Gastrointestinal stromal tumors—a review

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ABSTRACT Gastrointestinal stromal tumors (GISTs) may be defined as intraabdominal nonepithelial (mesenchymal) tumors that express the KIT protein or have an activating mutation in a class III receptor tyrosine kinase gene (*KIT* or *PDGFRA*). GISTs are diagnosed at a frequency of about 15 new cases annually per million, though small indolent GISTs are likely to occur more frequently in the general population. The clinical behavior is variable, and assessment of the malignancy potential is usually based mainly on the size and the proliferation characteristics of the tumor. The overwhelming majority of GISTs express the KIT protein, the transmembrane receptor tyrosine kinase for the stem cell factor. The majority of GISTs harbor a mutation in the *KIT* proto-oncogene that translates into constitutively activated KIT protein kinase, and a minority have mutated *PDGFRA* gene resulting in activated platelet-derived growth factor alpha receptor tyrosine kinase. Most GISTs respond to imatinib mesylate, which selectively inhibits both KIT and PDGFRA, and is now considered as the standard systemic therapy for advanced GIST. In contrast, responses to conventional chemotherapy are infrequent (generally less than 10%), but combination therapies with imatinib have not been explored. Research on adjuvant imatinib and novel targeted therapies is ongoing.

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms of the gastrointestinal tract, which probably arise from a precursor cell of the interstitial cell of Cajal (ICC) (Kindblom et al. 1998). These tumors were earlier commonly diagnosed either as leiomyoma, leiomyosarcoma or leiomyoblastoma, but it is now evident that GIST is a tumor entity different from all other mesenchymal tumors. GISTs differ from leiomyomas and leiomyosarcomas in their molecular pathology, clinical behavior and treatment, making the correct differential diagnosis of prime importance. GIST is the most common sarcoma of the gastrointestinal tract, whereas leiomyosarcomas and leiomyoblastomas are relatively rare in the gastrointestinal tract (Miettinen and Lasota 2001). Progress in the understanding of the molecular pathological mechanisms and evolution of novel targeted therapies has been particularly rapid in GIST within the field of cancer research.

Definition of GIST

In 1983, Mazur and Clark were the first to call gastrointestinal tract nonepithelial neoplasms that did not have the ultrastructural characteristics of smooth muscle cells, and lacked the immunohistochemical features of Schwann cells, as GISTs (Mazur and Clark 1983). A characteristic feature of GISTs is that they usually express strongly a protein called KIT in immunohistochemistry (Kindblom et al. 1998). Hirota and colleagues made an important discovery in 1998, when they found in GIST tumors gain-of-function mutations in the *KIT* proto-oncogene, which encodes the KIT protein (Hirota et al. 1998). The *KIT* proto-oncogene is a class III receptor tyrosine kinase gene containing 21 exons. The KIT protein is often located on the plasma membrane of the cells that express KIT, where the extracellular domain of the protein functions as the receptor for the stem cell factor (SCF), and the intracytoplasmic portion of the protein is a

tyrosine kinase in function. Recently, some GISTs that lacked *KIT* mutation were found to have an activating mutation in another class III receptor tyrosine kinase gene, the *PDGFRA* gene, which encodes the platelet-derived growth factor receptor-alpha receptor tyrosine kinase protein (Heinrich et al. 2003, Hirota et al. 2003).

GISTs have been defined as spindle cell, epithelioid, or occasionally pleomorphic mesenchymal tumors of the gastrointestinal tract that express the KIT protein (Miettinen and Lasota 2001). This definition is practical, since the KIT protein can easily be detected by immunohistochemical assays for the CD117 antigen (an epitope of KIT) using commercially available antibodies. However, the morphology of GISTs is highly variable (Figure 1), and a few GISTs may express KIT only weakly or very rarely not at all, and may require gene mutation analysis for diagnosis confirmation. Furthermore, GISTs may rarely arise outside the gastrointestinal tract within the abdominal cavity (Sakurai et al. 2001). Hence, based on the recent findings, the definition of GIST may need to be revised. GISTs may now be considered to encompass intra-abdominal nonepithelial (mesenchymal) tumors that express the KIT protein or have activating mutation in a class III receptor tyrosine kinase gene (*KIT* or *PDGFRA*). However, for most clinical purposes GISTs may be simply referred to as KIT protein expressing gastrointestinal tract sarcomas, though this definition is somewhat inaccurate.

