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EDITORIALS

Gastrointestinal stromal tumors – from a poorly defined pathologic oddity to a milestone in solid tumor oncology

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) rarely occur in mesenchymal neoplasms of the gastrointestinal tract, classically a non-surgical treatment refractory disease. Typically, GISTs arise predominantly in the stomach (60%) and the small intestine, but also occur in the rectum (5%), esophagus (2%) and a variety of other locations (5%), including appendix, gallbladder, pancreas, mesentery, omentum and retroperitoneum. About 5% of GISTs are metastasis or high-risk tumors at the time of diagnosis. These tumors are CD34+ and CD117+ and express c-Kit, a tyrosinkinase-receptor encoded by proto-oncogene „c-Kit", located on the long arm of chromosome 4 (4q11-q12) and whose ligand is a stem cell factor. This proto-oncogene has an important role in the development of normal haematopoiesis, as well as in stem cell migration. Generally speaking, surgical resection is the mainstay of localized GIST therapy. Actually, imatinib mesylate is indicated as first-line treatment of metastatic or non-resectable malignant GIST. Imatinib selectively inhibits the tyrosinkinase activity of c-Kit and platelet-derived growth factor receptor alpha. In less than half a decade, GISTs have emerged from historical anonymity to become an important focal point in trials of target therapeutics. The possibility of a deeper scientific understanding of GISTs became a paradigm for the development of new powerful therapeutic tools in solid tumor oncology.

Keywords: gastrointestinal stromal tumors, c-Kit, imatinib

Gastrointestinal stromal tumors *(GISTs) are rare stromal neoplasms that account for 5% of all the soft tissue sarcomas. Although relatively rare, GISTs represent the most common mesenchymal malignancy of the gastrointestinal tract. Before the advent of immunohistologyc methods, most spindle cell sarcomas of the gastrointestinal tract were considered to be leyomiomas or leyomiosarcomas, with occasional examples of neurogenic tumors (1).* ❑

GENERAL FEATURES

GIST defines a distinct group of gastrointestinal tumors that originate from the intestinal cells of Cajal (ICC). These cells act as regulators of bowel peristaltis, and therefore are also called *pacemaker cells*. ICC normally express c/Kit (CD117), which is a tyrosinkinase growth factor receptor. This c-Kit immunoreactivity is the best defining feature of GISTs, distinguishing them from the true smooth muscle tumors (i.e., leyomiomas and leyomiosarcomas) and tumors arising from neural crest derivates (i.e., schwanomas and neurofibromas); this is considered to be the most specific criteria for the diagnosis of GIST. In addition, targeting the c-Kit receptor with a c-Kit tyrosinkinase inhibitor *imatinib mesylate* (Glivec®) has been successfully used in treating patients with GIST (2).

Before 1999, the diagnosis criteria for GIST remained controversial and somewhat confusing. The term GIST was initially a purely descriptive term, developed in 1983 by Mazur and Clark, in order to define intraabdominal tumors that were not carcinomas and that also failed to exhibit features of either smooth muscle or nerve cells (3).

The incidence of GIST was vastly underrecognised before the year 2000, but this neoplasm was estimated to account for approximately 1% to 3% of all malignant gastrointestinal tumors. The annual incidence is estimated at 14.5 per million, with an estimated prevalence of GISTs of 10 to 20 cases per million.

GISTs arise predominantly in the stomach (up to 70%) and the small intestine (25%), but also occur in the rectum (5%), esophagus (2%), and a variety of other locations (5%), including appendix, gallbladder, pancreas, mesentery, omentum, and retroperitoneum.

GIST patients range in age from the teens to the 90s, but the peak incidence is around 60 years of age (4). ❑

PATHOLOGIC, HISTOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

Most GISTs exhibit an exophitic growth pattern, along the bowel wall. The tumors are generally between 2 and 30 cm in diameter at the time of diagnosis. For small lesions, the overlying mucosa is typically intact, but mucosal ulceration may occur in large and aggressive tumors. Surrounding organ invasion may occur in approximately one-third of cases (4). Metastatic disease is common and was reported in nearly 50% of patients in one study. The liver is the most common site of metastases (65%), followed by the peritoneum (21%). Metastases to the lymph nodes, lungs, and bones are considered rare. Most patients eventually develop recurrence after complete surgical resection. The liver and peritoneum are the two most common sites for recurrence.

At the moment of presentation, most patients are in their fifth an sixth decade of life, and GISTs are rarely seen in patients younger than 40 years of age. No gender predilection has been established, although some data showed male predominance. There is no association between race, ethnicity, occupation, or geographic location (5).

