
	>2 ≤5	Very Low	Low	Low	Low
	>5 ≤10	Low	Moderate	n.a.	n.a.
	>10	Moderate	High	High	High
>5	≤2	None†	High†	n.a.	High
	>2 ≤5	Moderate	High	High	High
	>5 ≤10	High	High	n.a.	n.a.
	>10	High	High	High	High

* defined as metastasis or tumour-related death; n.a. = not available (insufficient data); † small number of cases

Treatment of GIST

Resectable GIST

Surgery

Surgery remains the mainstay treatment of localised resectable GIST [33, 78]. A complete gross resection with preservation of an intact (pseudo-) capsule and negative microscopic margins should be the goal of surgery. Usually the resection can be accomplished with a segmental resection of the small intestine or a wedge resection of the stomach. However, tumour size and location may dictate more extensive surgery, including partial or total gastrectomy. In the case of oesophageal, duodenal and rectal GIST, wide resection is the preferred treatment of choice [79]. Every effort should be made to ascertain negative margins, although wide margins have not been shown to be beneficial [12]. The resection can be performed

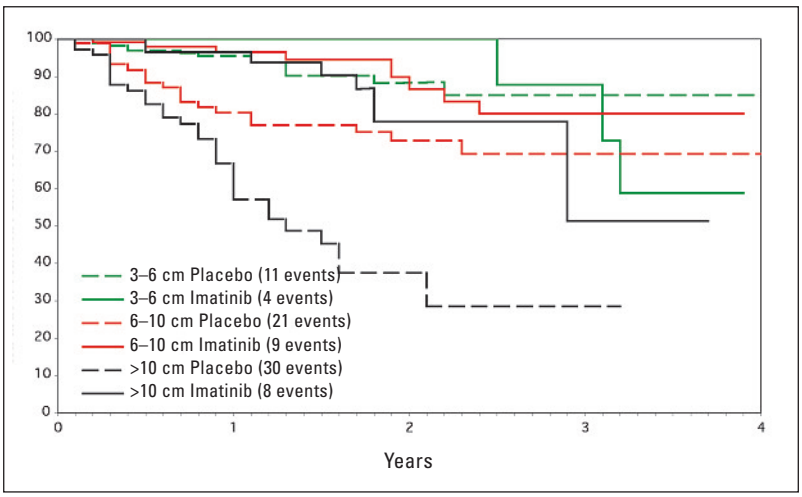

Figure 1

Recurrence-free survival and primary tumour size after complete surgery and adjuvant imatinib vs placebo for one year after resection. Z9001 interim data of 708 patients [from 88] (size 3–6 cm: p = 0.15; size 6–10 cm: p = 0.01; size >10 cm: p <0.001).

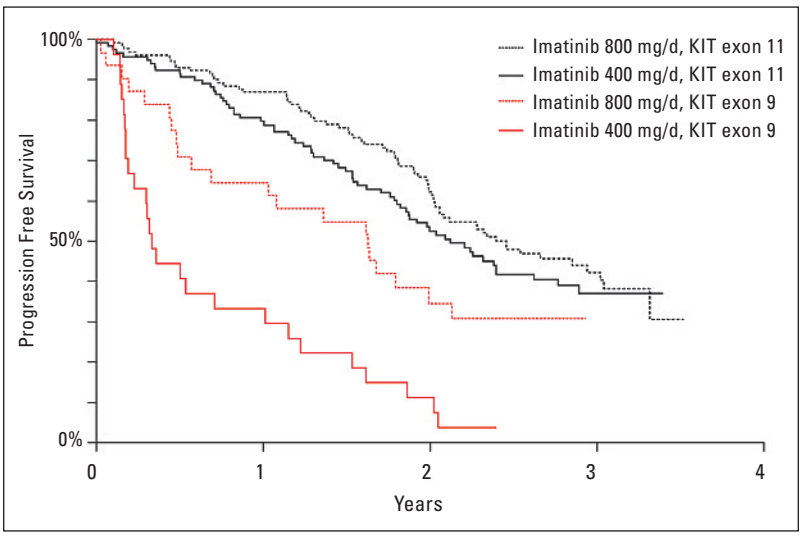

Figure 2

Impact of the randomly allocated initial dose of imatinib on time to progression in patients harbouring tumour with KIT exon 9 or 11 [data from 94].

