Gastrointestinal stromal tumour

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Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms that arise in the gastrointestinal tract, usually in the stomach or the small intestine and rarely elsewhere in the abdomen. They can occur at any age, the median age being 60–65 years, and typically cause bleeding, anaemia, and pain. GISTs have variable malignant potential, ranging from small lesions with a benign behaviour to fatal sarcomas. Most tumours stain positively for the mast/stem cell growth factor receptor KIT and anoctamin 1 and harbour a kinase-activating mutation in either *KIT* or *PDGFRA*. Tumours without such mutations could have alterations in genes of the succinate dehydrogenase complex or in *BRAF*, or rarely RAS family genes. About 60% of patients are cured by surgery. Adjuvant treatment with imatinib is recommended for patients with a substantial risk of recurrence, if the tumour has an imatinib-sensitive mutation. Tyrosine kinase inhibitors substantially improve survival in advanced disease, but secondary drug resistance is common.

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Introduction

Gastrointestinal stromal tumours (GISTs) are neoplasms that arise either from the mesenchymal (non-epithelial) tissue of the gastrointestinal tract or, rarely, from other intra-abdominal soft tissues (figure 1).[1] They probably originate from—or share a common stem cell with—the interstitial cells of Cajal.[2,3] These cells, which are located in the myentric plexus of the gastrointestinal tract, are pacemaker cells that cause gut peristaltic contractions. GISTs occur anywhere along the gastrointestinal tract; they are most common in the stomach (50–60%) and the small intestine (30–35%) and less frequent in the colon and rectum (5%) and the oesophagus (<1%).[4] GISTs found elsewhere within the abdominal cavity, usually in the omentum, mesentery, or the retroperitoneum (<5% of all GISTs), are referred to as extra-gastrointestinal tract tumours, or E-GISTs, but some of these could be metastases from an undetected primary tumour.[4,5]

The malignant potential of GISTs ranges from small lesions with a benign behaviour to aggressive sarcomas. About 40% of GISTs that are localised at the time of detection give rise to metastases,[4] and 10–20% of patients with GISTs present with overt metastases.[6,7] Metastases have a predilection to the liver, omentum, peritoneum, and other intra-abdominal sites, whereas metastases outside the abdomen are uncommon.[8]

The notion of GISTs was introduced in the 1980s,[9] but these neoplasms were not recognised widely until the start of the 21st century. In 1998, mutations in the *KIT* oncogene were noted in GISTs,[10] and in 2001, imatinib—a selective inhibitor of KIT, platelet-derived growth factor receptors (PDGFRs), and a few other tyrosine kinases—proved highly effective to treat advanced GIST.[11,12] Before this time, GISTs were sometimes classified as leiomyomas, leiomyosarcomas, or leiomyoblastomas, but now we know that most sarcomas arising from the gastrointestinal tract are GISTs, and that gastrointestinal tract leiomyosarcoma is a rare tumour, with fewer than 100 cases identified in a literature review covering the past 12 years.[13]

Search strategy and selection criteria

We searched PubMed and Scopus (includes Embase) from January, 2000, to October, 2012, using key terms including "gastrointestinal stromal tumour" and "GIST". Furthermore, we reviewed reference lists of relevant papers. We used the ClinicalTrials.gov website to identify important clinical trials. Meeting abstracts of the American Society of Clinical Oncology were reviewed in part. We restricted our search to papers published in English, and we gave preference to high-quality papers in which important observations were recorded or randomised clinical trials were reported.

Epidemiology

GISTs comprise a fifth of soft-tissue sarcomas, making them the most common single type of sarcoma.[14] The crude annual incidence of clinically detected GISTs is about ten cases per million in Europe,[14,15] and age-adjusted incidence is seven cases per million in Europe and the USA.[14,16,17] Incidence could be higher in Korea and Hong Kong (16–22 per million per year),[18,19] with a relatively high proportion of E-GISTs (10%) in Korea.[19] The global incidence is unknown. Prevalence is about 130 cases per million population.[15,18]

GISTs can arise at any age, but more than 80% are reported in individuals older than 50 years (median 63 years).[4,14] The few patients are who younger than 20 years (about 0·4%)[4] frequently have GIST associated with a syndrome. Men and women are affected at a roughly similar frequency.

Micro-GIST

GISTs less than 1·0 cm in diameter are referred to as micro-GISTs. They were recognised by Japanese investigators[20] and are frequent incidental findings in resection specimens of the gastro-oesophageal junction.[21] In a Japanese study of 100 gastric cancer resection specimens, meticulous microscopic inspection of grossly normal areas revealed one or more micro-GISTs in 35 cases.[22] In subsequent studies, based either on autopsy tissue or surgical specimens, micro-GISTs were confirmed in 10–22·5% of stomachs from middle-aged or elderly individuals.[23,24]