GISTs usually present with moderate to high cellularity, and tumor cells vary from spindle (70% to 80%) to epithelioid (20% to 30%). Spindle cell GISTs exhibit spindle cells that have elongated nuclei with tapered, blunt or rounded ends and eosinophilic or basophilic cytoplasm. Histologically, GISTs with spindle shaped cells may stimulate smooth muscle tumors or nerve sheath tumors. They may also have prominent vascularisation, hemorrhage, extensive hyalinization, or myxoid degeneration (6).

Epithelioid GISTs are made of round or polygonal cells, with central or slightly eccentric nuclei; they show mitosis, but typically, they have a more benign clinical course than spindle cell GISTs.

The biologic behaviour of GISTs range between benign and malignant, and making the difference in the two is based on the size, location, cellularity, and the degree of mitotic activity. Generally, malignant GISTs are large and more cellular than benign GIST. Tumor behavior varies significantly by location, and the cutoff tumor size also varies by location.

GISTs arising from the stomach are more likely to be benign than malignant. Gastric GISTs larger than 10 cm and with more than five mitoses per 50 high-power fields are considered malignant. Tumors with high mitotic activity (more than 50 mitoses per 50 high-power fields) are considered aggressive, with high-grade malignant potential. GISTs that arise from small cell intestine tend to be more aggressive than those arising from the stomach. Most esophageal, colonic and ano-rectal GISTs are malignant.

The diagnosis of GIST requires confirmation by immunostaining for CD117, which is expressed by all GISTs, both spindle and epithelioid type, regardless of their anatomic site or clinical behaviour. The presence and expression of CD117 is also found in the interstitial cells of Cajal, which are the pacemaker cells of the gastrointestinal tract. This association suggests that these cells are the common origin of GISTs (7).

Approximately 95% of GISTs stain positively for KIT (CD117). Staining for other markers is more variable, including Bcl-2 (80%), CD34 (70%), muscle-specific actin (50%), smooth muscle actin (35%), S100 (10%), and desmin

(5%). Because GISTs have a relatively broad morphological spectrum, the differential diagnosis includes a number of mesenchymal, neural, and neuro-endocrine neoplasms that occur in the abdomen. These include leiomyomas, leyomiosarcomas, schwanomas, malignant peripheral-nerve sheath tumors, solitary fibrous tumors, inflammatory myofibroblastic tumors, fibromatosis, synovial sarcomas, neuro-endocrine tumors (carcinoid and islet cell), gastric glomus tumor, malignant mesotheliomas, angiosarcomas, and sarcomatoids carcinoma. Recent success in treating GISTs with Imatinib has placed a new priority on accurately establishing the diagnosis. Fibromatosis and leiomyosarcoma are perhaps the two most frequenty mistaken for GIST tumors (7).

As far as biology is concerned, in 1983 immunohistochemical studies of gastrointestinal sarcomas documented frequent absence of muscle markers, that are typically found in the leiomyosarcomas located elsewhere in the body, and more recent studies have shown that these tumors expressed c-Kit a receptor tyrosinkinase encoded by the protooncogene c-Kit, which is located on the long arm of chromosome 4 (4q11-q12) and whose ligand is a stem cell factor. This protoncogene plays an important part in the development of normal haematopoiesis, as well as in the migration of stem cell, and is expressed in normal human mast cells, immature myeloid cells, melanocytes, epithelial breast cells and the interstitial cells of Cajal, which are considered to be the pacemaker cells for the autonomous movement (peristaltis) of the gastrointestinal tract. Interesting to notice is that the immunohistochemical profile of interstitial cells of Cajal is similar to that of the GIST: they are positive for c-KIT and CD34, and negative for desmine and S-100 antigens (8).

c-Kit is a 145 kD transmembranar glycoprotein, that serves as a receptor for stem cell factor (SCF) and has tyrosinekinase activity. As a member of the subclass III family of tyrosinkinases receptor, c-Kit is closely related to the receptors for PDGF, macrophage colony stimulating factor and FLT3 ligand. c-Kit function is critical to the development of ICC, as well as to the development of haematopoietic progenitor cells, mast cells and germ cells. The binding of SCF to c-Kit results in receptor homodimerisation, activation of tyrosinkinase activity, and, also, in the phosphorylation of a variety of substrates. In many cases, these substrates are kinases themselves and serve as effectors of intracellular signal transduction (8). ❑

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of patients with GIST can vary tremendously, based on anatomic location of the tumor, as well as its size and aggressiveness. For many patients, the detection of GIST may be due to non specific symptoms evaluation, or may even be an incidental finding (7).