laparoscopically for small to intermediate size tumours (<5 cm). In experienced hands minimally invasive resections have recurrence rates similar to open surgery and are associated with lower morbidity and shorter hospital stays [80–82]. Lymphadenectomy is warranted only for evident nodal involvement, since GIST rarely metastasise to lymph nodes and haematological spread, usually into the liver, is the main route of GIST dissemination. Since GIST are fragile, they must be handled with great care to avoid rupture and probable intraabdominal dissemination, which were shown to significantly shorten survival [6, 7]. For the same reason, preoperative percutaneous biopsy is not recommended for tumours strongly suspected to be GIST [83]. If performed at all, this should be in centres of expertise. Tumours of indeterminate type should be probed by endoscopic biopsy, or, if they are inaccessible by endoscopy, open biopsy should be chosen [84].

In approx. 85% of patients with localised primary GIST complete gross resection is achieved. In 70–95% of these completely resected cases negative microscopic margins are achieved. At least 50% of patients experience tumour recurrence after complete resection, and 5-year survival is usually some 50% [77, 85, 86].

Neoadjuvant therapy

The preoperative use of imatinib is recommended to avoid mutilating surgery [33, 36]. Neoadjuvant therapy aims at devitalising the tumour mass, which should facilitate resection (e.g., total gastrectomy, Whipple procedure). The use of preoperative imatinib in potentially resectable GIST is currently being tested in a phase II trial by the US Radiation Therapy Oncology Group (RTOG S-0132) and in a German phase II trial (CSTI571-BDE43).

Careful response assessment under neoadjuvant therapy is of particular concern. Early fusion PET/CT scan may serve to identify patients not responding to treatment who should be salvaged by surgery. Most authors performed PET/CT scans after one month of imatinib treatment. Responders should be operated on within 6–12 months of therapy. In patients with oesophageal or rectal GIST surgery may be delayed for up to one year, provided there is continuing response to imatinib treatment [33].

Adjuvant therapy

Irrespective of the quality of the surgical procedure, recurrence occurs in a considerable number of patients after long term follow-up [72]. The 2007 update of the NCCN clinical practice guidelines therefore suggests considering adjuvant imatinib therapy [33]. Recent evidence suggests that high risk patients with recurrent GIST after complete resection could profit from adjuvant imatinib [77]. Adjuvant imatinib is being studied in major clinical trials (ACOSOG Z9000 and Z9001, Scandinavian/German SSG XVIII/AIO, EORTC 62024).

Interim results in 107 patients of the ACOSOG Adjuvant Trial (Z9000) indicate that imatinib at 400 mg daily for 1 year following the resection prolongs recurrence-free survival and is associated with improved overall survival compared to historical controls (99, 97 and 97% after 1, 2 and 3 years respectively). The 1, 2, and 3 year recurrence-free survival rates were 94, 73, and 61% respectively. Half of the tumours were of gastric origin and 42% arose in the small intestine. Safety analysis showed adjuvant imatinib to be well tolerated in this setting [87].

The ACOSOG Adjuvant Trial (Z9001) showed that recurrence of GIST under adjuvant imatinib treatment correlated with tumour size. Patients were at considerably higher risk of recurrence when tumour size exceeded 10 cm. Compared to placebo, the estimated relative risk for tumour recurrence in patients receiving imatinib