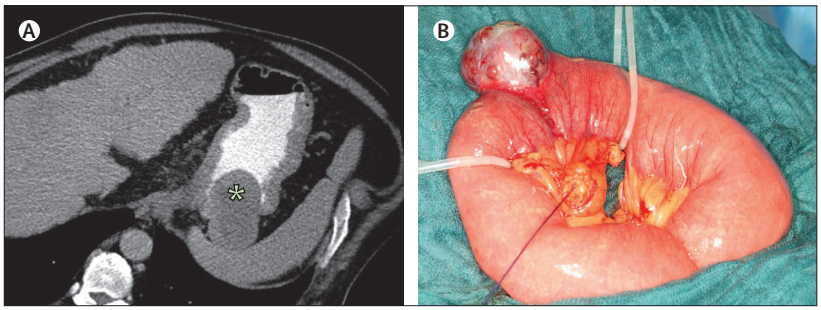

Figure 1: **Examples of GIST**
(A) GIST of the proximal stomach with intragastric (asterisk) and extragastric extension. (B) GIST of the small bowel with necrotic areas at the tumour surface (planned resection lines are indicated with the loops, note the hypervascular peritumoral bowel surface). GIST=gastrointestinal stromal tumour.

Most micro-GISTs arise at the gastro-oesophageal junction or proximal stomach, at which small leiomyomas are also common.[22,24] Micro-GISTs are infrequent at other sites of the gastrointestinal tract.[21] Few or no mitotic figures are present,[22] whereas hyalinisation and calcification are common.[23] Nevertheless, micro-GISTs frequently harbour mutations in *KIT* or *PDGFRA* that are identical to those seen in larger, clinically significant GISTs,[22,23,25,26] suggesting that a large pool of micro-GISTs exists in the general population, which serves as a reservoir for more advanced lesions, and that accumulation of further molecular alterations is probably necessary for macroscopic lesions to arise.

Risk factors

Most GISTs are sporadic and have no established risk factors. However, some GISTs arise in the setting of specific tumour syndromes.

Familial GIST

Heritable mutations in *KIT* exon 8, 11, 13, or 17 confer a high risk for developing one or more gastric or small-bowel GISTs, as early as age 18 years.[27–32] Diffuse hyperplasia of interstitial cells of Cajal is sometimes evident in the adjacent gut wall. Additional findings can include pigmented skin macules on the perineum, axilla, hands, and face, and urticaria pigmentosa. Patients with germline mutations in *PDGFRA* exon 12 are also at risk of GISTs and frequently develop inflammatory fibroid polyps of the stomach and small bowel.[33,34]

See Online for appendix

Carney's triad

The association of gastric GIST, paraganglioma, and pulmonary chondroma—known as Carney's triad—is a rare non-heritable syndrome that is seen mainly in girls and young women.[35] GISTs associated with Carney's triad do not have *KIT* or *PDGFRA* mutations[36] but they show loss of expression of succinate dehydrogenase subunit B (SDHB) by immunohistochemistry.[37] The cause for this enzyme deficiency is unknown, because mutations in genes encoding succinate dehydrogenase subunits have not been recorded in these tumours.

Carney-Stratakis syndrome

Patients with a germline mutation in any subunit of succinate dehydrogenase (genes *SDHA*, *SDHB*, *SDHC*, and *SDHD*) are at substantial risk for both paraganglioma and GIST. These affected individuals do not have *KIT* and *PDGFRA* mutations in GISTs but, by immunohistochemistry, show loss of expression of succinate dehydrogenase subunit B (and subunit A in patients with a mutation in *SDHA*).[38–41]

Type 1 neurofibromatosis

A subset of patients with type 1 neurofibromatosis (von Recklinghausen's neurofibromatosis) will develop one or more GISTs, mainly in the small intestine. In a study of 70 patients with this disease,[42] the prevalence of GISTs was about 7%. Tumours are strongly positive for KIT by immunohistochemistry yet they are generally negative for *KIT* mutations.[43,44]

Diagnosis

Although most patients have symptoms or a palpable tumour at presentation, 25% of GISTs are discovered incidentally during imaging or surgery for other disorders, and a few (about 5%) are found at autopsy.[15,16,45] The most frequent symptoms are bleeding into the bowel or abdominal cavity, anaemia, and abdominal pain, but others can include dyspepsia, nausea or vomiting, constipation or diarrhoea, frequent urination, and fatigue.[16,45,46] Haemorrhage, tumour rupture, and bowel perforation or obstruction might need emergency surgery.

A biopsy sample obtained by endoscopy is preferable to transcutaneous biopsy because the risk of tumour spillage into the abdominal cavity is smaller. If accessible liver metastases are present, a biopsy specimen from a metastasis can establish the diagnosis.

Endoscopic contrast-enhanced ultrasound is especially valuable for assessment of large gastric, duodenal, rectal, or rectovaginal GISTs.[47] A small gastric GIST could have a large extragastric extension not visible at endoscopy (figure 1A). Because metastases are infrequent outside the abdomen, imaging of the abdomen and the pelvis with contrast-enhanced CT or MRI will usually suffice.