Epidemiology of GIST and clinical features

Little reliable data has been available on the incidence and prevalence of GIST. GIST is a novel tumor entity, and GISTs are currently not registered in population-based cancer registries as a separate entity from soft tissue sarcomas. The first population-based study performed in South-Western Sweden found the annual incidence of GIST to be about 15 new cases per million and the prevalence approximately 130 per million. More than 40% of all clinically detected, symptomatic GISTs were found to be either of the high risk type or overtly malignant ones presenting with metastases (Kindblom et al. 2002).

GISTs occur in both genders at about similar frequency, and the median age at presentation is about 60. GISTs may occasionally be found in young adults, but they are practically never diagnosed in children younger than 10. GISTs are most commonly found in the stomach (40 to 70%), the small intestine (20 to 50%), and the colon and rectum (5 to 15%), but they may rarely be found also in the oesophagus, omentum, mesentery, or the retroperitoneum (DeMatteo et al. 2000, Miettinen and Lasota 2001, Emory et al. 1999, Strickland et al. 2001). Unlike carcinomas that often grow within the gastrointestinal tract causing early erosion and ulceration of the intestinal lumen, GIST typically grow parallel to the bowel lumen and between the intraabdominal organs ("endophytically"), often causing ulceration of the overlying gastrointestinal mucosa at a relatively late stage. The growth pattern of GIST between, rather than within, the bowel segments may explain why many GISTs are large in size at the time of the diagnosis. The median tumor diameter at diagnosis is about 8 cm, but GISTs as large as 40 cm in diameter have been diagnosed (Emory et al. 1999). On the other hand, incidentially found GISTs are often small, and may be only a few mm in diameter. GISTs are often lobulated and grey to brown-reddish. Larger GISTs are often necrotic and hemorrhagic, and may bleed into the abdominal cavity or into the bowel lumen. GISTs also easily spill into the abdominal cavity at tumor removal, which is associated with a high risk of tumor recurrence. The tumors are often solitary and well circumscribed, and they are surrounded by a thin pseudocapsule as soft tissue sarcomas (Pidhorecky et al. 2000).

At presentation, about 10 to 30% of GISTs invade the surrounding structures (Nishida et al. 2000), and up to one third have been reported as overtly metastatic (Rudolph et al. 1998, DeMatteo et al. 2000, Crosby et al. 2001). GISTs are sometimes diagnosed at an emergency laparotomy performed due to suspected intraabdominal hemorrhage, gastrointestinal perforation, or due to severe abdominal pain (Catena et al. 2000). Common symptoms and signs at presentation include abdominal discomfort or pain, anemia, and presence of a palpable abdominal tumor. GIST may also cause bowel obstruction or perforation, dysphagia, fever, or obstructive jaundice. Small GISTs usually cause no symptoms, and are found incidentally at laparotomy or at endoscopy for other conditions.

Unlike leiomyosarcomas, GISTs characteristically recur intraabdominally, and extraabdominal metastases are rare. The most commonly involved sites are the peritoneum and the liver (DeMatteo et al. 2000, Clary et al. 2001). Tumor cell seeding from the primary tumor into the peritoneal cavity may give rise to peritoneal metastases or "implants", and tumor cells seeded into the portal vein may result in liver metastases. As with most other soft tissue sarcomas, regional lymph node metastases are very rare (Fong et al. 1993).

Histopathological features of GIST

Since histological morphology of GIST is variable, the differential diagnosis may be demanding (Figure 1). Roughly, about two thirds of GIST are mainly composed of spindle cells ("the spindle cell variant") and one third of epithelioid or round cells ("the epithelioid variant"), but many mixed forms exist, and some GISTs have unusual morphologic features, making the light-microscopic differential diagnosis difficult. Gastrointestinal autonomic neural tumors (GANTs) are now considered as a type of GIST based on their generally similar protein expression pattern and presence of similar *KIT* mutations as in GISTs (Miettinen and Lasota 2001, Miettinen et al. 1999).