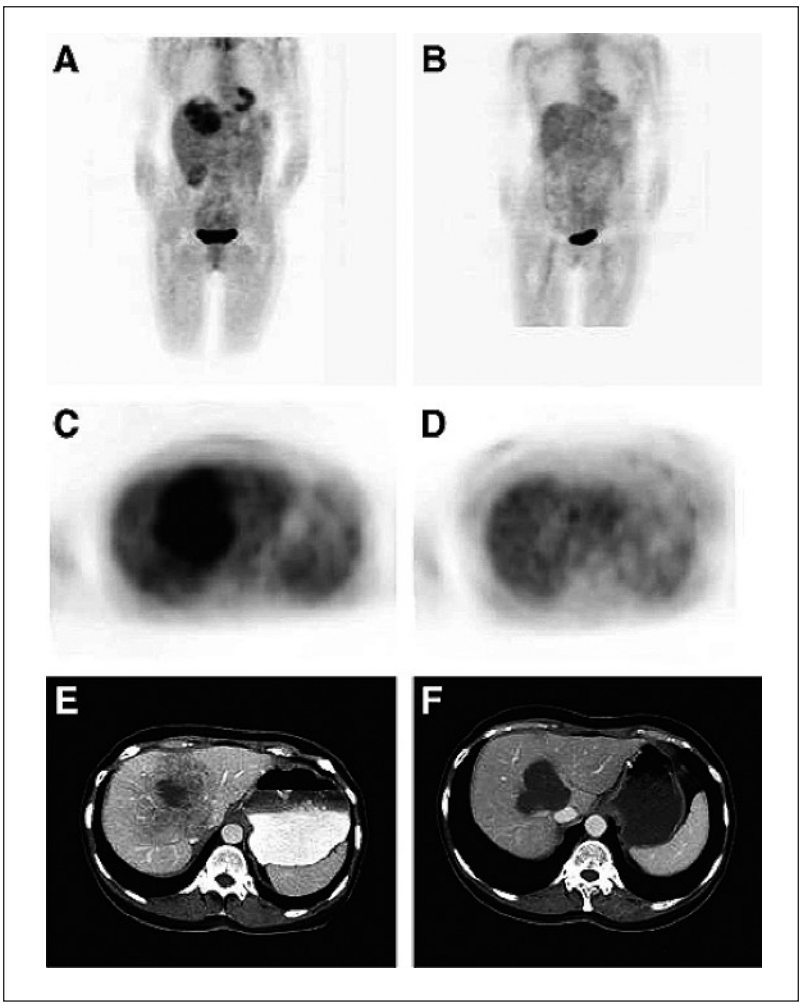

Figure 3

^{18}FDG-PET can detect imatinib response earlier than CT. ^{18}FDG-PET scans (A, C) and a CT scan (E) with large tumour metastases in the liver one year after resection, before the start of imatinib therapy. ^{18}FDG -PET (B, D) and CT (F) imaging evaluations after two months of imatinib therapy. No pathological FDG uptake can be observed in the liver. However, residual tumour on the CT scan remains considerable. From [110], with permission from AlphaMed Press, 318 Blackwell Street, Suite 260, Durham, NC 27701, U.S.A.

at 400 mg daily was progressively lower with increasing tumour size. Compared to placebo, imatinib delayed recurrence in all tumour size strata (fig. 1) (one year RFS: 97% vs 83%; p =0.0000014), with adjuvant imatinib having greatest impact in patients with larger tumours. The hazard ratio (imatinib vs placebo) for patients with tumours 10 cm and larger was 0.19 (0.09–0.41; p <0.001), for patients with tumours 6–10 cm 0.37 (0.17–0.81; p <0.01) and, although not statistically significant, 0.76 (0.17–3.4; p <0.15) for patients with 3–6 cm tumours. Overall survival was unchanged [88].

A controlled randomised phase 3 trial is ongoing to investigate OS, relapse-free survival, relapse-free interval, and safety in 900 patients receiving imatinib at 400 mg daily vs no further therapy for two years after complete resection of KIT positive GIST (EORTC 62024). Another open-label, multicenter, prospective, randomized phase III study in Scandinavia and Germany (SSGXVIII/AIO) investigates the efficacy and safety of imatinib at 400 mg daily for either 12 or 36 months following macroscopically radical surgery of GIST in patients estimated to be at a high risk of disease recurrence. Accrual has recently been closed at 400 patients.

On the basis of available data Swiss guidelines recommend that patients at high and intermediate risk of recurrence (according to the Fletcher criteria [22] and/or tumour location [72]) after resection of primary GIST enrol in prospective trials of adjuvant imatinib and should be treated for at least one year [36].

Non-resectable and/or metastatic GIST

Treatment options for patients with unresectable or metastatic GIST were very limited in the pre-TKI era, as GIST respond poorly to chemotherapy or radiation therapy. Before the advent of imatinib median survival was 18–24 months [8, 89]. Today, as a general rule R1/R2 resections and debulking or mutilating surgery are no longer recommended and instead systemic treatment with imatinib should be the standard choice [33, 36]. The introduction of imatinib has changed the natural history of the disease to the extent that median survival after receiving diagnosis has increased to 4.8 years [33].