Pathology

Three morphological patterns are seen in GISTs: spindle cell, epithelioid, and mixed (appendix pp 2–3).[48,49] These patterns overlap with various other tumours affecting the gastrointestinal tract, including non-GIST sarcomas, sarcomatoid carcinomas, and even metastatic melanoma. Therefore, immunohistochemical stains are used to confirm a suspected diagnosis (appendix p 1). KIT (also known as CD117) and anoctamin 1 (ANO1; also known as DOG1) are the two most sensitive and specific markers for GIST.[50–52] About 5% of GISTs are negative for KIT

expression, but many of these express ANO1. This expression is important because a subset of KIT-negative GISTs will respond to KIT-targeted treatment.[53]

Molecular pathology

Most (75–80%) GISTs have *KIT* mutations,[2,10] typically affecting the juxtamembrane domain encoded by exon 11 (figure 2). The alterations might be in-frame deletions or insertions, missense mutations, or combinations thereof. Mutations also arise in the extracellular domains of *KIT* (usually exon 9; prevalence about 6%) and in the kinase I and II domains (exons 13 and 17; about 2%).[54] 20–25% of GISTs do not have *KIT* mutations, and of these tumours about a third have *PDGFRA* mutations in domains homologous to those in *KIT* (prevalence of *PDGFRA* mutations is about 10%).[55,56] *KIT* and *PDGFRA* mutations are mutually exclusive.

KIT and PDGFRA kinase domains are activated normally through binding of their respective ligands (stem-cell factor or platelet-derived growth factor), leading to receptor dimerisation.[57] The juxtamembrane regions of these kinases serve to regulate dimerisation, thus, mutations in these domains disrupt this function.[58,59] By contrast, alterations in the kinase II domains of KIT and PDGFRA alter the activation loop that conformationally regulates the ATP-binding pocket of each kinase (figure 2). Through these and probably other mechanisms, mutations of *KIT* and *PDGFRA* promote oncogenic signalling through the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) pathways (figure 3).[2,60]

10–15% of GISTs do not have a detectable *KIT* or *PDGFRA* mutation. These so-called wild-type tumours form a heterogeneous group, some of which are driven by oncogenic mutations acting downstream of the receptor kinases. Wild-type GISTs include neurofibromatosis 1 (*NF1* gene mutation), Carney-Stratakis syndrome (rare), Carney's triad (rare), *BRAF* mutation (rare), succinate dehydrogenase subunit mutations (*SDHA*, *SDHB*, *SDHC*, *SDHD*), and RAS-family mutations (*HRAS*, *NRAS*, *KRAS*).[44,61–63] In wild-type GISTs without succinate dehydrogenase activity, upregulation of hypoxia-inducible factor α (HIF1α) might lead to increased growth signalling through insulin-like growth factor receptor 1 (IGF1R) and vascular endothelial growth factor receptor 2 (VEGFR2; figure 3).[41,64,65]

Several chromosomal changes are associated with malignant progression of GISTs. These include deletions on 14q, 22q, 1p, and 9p.[2] A key gene on chromosome 9p is *CDKN2A*, which encodes an important cell-cycle regulator and is commonly inactivated in GISTs.[66] Gains on chromosomes 8q and 17q have been associated with metastatic behaviour.[67,68]

Treatment of localised GIST

Surgery

Detected or suspected GISTs that are 2 cm or larger should be removed, whereas smaller tumours can be excised or monitored by endoscopy at intervals of 6–12 months.[69] Complete (R0) resection of GISTs without rupturing the tumour pseudocapsule is the main aim of surgical treatment.[70] Large GISTs are typically soft and fragile and the thin pseudocapsule can rupture if handled boldly.

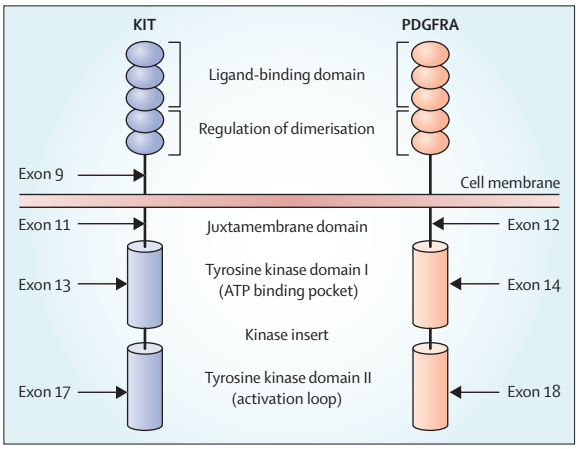

Figure 2: **Structure of KIT and PDGFRA receptor tyrosine kinases**

A macroscopic margin of 1–2 cm could be sufficient to achieve microscopically negative margins. Gastric or oesophageal GISTs should not be excised at endoscopy because R0 resection might not be achieved. Similarly, GISTs located in the rectum or rectovaginal septum should not be treated with local excision unless preoperative imatinib shrinks the tumour.

Lymph-node dissection is generally not indicated because lymph-node metastases are rare (prevalence is about 1%). However, in paediatric, syndromic, and paediatric-type GISTs arising in adults younger than 40 years, lymph-node metastases are recorded in 20–59% of patients.[71–73]

Small gastric GISTs can be excised at laparoscopy by a skilled surgical team using an extraction bag. In a pooled series of 540 patients treated with laparoscopic tumour excision,[74] intraoperative and postoperative complication rates were 6·8% and 7·7%, respectively. R0 resection was achieved in 466 (99%) of 473 individuals and 14 (3%) of 496 tumours recurred during median follow-up of 2·5 years.[74] These findings need to be interpreted cautiously since 88% of the tumours had a low or very low estimated risk of recurrence.