Immunohistochemistry is essential in the differential diagnosis between GISTs and the rarer gastrointestinal mesenchymal tumors, such as leiomyosarcomas, leiomyomas, and schwannomas. GISTs are usually strongly positive on immunostaining for the CD117 antigen, whereas leiomyomas, leiomyosarcomas and schwannomas are not. GISTs express also vimentin, and frequently CD34 (a glycoprotein found also in endothelial cells and hematopoietic progenitor cells; 70 to 80% of gastric GISTs and almost 50% of intestinal GISTs), and smooth muscle antigen (SMA, 20 to 40%), but only rarely desmin (less than 5%, an intermediate filament typical of muscle), or S100 (about 10%, a neural cell marker). This contrasts with schwannomas that are positive for S-100 but negative for CD117 and usually for CD34, and leiomyosarcomas, which express desmin and SMA, but not KIT. KIT expression is not a unique feature of GISTs, since many other types of human tumors including germ cell tumors, small cell lung carcinomas, melanomas, adenocystic carcinomas and some types of sarcoma may also express KIT (Tsuura et al 1994).

Origin of GIST

The predisposing factors for GIST are not known. Most GISTs are sporadic, but rare familial GISTs with germline *KIT* mutation have been identified. No hereditary GISTs have been reported from the Scandinavian countries. The individuals with hereditary GISTs have multiple tumors associated with diffuse spindle cell hyperplasia in the myenteric plexus layer of the gastrointestinal tract. Occasionally hyperpigmentation of the skin and the mucous membranes is present, as well as urticaria pigmentosa, multiple skin nevi, and systemic mast cell disease (Nishida et al. 1998, Beghini et al. 2001, Maeyama et al. 2001). Carney's triad is a rare syndrome of unknown cause that primarily affects young women. In addition to GIST usually arising from the stomach, patients with the triad may have extraadrenal paraganglioma and pulmonary chondroma (Carney 1999). The molecular genetic mechanism of the triad is not known. GISTs are found more commonly than expected in patients with neurofibromatosis type 1 (von Recklinghausen's disease), and the molecular pathogenesis of these GISTs appears to be unique (Kinoshita et al. 2004).

GISTs probably originate from precursor cells that may differentiate towards the interstitial cells of Cajal (ICCs) (Kindblom et al. 1998). ICCs are pacemaker cells that regulate autonomous contractions of the gastrointestinal tract. They occur in and around the myenteric plexus, where they intercalate between nerve fibres and muscle cells (Miettinen and Lasota 2001). Normal ICCs and GISTs have similar ultrastructural features, and both express the KIT protein. However, unlike most GISTs, ICCs did not stain for CD34 in studies performed with confocal microscopy, which together with the occasional coexpression of smooth muscle antigens in GISTs supports the hypothesis that GISTs may originate from a primitive precursor cell that may differentiate to the ICCs (Vanderwinden et al. 2000).

Diagnosis

The diagnosis of GIST is based on a tissue biopsy that is usually taken at endoscopy or laparotomy.