Standard dose imatinib

A long-term analysis of 147 imatinib-treated patients with primarily unresectable or metastatic, KIT expressing GIST, revealed that 52% of them survived for more than five years [90] (phase II study B2222 and extension). Partial response and stable disease resulted in a similar survival benefit. The study with a median follow-up of 63 months and longer also showed that long-term imatinib treatment was well tolerated and that a daily dose of 600 mg was not superior to standard 400 mg [91].

High dose imatinib

An imatinib starting dose of 400 mg or 800 mg daily was compared in studies EORTC 62005 and SWOG S0033 with the option of crossover to the higher dose regimen upon progression at the lower dose [92, 93]. The analysis included 1640 patients with a median follow-up of 42 and 55 months (EORTC and SWOG respectively), for almost half of which mutation data were available. Patients progressing on imatinib at 400 mg per day significantly benefited from cross-

ing over to 800 mg imatinib per day. In both trials response rates and PFS did not differ significantly between the two initial dosing arms [74].

Subgroup post-hoc analyses of the combined data of the EORTC 62005 and the SWOG S0033 studies (Meta-GIST) showed that patients with a GIST harbouring a KIT exon 9 mutation had a significant PFS benefit from starting with imatinib 800 mg per day as compared to 400 mg per day (HR 0,89). For KIT exon 11 carriers the higher dose advantage is less significant (fig. 2). There was no evidence of prolonged overall survival [74, 94]. Based on these analyses the ESMO clinical guidelines and the Swiss guidelines recommend 800 mg as the starting dose for patients harbouring an exon 9 mutation [35, 36].

Duration imatinib therapy

The French phase III trial BFR14 randomised 58 patients with metastatic or unresectable GIST after one year of tumour control on treatment with 400 mg imatinib daily to continue or stop treatment. Patients whose imatinib therapy was interrupted had a significantly higher risk of relapse ($p < 0.0001$) [95]. These findings were confirmed after three years of tumour control in 35 patients [96]. No differences in overall survival or imatinib resistance were observed between the two arms. Although more than 92% (after one year, 100% after three years) of the patients with disease progression after interruption responded to the reintroduction of imatinib treatment [95, 96], Swiss guidelines discourage interruption of treatment outside of a clinical trial, unless progression, intolerance or patient refusal occurs [36].

Management of progression

Under prolonged TKI treatment in patients with advanced GIST the risk of resistance to therapy is elevated [97]. An increasing frequency of secondary mutations in KIT or PDGFRα has been reported [98, 99]. While metastases usually carry the primary mutations and continue to respond to TKI therapy, clones of new additional KIT mutations (rarely PDGFRα mutations) are found in a proportion of several lesions [99]. Polyclonal resistance is indicated by the presence of several different new mutations, as reported in chronic myelogenous leukaemia under imatinib therapy [100]. Secondary mutations are missense mutations and are largely located in the kinase domains (KIT exons 13–17) [14] of the same allele to the primary mutations [101]. GIST with secondary mutations in exon 13 and 14 were reported to be sensitive to sunitinib [14]. Surgical resection of the lesions with acquired resistance may be indicated [102, 103], while still responding tumour masses would not need surgical intervention during an ongoing TKI regimen.

A correlation between plasma imatinib levels and clinical benefit was recently reported. Patients of the B2222 study with plasma imatinib levels above 1100 ng/ml showed significantly longer time to progression (TTP) compared to patients with lower plasma imatinib levels (median TTP 30.6 vs 11.3 months; $p = 0.0029$) [90]. As the pre-existing tumour tissue continues to respond to imatinib, escalation of the imatinib dose regimen can slow the growth of the resistant lesions [104]. In the event of disease progression Swiss guidelines recommend to checking plasma imatinib levels and considering a dose escalation to 800 mg per day [36]. But now patient adherence to treatment is also an important issue that should not be ignored, with up to 30% of patients stopping taking their pills [105].

After disease progression on high dose imatinib or imatinib intolerance, switching to second-line therapy with sunitinib may be successful [89]. The effectiveness of sunitinib could depend on the mutational status, as wild-type or KIT exon 9 mutants have shown a better response than KIT exon 11 mutants. Close monitoring for adverse effects of sunitinib is mandatory. The approved schedule for sunitinib is 50 mg per day for four weeks followed by a two-week rest, although continuous administration of 37.5 mg per day has proved equally effective and better tolerated [106]. The latter administration schedule may also avoid tumour regrowth in the off-treatment interval. The continuous regimen is recommended in Switzerland [36].