Small-bowel GIST is usually resected with a bowel segment (figure 1B). Preoperative imatinib should be considered when an extended procedure—such as a Whipple's operation for duodenal GIST or abdominoperineal excision for rectal GIST—is needed to remove the tumour. Uncertainty surrounds whether residual microscopic disease at resection margins (R1 resection) will affect outcome. Re-resection is, therefore, recommended only when the site of microscopic disease left behind can be identified and the planned operation has little morbidity.

Preoperative imatinib

A few prospective non-randomised studies have been done to assess preoperative imatinib for treatment of locally advanced GIST.[75,76] In these studies, imatinib was usually administered for 2–6 months before surgery. The findings are subject to interpretation in the absence of a control group, but most tumours shrank in size and became less vascular with preoperative imatinib. These effects of imatinib might facilitate resection and allow organ-sparing surgery.[77] Preoperative imatinib could be considered for selected individuals if tumour shrinkage lessened post-operative morbidity. Tumour mutation analysis and longitudinal imaging should be done to identify patients who do not benefit from preoperative imatinib.

Outcome after surgery

Survival

In a pooled analysis of data from ten population-based series and 2459 patients,[4] estimated 5-year and 15-year recurrence-free survival rates for GISTs treated with surgery alone were 70·5% and 59·9%, respectively. Only a few tumours recurred after the first 10 years of follow-up, suggesting that most patients (about 60%) with operable GIST are probably cured by surgery.

Prognostic factors

The most important independent prognostic factor for GIST recurrence after surgery is a high tumour mitotic rate.[4,78–80] Immunostaining for the Ki67 antigen has been