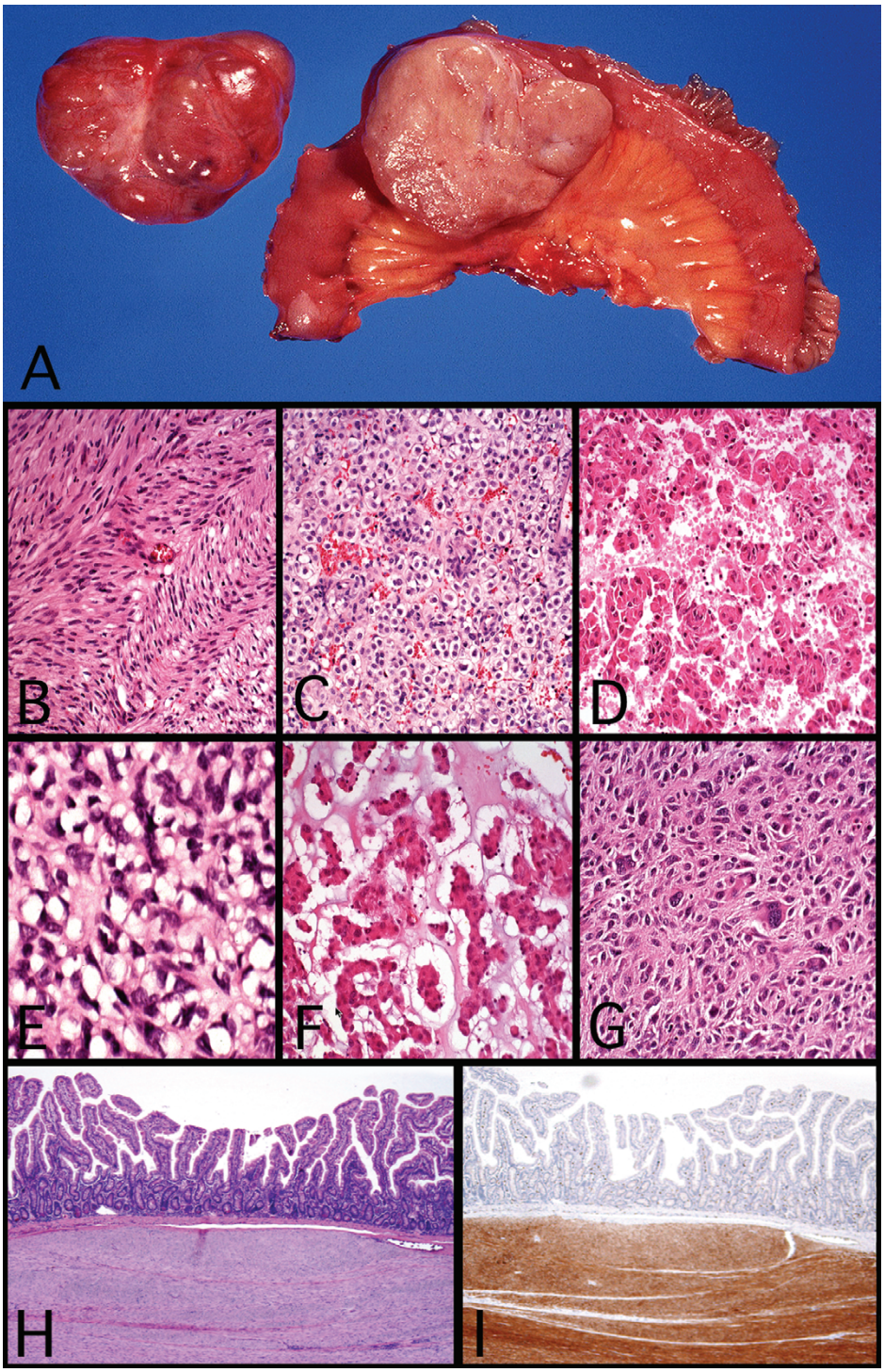

Figure 1. Surgical specimen of GIST of the small bowel (A). The morphologic spectrum of GIST includes predominantly spindled lesions (B), as well as a variety of epithelioid patterns that may simulate paraganglioma (C) and carcinomas (D-F). Occasionally, GIST may be focally pleomorphic, resembling soft tissue sarcoma of malignant histiocytoma type (G). GIST of the small bowel (H) showing strong immunoreactivity for KIT (CD117,

Table 1. Assessment of the risk of recurrence in resectable GIST [a]

	Size	Mitotic count
Very low risk	<2 cm	<5/50 HPFs [b]
Low risk	2–5 cm	<5/50 HPFs
Intermediate risk	<5 cm	6–10/50 HPFs
	5–10 cm	<5/50 HPFs
High risk	>10 cm	Any mitotic rate
	any size	>10/50 HPFs
	>5 cm	>5/50 HPFs

[a] adapted from Fletcher et al. 2002
[b] HPF, high power field

Immunostaining for CD117 (KIT) should be performed with appropriate controls. Since mast cells and ICCs stain strongly for CD117, they are useful positive internal controls. Apart from KIT, immunostainings for CD34, SMA, desmin, and S-100 need to be performed. *KIT* mutation analysis is not mandatory, but it may be of value in prediction of the likelihood of response to imatinib and duration of failure-free survival (Heinrich et al. 2003), and in establishing the diagnosis in the rare cases where KIT expression is weak or absent. CT or MRI are used to assess the primary tumor extension and the presence of metastases. Positron emission tomography (PET) is not considered as mandatory, but PET may give information beyond to that provided by the other imaging examinations regarding tumor spread, and PET may be useful in the evaluation of tumor response to imatinib therapy (Van Den Abbeele 2001).

Prognostic features

Assessment of the risk of GIST recurrence will be of importance provided that adjuvant therapy will become a standard praxis in the treatment of GIST. Assessing the malignant potential of GIST is not straightforward, and many GISTs have uncertain malignant potential. The most commonly used scheme to assess the malignancy potential is based on the primary tumor diameter and the mitotic count (Table 1, Fletcher et al. 2002). Large primary tumors (>10 cm in diameter), tumors with a high mitotic count (>10/50 high power fields, HPFs), and tumors that manifest with both of these features (are >5 cm in diameter and have >5 mitotic figures/50 HPFs) are considered to be at a high risk for tumor recurrence.