In the event of localised progression invasive therapeutic options, such as surgery or radiofrequency ablation, may be considered for selected patients [33].

Imaging and monitoring

CT and PET scan

Although abdominal computed tomography (CT) is considered the imaging method of choice for treatment monitoring and staging of GIST, positron emission tomography (PET) is a valuable complementary tool. CT is recommended for initial abdominal imaging as well as surveillance of metastatic disease after surgical resection of GIST and monitoring of systemic therapy. NCCN guidelines recommend CT within three months of initiating TKI therapy, to be repeated every 3–6 months. The 2008 ESMO guidelines maintain that risk assessment based on mitotic count, tumour size and tumour site may help in choosing the routine follow-up policy, but leave it to the discretion of the institution to choose a routine follow-up scheme with CT. Intermediate and high-risk patients could, for example, undergo a

routine follow-up with CT scan every 3–4 months for 3 years, then every 6 months up to 5 years, and yearly afterwards; for low-risk tumours follow-up could be carried out with CT scan every 6 months for 5 years. The 2008 ESMO guidelines also state that very low risk GIST probably do not deserve routine follow-up, although one must be aware that the risk is not nil [35]. As imatinib therapy may "unmask" small hepatic metastases not seen on baseline CT scans, their appearance should not be misinterpreted as emergence of new foci of progressive disease. Tumour size-based assessment of GIST stage should be applied cautiously, as an apparent increase in tumour mass may be due to intratumoral haemorrhage caused by treatment response [33, 78]. Some of these pitfalls may be avoided by PET functional imaging. The use of whole-body 18F-2-fluoro-2-deoxy-D-glucose PET (^{18}FDG-PET) appears limited for staging of GIST due to the low rate of extra-abdominal tumoural involvement and lower sensitivity than CT. ^{18}FDG-PET may still be useful, particularly when morphological findings are ambiguous, treatment efficacy is uncertain or the CT scan indicates disease progression, especially when these findings disagree with clinical data. In combination with CT, ^{18}FDG-PET allows detection of otherwise inconspicuous metastatic sites, early confirmation of treatment response (fig. 3) and also detection of resistance to TKI treatment. Response to imatinib can be seen as early as 24 hours after administration of a single dose [107] and is prognostic, i.e., predictive for PFS and OS [108]. ^{18}FDG-PET is recommended before surgery of patients with advanced disease considered for neoadjuvant therapy, and as a baseline measure before initiation of systemic therapy in this group of patients [36]. ^{18}FDG-PET images are thus reliable surrogate markers of response to imatinib and outcome [33]. Recent data confirmed that a single PET performed after one month on sunitinib was also predictive of patient outcome [109]. Commercial hybrid PET/CT systems are available and have been shown to be useful in GIST [110]. ESMO guidelines recommended ^{18}FDG-PET only if early detection of tumour response to imatinib treatment is required for the purpose of planning surgery or response evaluation is equivocal [34]. Swiss guidelines recommend performing ^{18}FDG-PET in non-resectable GIST and as a baseline measure before initiation of neoadjuvant TKI therapy and one month after treatment start [36].

New CHOI criteria vs conventional RECIST criteria

It is essential for the management of advanced GIST that response to treatment be determined accurately and early. The conventional Response Evaluation Criteria in Solid Tumours (RECIST) [111] and SWOG criteria [112] are based on tumour size and are limited in assessing responses in the era of TKI, because of several particular response characteristics of GIST. GIST responding to TKI-therapy, for example, may increase in size due to fluid-volume expansion. Tumour vascularity and density, which also play a role, are not captured by these criteria. Overall clinical benefit is also underestimated by RECIST and SWOG criteria as they ignore stable disease as response. To address these shortcomings, modified CT imaging criteria have been proposed that are based on changes in tumour size and density (table 5) [113, 114]. These "Choi criteria" are sensitive and specific for assessing tumour response to TKI. They predicted maximum lesional standardised uptake values (SUVmax) and time to progression by a more than 10% decrease in tumour size or a more than 15% decrease in tumour density (as measured by Hounsfield Units). Sensitivity and specificity for identifying responders by ^{18}FDG-PET were 97% and 100% respectively. Good and poor ^{18}FDG-PET responders could be significantly differentiated by excellent prediction of TTP ($p = 0.0002$). A significant difference in disease-specific survival was also detected after 60 months of imatinib treatment ($p = 0.04$) [115]. The accuracy of the "Choi criteria" may be compromised, however, by the presence of haemorrhage, calcification, and perforation of lesions.