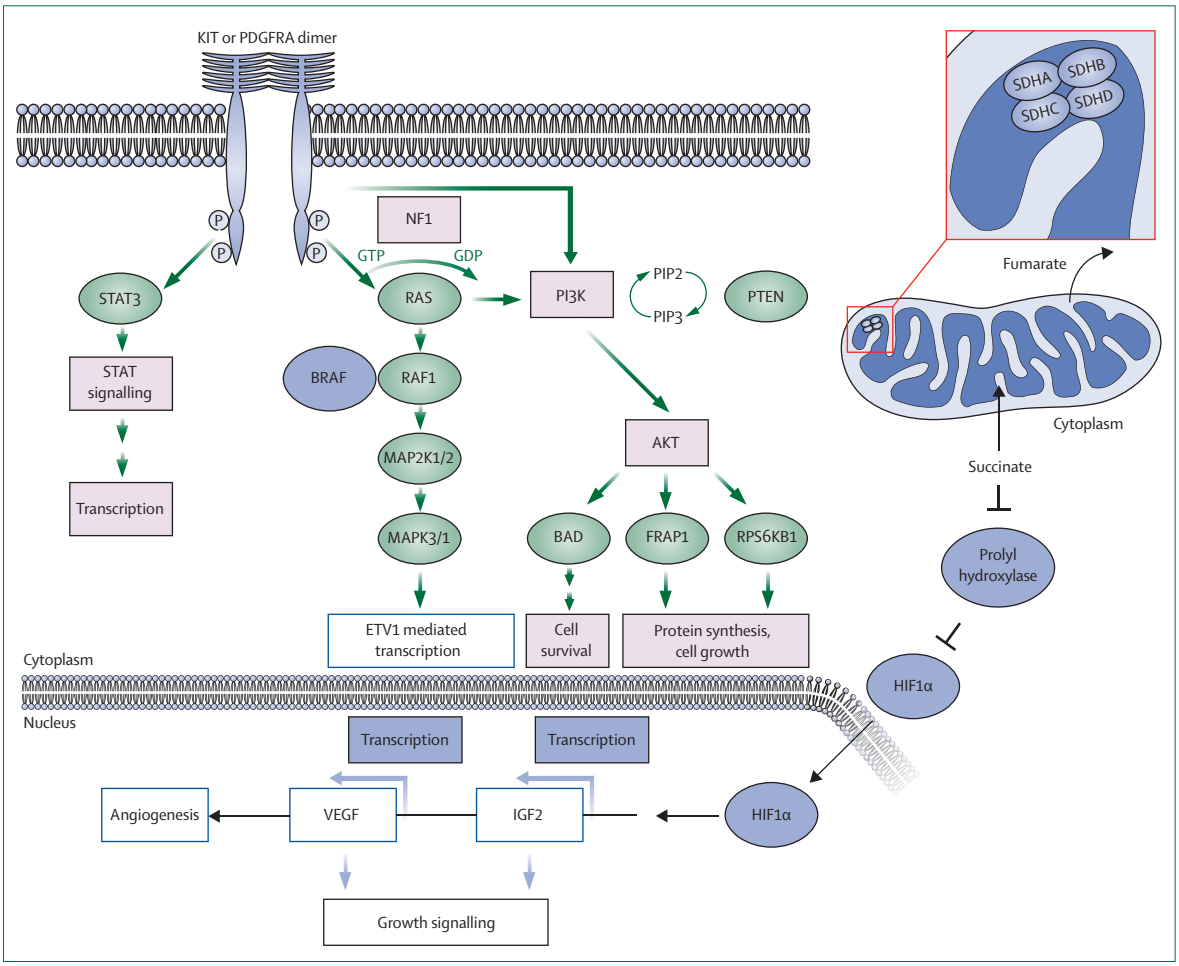

***Figure 3*: Predominant oncogenic intracellular signalling pathways in GISTs**

KIT or *PDGFRA* mutation initiates the relevant signalling pathway, resulting in constitutive activation of the MAPK, PI3K, and STAT3 signalling cascades. Some GISTs harbour mutations in *NF1*, a *RAS*-family gene, or *BRAF*, resulting in downstream activation of the MAPK pathway. Loss of the SDH complex within mitochondria leads to increased levels of HIF1α, which in turn stimulates transcription of *VEGF* and *IGF2*. AKT=v-akt murine thymoma viral oncogene homolog. BAD=BCL2 antagonist of cell death. BRAF=v-raf murine sarcoma viral oncogene homolog B1. ETV1=ETS translocation variant 1. FRAP1=FK506 binding protein 12-rapamycin associated protein 1 (mTOR). GDP=guanosine diphosphate. GIST=gastrointestinal stromal tumour. GTP=guanosine triphosphate. HIF1α=hypoxia-inducible factor α. IGF2=insulin-like growth factor 2. KIT=v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog. MAPK=mitogen-activated protein kinase. MAP2K1/2=mitogen-activated protein kinase kinase 1/2 (MEK1/2). MAPK3/1=mitogen-activated protein kinase 3/1. NF1=neurofibromin 1. P=phosphate. PDGFRA=platelet-derived growth factor receptor A. PI3K=phosphoinositide-3-kinase. PIP2=phosphatidylinositol-4,5-bisphosphate. PIP3=phosphatidylinositol-3,4,5-triphosphate. PTEN=phosphatase and tensin homolog. RAF1=v-RAF-1 murine leukaemia viral oncogene homolog. RAS=rat sarcoma. RPS6KB1=ribosomal protein S6 kinase, 70 kD, 1. SDHA/B/C/D=succinate dehydrogenase A/B/C/D. STAT3=signal transducer and activator of transcription 3. VEGF=vascular endothelial growth factor. Modified from reference 60, with permission of Elsevier.

suggested as an alternative for mitosis counting.[81,82] Also, large tumour size, tumour site, and tumour rupture before surgery or at surgery have been identified as independent prognostic factors for recurrence.[4,70,78–80,83] Gastric GISTs have a lower risk of recurrence compared with non-gastric GISTs.[4,80,84] Of non-gastric GISTs, tumours that arise in the duodenum, jejunum, ileum, colon, or rectum have roughly similar risks for recurrence, whereas E-GISTs have a higher risk.[4]

Many other patient or tumour characteristics have prognostic relevance. Individuals with a *PDGFRA* Asp842Val mutation usually have a favourable outcome, whereas alterations in *KIT* exon 9 or deletions in *KIT* exon 11 are associated with frequent tumour recurrence.[80,85,86] A prognostic expression signature of 67 genes related to genome complexity was strongly predictive for GIST recurrence.[87]

Risk-stratification methods

National Institutes of Health (NIH) consensus criteria,[49] Armed Forces Institute of Pathology (AFIP) criteria,[84] and modified NIH criteria[88] are used frequently to estimate the risk of recurrence after surgery. NIH consensus criteria stratify risk by tumour size and mitotic count whereas AFIP criteria also include tumour site. Modified NIH criteria encompass four factors: size, mitotic count, site, and rupture (table). The prognostic performance of these schemes has been validated,[4,83,88] and their prognostic accuracy is roughly similar.[4]

Two nomograms have been proposed for risk estimation.[89,90] Prognostic heat maps and contour maps, based on non-linear modelling of tumour size and mitotic count and on tumour site and rupture, were slightly more accurate for estimation of recurrence risk than were NIH criteria, AFIP criteria, or modified NIH criteria.[4]

Adjuvant treatment

Randomised trials

Imatinib is the only treatment for GISTs that has been evaluated in the adjuvant setting, with results available from two randomised trials.[91,92] In a US trial of 713 patients who underwent surgery for GIST (diameter ≥3 cm), individuals were randomly allocated after surgery to either imatinib (400 mg daily) or placebo, for 1 year.[91] Study accrual was stopped early when interim results crossed the efficacy boundary set for recurrence-free survival. Median follow-up at this time was only 19·7 months. Imatinib improved recurrence-free survival compared with placebo (98% *vs* 83% at 1 year; hazard ratio 0·35, 95% CI 0·22–0·53; one-sided p<0·001). Overall survival did not differ between groups. On the basis of these findings, imatinib was approved for adjuvant treatment of KIT-positive GIST in the USA and Europe.

In a European imatinib trial, 400 patients with either a high risk of recurrence (according to NIH consensus classification) or with ruptured GIST were randomly assigned to either 12 or 36 months of adjuvant imatinib (400 mg once daily).[92] Median follow-up at the time of analysis was 54 months. Patients assigned to 36 months of imatinib had more favourable recurrence-free survival than did those assigned to 12 months (66% *vs* 48% at 5 years; hazard ratio 0·46, 95% CI 0·32–0·65; p<0·0001). Overall survival favoured the 36-month treatment arm (92% *vs* 82% at 5 years; 0·45, 0·22–0·89; p=0·019).