The consensus criteria for prognostication presented in Table 1 do not include all prognostic factors identified, and there is no accepted staging system for GISTs. Patients who have overtly metastatic disease but have been rendered free from macroscopic metastases by surgery are at almost 100% risk of recurrence. Prognosis differs also with tumor location, since tumors arising from the small bowel, colon, rectum or mesentery are generally associated with less favorable outcome than those arising from the stomach (Emory et al. 1999). Our own experience is that Ki-67 antigen expression in immunohistochemistry may be comparable to or superior to the tumor mitotic count in prognostication. Small (<1 cm), incidentally found GISTs behave almost invariably in a benign fashion, though neither any cut-off diameter nor any single mitotic count predicts subsequent malignant behavior with certainty. Other factors suggested to be associated with an adverse outcome include incomplete surgical resection and tumor infiltration to the adjacent structures, tumor rupture into the peritoneal cavity, presence of tumor necrosis, high cellularity and marked pleomorphism, a high S-phase fraction, DNA aneuploidy, presence of telomerase activity, and presence of *KIT* mutation (reviewed in Joensuu et al. 2002).

Outcome

The survival data of older series probably largely reflects that of patients with true GISTs, though these series are likely to be contaminated by other tumor types. Most recurrences appear to take place within the first 3 years from the primary diagnosis, but a subset of GISTs proliferate slowly, and metastases may appear only up to 15 years after the primary diagnosis. Hence, outcome of GIST varies greatly based on the clinical and histopathological features. In a population-based series from Sweden, less than 1% of patients within the very low, low and intermediate risk groups died from GIST-related causes, while 63% of the patients with a high risk for recurrence according to the consensus criteria and 83% of those with overtly malignant GIST died from tumor, usually within the first 2 years from the diagnosis (L-G Kindblom et al. unpublished data).

Molecular pathology

Activation of class III receptor tyrosine kinases (usually KIT) appears to be of fundamental importance in the molecular pathology of GISTs. The ligand of KIT, the SCF (also known as the mast cell growth factor or the Steel factor), exists predominantly as a bivalent dimer in the extracellular fluid. Following binding of SCF to KIT, homodimerization of the KIT protein takes place. This results in activation of the SCF-KIT dimer complex via cross-phosphorylation of the intracellular tyrosine kinases of the dimer (Yarden et al. 1988, Broudy 1997, Nishida and Hirota 2000). Activated KIT tyrosine kinases transfer phosphate groups from ATP to the tyrosine residues of the target proteins. The down-stream intracellular signaling cascade may include activation of AKT, PI3 kinases, MAP kinase, STAT, and JAK2 and other signaling molecules (Weiler et al. 1996, Hemesath et al. 1998, Brizzi et al. 1999, Heinrich et al. 2002). Most GISTs have constitutive activation (phosphorylation) of the KIT receptor tyrosine kinase (Rubin et al. 2001).

The *KIT* proto-oncogene encoding KIT is located in chromosome 4q11-12. Most GISTs have in-frame mutations which preserve the expression of KIT. The frequency of *KIT* mutations varies in different series, but up to 80 to 90% of metastatic GISTs have mutated *KIT*, and *KIT* mutations have been found frequently even in indolent GISTs 1 cm or smaller in diameter (Corless et al. 2002). Mutated *KIT* may not require SCF for dimerization and subsequent autophosphorylation, which leads to a shift in the balance between cell survival and proliferation away from apoptosis. *KIT* mutations are found most commonly in exon 11 (as many as about 70% of all GISTs) that encodes for the intracellular juxtamembrane region of the KIT receptor tyrosine kinase, but mutations are sometimes found also in exon 9 (5 to 20%, encodes for a region located in the proximal extracellular domain), and rarely in exons 13 (located in the first part of the intracellular split kinase domain) or 17 (the phosphotransferase domain, reviewed in Heinrich et al. 2002). Family members with germline mutation of *KIT*, who have GIST tumours from a young age, have the same mutation in the germline and in GIST (Nishida and Hirota 2000). A small proportion of patients with metastatic GIST have mutation in the platelet-derived growth factor receptor-alpha gene (*PDGFRA*), which is a class III receptor tyrosine kinase gene as *KIT* (Heinrich et al. 2003, Hirota et al. 2003). No mutations have been described in the other class III receptor tyrosine kinases, but *NF2* gene mutations have been found in GISTs (Fukasawa et al. 2000), as well as *NF1* mutations in GISTs arising in neurofibromatosis patients (Kinoshita et al. 2004). Many other gene changes are likely to be involved in the molecular pathogenesis of GIST, and loss of the entire chromosomes 1p, 14q, and 22q may occur in 50% or more of GISTs (El-Rifai et al. 1996, Fukasawa et al. 2000). Despite such extensive genome alterations, mutational activation of the class III receptor tyrosine kinases are likely to be of prime importance, and recognition of this paved the way for the use of tyrosine kinase inhibitors in the treatment of GIST (Joensuu et al. 2001).