Table 5

RECIST and modified CT response evaluation criteria [111, 113].

RECIST definition [111]	Response	«Choi» definition [113]
Disappearance of all lesions No new lesions	Complete (CR)	Disappearance of all lesions No new lesions
30% decrease in size No further increase	Partial (PR)	≥10% decrease in size OR ≥15% decrease in density (HU) on CT No new lesions No obvious progression of non-measurable disease
Does not meet criteria for partial response or progression	Stable disease (SD)	Does not meet criteria for complete response, partial response, or progression No symptomatic deterioration attributed to tumour progression
20% increase in size AND criteria for CR, PR or SD not met before increased disease	Progression (PD)	≥10% increase of tumour size AND does not meet criteria of PR by tumour density (HU) on CT New lesions New intratumoral nodules or increase in size of existing intratumoral nodules

Future directions

Other candidate compounds for second- or third-line therapy of imatinib-refractory GIST are being tested [116, 117], e.g., the kinase inhibitors nilotinib [118], dasatinib [119], sorafenib [120], masatinib [121], vatalanib [122], cediranib [123], motesanib [124, 125], the PKC inhibitor PKC412 [118], the rapamycin target protein (FRAP1 or mTOR) inhibitor everolimus [126], and the heat shock protein 90 (HSP90) inhibitor IPI-504 [127]. Some of these substances may be effective through their antiangiogenic effect, e.g., sorafenib, cediranib, motesanib and everolimus, as well as sunitinib.

Economic considerations

Although efficacy and safety are the most important conditions for approval of new therapies, the financial impact on a healthcare system must also be assessed. Currently, two full reports on the cost-effectiveness of imatinib in GIST are available: a very recent assessment from a US society perspective based on a median of 52 months' follow-up data [128] and a health technology assessment of the UK National Health Service from 2005 based on a median of 25 months' follow-up data [129]. Based on the more robust survival projections (5.8 years life expectancy with imatinib therapy compared to 3.1 years without imatinib), the US assessment yielded a cost-effectiveness ratio of $38,723 per QALY. Cost-effectiveness in the report of the UK NHS was in the range of £21,404–33,976 per QALY, yet both figures are within the range considered as societal willingness to pay for a medical treatment (<$100,000 or <£35,000 per QALY) [130, 131]. A recent third investigation in Canada also concluded that imatinib treatment is cost-effective. The annual incremental cost-effectiveness ratio was established at $15,882 per median life year gained and $23,603 per median year of PFS [132].

Conclusion

Recent advances in molecular pathology, imaging techniques, surgical procedures, and systemic drug therapy with tyrosine kinase inhibitors (TKIs) have augmented the available options for diagnosis and treatment of GIST. Most notably, the introduction of imatinib therapy has significantly improved clinical outcomes of patients with advanced and metastatic GIST, nowadays also in adjuvant and neoadjuvant settings. Diagnosis of GIST is based on the histological and immunohistochemical presentation. Molecular typing (mutational analysis) of tumour tissue can aid in assessing prognosis and optimising drug therapy. Conventional (CT scan) and novel imaging techniques (functional PET) are valuable tools for disease staging and monitoring tumour size and location during therapy. Complete gross surgical resection with negative microscopic margins remains the mainstay treatment of localised resectable GIST. High risk patients with recurrent GIST after complete resection, in particular those with larger tumours, could profit from adjuvant imatinib therapy. Neoadjuvant (preoperative) therapy with imatinib is a promising new option currently tested in clinical trials. Advanced, nonresectable and/or metastatic GIST is safely and continuously treated with imatinib at 400 mg daily, with the option of dose escalation to 800 mg daily on disease progression or in the cases with exon 9 mutations. In salvage cases, surgery or novel compounds such as sunitinib may be indicated.

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