Adjuvant imatinib was deemed generally well tolerated. Nevertheless, 46 (13%) and 96 (27%) patients in the US study[91] from the placebo and imatinib groups, respectively, discontinued imatinib early for reasons other than GIST recurrence, and 25 (13%) and 51 (26%) patients in the European trial[92] from the 12-month and 36-month arms, respectively, stopped treatment. Severe (grade 3–5) adverse events were reported in 104 (31%) patients assigned imatinib in the US study and 63 (18%) allocated placebo.[91] In the European study,[92] 65 (33%) and 39 (20%) patients in the 36-month and 12-month groups, respectively, had severe (grade 3–5) adverse events. The most frequent side-effects included anaemia, periorbital oedema, fatigue, nausea, diarrhoea, and muscle cramps.[92] Some of these adverse effects can be alleviated with symptomatic treatments.[93]

	Tumour characteristic			Proportion of operable GISTs* (%)	10-year recurrence-free survival* (%)
	Diameter (cm)	Mitotic count (per 50 HPFs)	Location		
Modified NIH criteria†					
Very low risk	<2·0	≤5	Any	11·9	94·9
Low risk	2·1–5·0	≤5	Any	28·7	89·7
Intermediate risk	≤5·0	6–10	Gastric	13·5	86·9
Intermediate risk	5·1–10·0	≤5	Gastric	13·5	86·9
High risk	>10·0	Any count	Any	45·8	36·2
High risk	Any size	>10	Any	45·8	36·2
High risk	>5·0	>5	Any	45·8	36·2
High risk	≤5·0	>5	Not gastric	45·8	36·2
High risk	5·1–10·0	≤5	Not gastric	45·8	36·2
AFIP criteria					
Group 1	<2·0	≤5	‡	12·7	95·0
Group 2	2·1–5·0	≤5	‡	29·3	89·6
Group 3a	5·1–10·0	≤5	‡	19·0	79·7
Group 3b	>10·0	≤5	‡	8·9	61·9
Group 4	<2·0	>5	‡	0·5	45·7
Group 5	2·1–5·0	>5	‡	7·7	48·9
Group 6a	5·1–10·0	>5	‡	12·1	25·1
Group 6b	>10·0	>5	‡	9·9	9·4

AFIP=Armed Forces Institute of Pathology. GIST=gastrointestinal stromal tumour. HPF=high power microscope field. NIH=National Institutes of Health. *Data from ten pooled population-based series.[4] †If rupture is present, any size, count, or location. ‡Criteria available for gastric, duodenal, jejunal and ileal, and rectal GISTs.[84]

Table: **Criteria for risk-stratification of GIST recurrence after surgery**

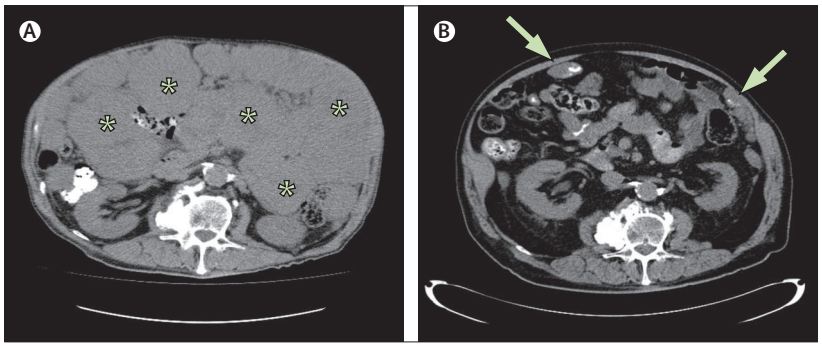

Figure 4: **Response of GIST metastases to imatinib treatment**
(A) CT scan of a 76-year-old man with *KIT* exon 11 (Val560Asp) mutation showing many large intra-abdominal GIST metastases (stars) before initiation of imatinib in December, 2008. (B) In the same patient, ongoing partial response to imatinib with a few, small, partly calcified persisting metastases (arrows) in August, 2012. GIST=gastrointestinal stromal tumour.

Patient selection for adjuvant treatment

Individuals at intermediate or high risk of recurrence can be considered for adjuvant treatment.[69] When AFIP criteria are used, about 36% of patients with operable GIST have intermediate-risk tumour (groups 3a–5) and 22% have high-risk GIST (group 6), with estimated 10-year recurrence-free survival of 46–80% and 9–25%, respectively.[4] With modified NIH criteria, fewer patients (14%) have intermediate-risk GIST and a larger proportion (46%) have high-risk tumour, with 10-year recurrence-free survival of 87% and 36%, respectively, suggesting that with these criteria only high-risk patients might be considered for adjuvant treatment (table).