Surgery and radiation therapy

Until recently, surgery was the only effective treatment for GIST. Surgery remains the standard initial treatment for nonmetastatic GISTs, though neoadjuvant imatinib therapy may be considered for patients who would otherwise require major surgery resulting in significant loss of organ function or permanent stoma. The tumor with its pseudocapsule should be removed en-bloc with tumor-free resection margins whenever feasible (Pidhorecky et al. 2000). The optimal width of the tumor-free margin has not been defined, but patients who have complete tumor resection (R0) have more favorable outcome than those with less complete surgery. GISTs give rise to lymph node metastases only infrequently, and extensive lymphadenectomy is thus not recommended. Since tumor rupture at or prior to surgery is associated with an increased risk for peritoneal implant tumors, every effort should be made to avoid tumor spillage at laparotomy (Ng et al. 1992).

About one half (40 to 80%) of malignant GISTs recur despite histopathologically complete tumor resection. The usefulness of resection of recurrent disease or intraabdominal metastases is not proven, but metastasectomy may improve survival in selected patients. Patients with longer than 12 month disease-free interval between the diagnosis and detection of metastases and those with few

liver metastases are more likely to benefit from metastasectomy than patients who have rapidly progressing or widespread GIST (Karakousis et al. 1992, Chen et al. 1998). Patients with obstructing or bleeding tumors can often be palliated by tumor excision. It is not known whether surgery should be carried out to remove residual masses which remain following tyrosine kinase inhibitor therapy, but this may be worthwhile in cases with few and resectable metastases. Selected patients who have single metastases that begin to grow during imatinib therapy may benefit from surgical removal of the growing tumors, but this policy remains to be shown effective.

The efficacy of radiotherapy in the treatment of GIST has not been investigated in depth. At present postoperative radiotherapy is not standard, and may be reserved for palliation of symptoms. Organ motility and relocation of bowel loops to remote sites may result in large target volumes, and radiation tolerance of the intraabdominal organs may also limit the usefulness of radiotherapy. Recurrences both within and outside of the target volume have been encountered (Crosby et al. 2001).

Conventional chemotherapy

Systemic chemotherapy with conventional drugs is generally considered to have only limited efficacy in the treatment of advanced disease. In general, only less than 10% of GIST patients treated with different types of chemotherapy protocols have responded, and most responses have been short-lived. The reasons for resistance of GISTs to drugs commonly used in the treatment of soft-tissue sarcomas is not known, but in one study GISTs expressed the P-glycoprotein and the multidrug resistance protein-1 (MDR-1) more frequently than gastrointestinal leiomyosarcomas in immunohistochemistry (Plaat et al. 2000). Combination therapies of conventional cytotoxic drugs and tyrosine kinase inhibitors have not been explored.

Tyrosine kinase inhibitors

Imatinib mesylate (formerly known as STI571, trade names Glivec® in the Europe or Gleevec™ in the USA) is the first effective systemic therapy for advanced GIST. Imatinib inhibits competitively a few tyrosine kinases including KIT, PDGFRα, PDGFRβ, ABL and ARG, and the BCR-ABL fusion protein present in some leukemias, but it has little effect on numerous other tyrosine or serine/threonine kinases present in cells (Buchdunger et al. 1996, Druker et al. 1996). Imatinib competes with ATP for its binding site in the kinase intracellular domain, and thus prevents the kinase from transferring phosphate from ATP to tyrosine residues of the substrates. The orally administered daily dose ranges from 400 to 800 mg. Maintenance serum levels above 1 μmol/L are considered to be required for optimal therapeutic effects, and such levels are usually obtained with daily doses of 300 mg or greater.