Specific gene mutations confer insensitivity to imatinib and, therefore, must be identified. The most common of these is a substitution mutation in *PDGFRA* exon 18 (Asp842Val),[94,95] which is seen in up to 10% of patients with high-risk GIST.[7] In a study, none of 31 patients with advanced GIST and this mutation responded to imatinib.[96] Most of the infrequent mutations recorded at the Asp842 locus are also imatinib-resistant (Arg-Asp841-842Lys-Ile, Asp-Ile842-843Ile-Met, Asp842Tyr, Asp842Ile, and Ile843del).[94,97] Evidence to suggest that patients with wild-type GIST benefit from adjuvant imatinib is unconvincing,[92,98] and treatment of this group remains controversial. GISTs with a mutation in *KIT* exon 9 (almost all are Ala-Tyr502-503 duplications) are imatinib-responsive, but patients with this mutation might benefit from a dose higher than 400 mg daily, on the basis of observations made in the treatment of advanced GIST.[99]

Duration of adjuvant imatinib

Adjuvant imatinib for at least 3 years has been recommended after surgery for high-risk patients,[69] but treatment for longer than 3 years has not been assessed in randomised trials. At present, a reasonable choice is to treat patients with 3 years of adjuvant imatinib if they are at substantial risk for recurrence and have a GIST with an imatinib-sensitive mutation.

Follow-up

The optimum follow-up scheme is unknown. In randomised studies of adjuvant imatinib, patients underwent physical examination and had blood-cell counts and biochemistry variables measured at intervals of 1–3 months; CT or MRI of the abdomen and pelvis was done every 3–6 months for the first 2 years, twice a year for the next 3–5 years, and then annually.[91,92] Abdominal CT delivers an average effective radiation dose of about 8·0 mSv, which equals the dose received from a 3·3-year period of natural background radiation.[100] Therefore, replacing CT with MRI could be considered for young people. Since 20–35% of GISTs recur during the first 2 years after completion of adjuvant imatinib, more frequent imaging at intervals of 3–4 months during this period might be justified.

Advanced GIST

First-line systemic treatment

Metastases can cause abdominal pain or discomfort, bleeding, or bowel obstruction, but asymptomatic metastases are now detected frequently at prescheduled follow-up. First-line systemic treatment of advanced GIST is imatinib, unless the tumour has a gene mutation that encodes an imatinib-resistant kinase. With imatinib treatment, 83–89% of patients either respond or achieve durable stable disease whereas only 11–17% progress (figure 4).[101–103]

Responding liver metastases typically become hypodense and sometimes cyst-like on CT and can decrease in size (appendix p 4).[104] Measurement of lesion density is essential for response assessment. In one study, a decline in lesion size on CT of more than 10%, or a fall in density greater than 15%, had 97% sensitivity and 100% specificity for identification of patients who showed a response on PET.[105] Imaging with ^{18}F-fluorodeoxyglucose (FDG) PET might allow early assessment of treatment response and prediction of clinical outcome.[106] Detection by imaging of a new mass or a growing lesion within a pre-existing hypodense (responding) liver lesion should be judged disease progression (appendix p 5).[104]

Imatinib has not been compared with chemotherapy in a randomised study because GISTs were deemed chemoresistant, with frequent expression of multidrug-resistant proteins,[107] and imatinib proved highly effective.[12,108] In two randomised trials of 746 and 946 patients, in which the standard daily dose of imatinib (400 mg) was compared with a higher dose (400 mg twice daily), median time to disease progression on imatinib was about 2 years.[101,102] No survival difference was noted between the two doses but, in a subgroup analysis, patients with a mutation in *KIT* exon 9 had significantly longer progression-free survival, but not overall survival, when treated with 400 mg twice daily.[109–111]

Most GISTs that recur with overt metastases after completion of adjuvant treatment are imatinib-sensitive and decrease in size or stabilise on reinstitution of

imatinib.[112] Tumours that recur during adjuvant imatinib can be managed as imatinib-resistant disease, but no clinical trial has addressed this population of patients.

Imatinib is administered continuously until disease progression, because interruption of administration in responding patients usually results in GIST progression within 1 year of interruption.[113] Patients with the *KIT* exon 11 mutant genotype respond more frequently to imatinib and have longer time to disease progression and longer survival on imatinib compared with individuals with a mutation in *KIT* exon 9 or those with no mutation in *KIT* or *PDGFRA*.[99,110,114]

Imatinib resistance

Imatinib pharmacokinetics vary substantially between patients, and tumour progression on imatinib can sometimes result from low amounts of imatinib in tissue. Low trough concentrations of imatinib in plasma (<1100 μg/L) 4 weeks after imatinib initiation were associated with a shorter time to GIST progression than were higher amounts of imatinib.[115] The relative bioavailability of imatinib fell by about 30% from baseline during the first 3 months on treatment in a prospective study, but concentrations stabilised when patients were treated for longer than this time.[116] This observation accords with improved tolerability of imatinib with time on treatment.[117] The mechanism of reduced imatinib bioavailability over time is unknown.[118] Trough concentrations of imatinib in plasma might be lower in patients undergoing subtotal or total gastrectomy compared with those having lesser resections.[119] In patients with suspected low concentrations in plasma of imatinib, measurement of trough concentrations in plasma after 3 months on treatment, and an increase in dose, might be justified.[118]

Tumour genotype—such as an alteration in *PDGFRA* at the Asp842 locus or a *KIT* exon 9 mutation—is another potential cause of early progression on imatinib. GISTs deficient in succinate dehydrogenase and tumours arising in patients with neurofibromatosis type 1 generally respond poorly to imatinib.[44,120]

Most GISTs respond to imatinib for a period of 12–36 months but, in more than 80% of patients, secondary resistance begins to manifest. Acquired mutations in *KIT* or *PDGFRA* that interfere with drug binding cause nearly all this resistance.[121–123] Although other kinase inhibitors are effective against some of these mutations, none is effective against all of them. Moreover, different tumour lesions within a patient can harbour different resistance mutations.[124,125] Substitutions in *KIT* at the Asp816 locus are especially difficult to suppress with currently available inhibitors.

Treatment of GIST progressing on imatinib

Imatinib dose escalation can occasionally control advanced GISTs that progress on imatinib. After an increase to 600 mg or 800 mg per day, about a third of patients achieve stable disease and 2% respond. Of those who respond or have stable disease on the 800 mg dose, just under two-thirds remain progression-free for more than 2 years after dose escalation.[126]

Sunitinib, an inhibitor of several tyrosine kinases including KIT, PDGFRs, and VEGFRs,[127] is the standard treatment for patients whose GIST is imatinib-resistant or who do not tolerate imatinib. In a study in which 312 such patients were assigned either placebo or sunitinib (50 mg a day, orally, in 6-week cycles, 4 weeks on and 2 weeks off), median time to disease progression was 6·3 months on sunitinib and 1·5 months on placebo (hazard ratio 0·33, 95% CI 0·23–0·47; p<0·001). Fatigue, diarrhoea, skin discolouration, and nausea were common side-effects.[127] Progression-free survival and survival were longer for patients with a mutation in *KIT* exon 9 or wild-type genotype than for those with an alteration in *KIT* exon 11.[128]

Findings of a randomised placebo-controlled study, in patients who had progressed on imatinib or who were intolerant to imatinib and who also had progressed on sunitinib, showed that the oral multikinase inhibitor regorafenib was effective and relatively well tolerated. Patients who received regorafenib had median progression-free survival of 4·8 months compared with only 0·9 months in those on placebo (hazard ratio 0·27, 95% CI 0·18–0·39; p<0·001).[129]

Metastasis surgery

Patients with a small tumour burden have the longest progression-free survival times on imatinib treatment[102] and, hypothetically, reduction of tumour mass by surgery might prolong the time to drug resistance. Unfortunately, randomised trials to evaluate surgery to reduce tumour mass were closed early because of poor accrual. In single-centre series, 65–69% of patients treated first with imatinib and then with tumour bulk-reducing surgery were free from disease progression 2 years after resection, but these findings could have been confounded by patient selection.[130,131]

Excision of a metastasis progressing during kinase inhibitor treatment could be considered, but the median progression-free survival after resection is fairly short (8–9 months) and 2-year progression-free survival is only 9·7%.[131,132] Surgery for GIST progressing at several sites is not recommended, except to relieve severe symptoms resulting from bowel obstruction or to stop bleeding, because operative morbidity is substantial and the time to disease progression rarely exceeds a few months.[130,132]

Other treatments

Scant data suggest that GIST is sensitive to radiotherapy. Local control of abdominal metastases and relief of symptoms have been achieved, with few acute side-effects, with a cumulative target dose of 30–50 Gy delivered in 2–3 Gy daily fractions.[133]

Effective palliation of liver metastases can be achieved with arterial embolisation or chemoembolisation,[134,135] radiofrequency ablation,[136] or, in our experience, with selective internal radiation therapy with ^{90}Y microspheres. Evidence for treatment of metastases by liver transplantation is anecdotal.[137]

Survival with metastatic disease

Before the imatinib era, median survival of patients with recurrent or metastatic GIST was 10–20 months,[138] but after the introduction of tyrosine kinase inhibitors survival has increased substantially. Median survival of participants in two studies looking at imatinib for treatment of advanced GIST was 51–57 months.[102,103] The estimated proportion of patients achieving progression-free and overall survival at 9 years was 14% and 35%, respectively.[139] Those whose tumour bulk was within the lowest quartile at the time of imatinib initiation had the best 9-year progression-free and overall survival (29% and 58%, respectively).[139] These survival times will probably improve because of early detection of metastatic disease in CT-based follow-up programmes and availability of effective systemic treatments after imatinib failure.

Future

Prevention of GIST is challenging because no risk factors for sporadic GIST are known and the molecular events that lead to its genesis can arise by chance. In the adjuvant setting, the best dose of imatinib and duration of treatment, and methods to detect early recurrence, warrant further study. The role of debulking surgery in extending the time to drug resistance for patients with metastatic GIST who respond to systemic treatment remains a key research topic.

According to ClinicalTrials.gov, as of Oct 5, 2012, at least 13 agents are under investigation in clinical trials of advanced GIST. These include multikinase inhibitors (regorafenib, dasatinib, masitinib, nilotinib, pazopanib, sorafenib), immunomodulating agents (ipilimumab, interferon alfa), inhibitors of heat-shock protein, a phosphoinositide-3-kinase inhibitor, and an insulin-like growth factor 1 receptor inhibitor. In a preclinical model, the potency of a PDGFR tyrosine kinase inhibitor was more than 100-fold greater than that of imatinib for inhibition of the Asp842Val mutation;[97] a clinical trial for patients with Asp842-related mutations is ongoing. Patients with *BRAF*-mutated GIST could benefit from an inhibitor of mutated BRAF.[140]

Contributors

All authors contributed to writing of the report and produced some of the illustrations.

Conflicts of interest

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