About two thirds of GIST patients treated with imatinib achieve an objective response, defined as 50% or greater tumor volume reduction (van Oosterom et al. 2001, Demetri et al. 2002). In addition, another 20% of patients have stabilized disease, and as many as about 90% of symptomatic patients have relief of symptoms. However, approximately 10% of patients have primarily resistant tumors and have disease progression despite imatinib therapy. The median time to response as assessed with CT is about 3 months, but decrease in tumor fluorodeoxyglucose (FDG) uptake in PET is frequently seen in even within a few hours to a few days after the first dose of imatinib (Joensuu and Dimitrijevic 2001). Most responses are durable with the median time to treatment failure of about 1.5 years. Responding liver lesions often acquire a cyst-like appearance and become better delineated in MRI or CT, which should not be confused with appearance of new lesions or progressive disease. The cyst-like lesions often consist of hyaline degeneration with a few remaining KIT positive cells, which probably represent dormant or slowly proliferating GIST cells (Joensuu et al. 2001).

The likelihood of response to imatinib depends on the tumor *KIT* gene mutation site. In one study, 84% of the patients with metastatic GIST with exon 11 mutation responded to imatinib as compared to 48% of those with exon 9 mutation and 0% of those with no detectable *KIT* or *PDGFRA* mutation (Heinrich et al. 2003). In this study patients with GIST with *KIT* exon 11 mutation also had a longer event-free and overall survival than those with GIST with *KIT* exon 9 or with no

mutation. A subset of GISTs with *PDGFRA* mutation are sensitive to imatinib.

The optimal dose of imatinib in the treatment of GISTs is currently being studied in randomized phase III trials. One trial found no statistical difference in the response rate between the 400 mg and 600 mg daily doses, but this trial was underpowered to address this question (Demetri et al. 2002). Preliminary data from 2 large trials comparing the daily doses of 400 mg and 800 mg have not yet reached any definitive conclusion (Benjamin et al. 2003, Verweij et al. 2003). Doses less than 300 mg may be too small for the competitive inhibition of the BCR-ABL kinase in chronic myeloid leukemia, and should generally be avoided (Druker et al. 2001). Taken together, the available data suggests that a daily dose of 400 mg or higher needs to be used in the treatment of advanced GIST. At this writing the longest treatment durations are about 40 months in advanced disease. The presently available data suggests that for most patients with metastatic disease chronic treatment until treatment failure is mandatory, and that treatment interruptions will result in GIST progression.

Adjuvant treatment of GIST

Since imatinib is effective and relatively well tolerated in the treatment of overtly metastatic disease, adjuvant therapy with imatinib following complete surgical resection of GIST is an attractive concept. Trials comparing 12 or 24 months of adjuvant imatinib therapy following surgery to no adjuvant therapy are currently being planned or are ongoing, and the results are awaited with interest. The Scandinavian Sarcoma Group will initiate a trial in GIST patients with an estimated risk of recurrence greater than 50% within the first 5 years following surgery. In this trial efficacy and tolerability of adjuvant imatinib therapy given either for 12 or 36 months following surgery will be compared. At least one trial running in the U.S. is assessing the role of neoadjuvant imatinib therapy.

Ongoing research

The molecular mechanisms of imatinib resistance are being actively studied. Such mechanisms are likely to be heterogeneous. New mutations, sometimes affecting the binding site of imatinib, have been described both in CML and GIST patients who have developed acquired resistance to imatinib, and the target gene amplifications may also occur in cancers resistant to imatinib (Gorre et al. 2001, Fletcher et al. 2003). In some cases with acquired resistance to imatinib another receptor tyrosine kinase than KIT may be activated accompanied by a loss of KIT expression. However, in many GISTs with acquired resistance no specific molecular genetic mechanism for imatinib resistance has been identified, and either KIT or PDGFRα receptor tyrosine kinase remains constitutively activated (Fletcher et al. 2003).

Other tyrosine kinase inhibitors than imatinib may also be effective in the treatment of metastatic GIST. SU11248 has shown promising activity in imatinib resistant GIST. In addition to KIT and PDGFRs, this drug also targets the FLT3 and VEGF receptors (Demetri et al. 2003). Other molecules that are being considered for evaluation include PTK787, which is also an inhibitor of KIT, PDGFRs and VEGFR-2, and the protein kinase C inhibitor PKC412. Combination therapies involving kinase inhibitors and conventional cytotoxic drugs also deserve to be evaluated in the clinical setting.

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