The tumor size is extremely variable, ranging from small lesions to large masses. Small tumors are usually asymptomatic and are incidentally diagnosed during imaging, endoscopy or surgery. GISTs may remain clinically silent because of their submucosal origin and tendency to grow exophytically. Symptomatic GISTs are usually large and may present with gastrointestinal bleeding from mucosal ulceration. Symptoms at presentation may include abdominal pain, an abnormal abdominal mass, nausea, vomiting, anorexia, hematemesis, melena, signs of anemia (occult bleeding) and weight loss. The submucosal location of the tumor may cause obstruction or perforation, especially those arising from the esophagus or small intestine. Tumors in the esophagus may present with disphagia, and those arising in the duodenum may compress the adjacent pancreatic head, resulting in fever and jaundice. Rectal GISTs may present with symptoms of mass effect, such as frequent, hesitant, or poor urinary stream, due to invasion in the urinary bladder (9).

Many imaging methods are available for the evaluation of patients with GISTs, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). CT is essential for evaluating the primary tumor and for accurate staging of the disease. MRI can also be used to detect hepatic metastases, although CT is usually an adequate technology, as long as appropriate techniques of both non-contrast administration and early and late visualization after intravenous contrast administration are used. CT is currently the first imaging method requested in patients with suspected bowel obstruction, which is reported in up to 30% of GISTs. Occasionally, a small bowel neoplasm may be detected in these cases. CT may also be used to guide tissue biopsy. CT is the most common technique for evaluating hepatic metastases (9). ❑

Prognosis

A consensus has been reached among expert pathologists with an interest in GIST: the most reliable prognostic factors are the size of the primary tumor (< 5 cm versus > 5 cm) and the mitotic index, which measures the proliferative activity of the cells. Mitotic index, whether assessed by direct counting or immunohistochemistry for a cell cycle marker (PCNA and Ki-67), has been linked to prognosis in a large number of studies and should be included in the evaluation of any primary tumor. Aneuploidy is a negative prognostic factor in GISTs, but ploidy analysis by flow cytometry is not generally used in routine diagnosis. Another prognostic feature is tumor location. In several studies, it has been noted than patients with primary gastric tumors do significantly far better than those with small bowel and rectal primary tumor. Other factors, such as specific histological subtype (epithelioid vs. spindle cell), the degree of cellular pleomorphism, and patient age, may have some contribution to prognosis, but are most likely to play a minor part in determining the clinical outcome. Up to 30% newly diagnosed GISTs are overtly malignant or have features than connote a high malignant potential (8).

Recurrence and survival rates have been reported to correlate with the location of the primary GIST lesion, small bowel tumors showing a somewhat worse prognosis.

TREATMENT

Surgical resection of the primary disease followed by observation is the conventional treatment for patients with GIST and offers the best cure rate. The primary goal of surgery is a complete resection, avoiding the tumor rupture. Because GIST does not infiltrate the organ of origin, wedge resection of stomach or segmental resection of small intestine provides adequate therapy (5, 7). A safety margin of normal surrounding soft tissue or bowel should be included, if possible, to reduce the risk of recurrence. Because lymph node metastases are rare, extensive lymphadenectomy is not routinely performed. Traditionally, the standard care after complete resection of a primary tumor has been observation only: in part, this reflects the inadequacy of conventional chemotherapy. In a recent analysis, the 1- and the 3-year survival rate were 90% and 58%, respectively (2). For resectable GIST, preoperative histological confirmation is not usually necessary, as these tumors may bleed, rupture, or disseminate as a result of the biopsy. For the same reasons, the tumor should be removed *en bloc* during surgery (9).

Disease recurrence has been reported in up to 80% of cases, despite complete resection with pathologically proven negative margins, and the 5 year survival is 54% (2). Although most recurrences occur within 2 years, tumors with low mitotic index may take more than 10 years to have metastases. Recurrence is commonly local and peritoneal, often associated with liver metastases. Lymph node involvement is unusual. Most metastatic GISTs are confined to the abdomen, unlike other soft tissue sarcomas, which metastasize to the lungs.

Hepatic artery embolization or chemoembolization was an attractive palliative option for patients with liver metastases from GIST. Arterial occlusion is effective, because the tumor is typically a hypervascular one. It is not clear whether the results of chemoembolization are due to an improved local delivery of chemotherapy, or to the interruption of arterial blood supply.

Although radiotherapy is essential in local therapy of extremity soft tissue sarcoma, its role in primary GIST is minimal, because of its potential toxicity on the surrounding structures and the need of large field or irradiation.

Radiation therapy has only an occasional role in the management of metastatic GIST. It can be used for palliative reasons in patients bleeding from peritoneal recurrence, if the responsible tumor bulk can be identified.

In GIST, the general opinion was that advanced disease represented a pressing medical need, before the onset of molecularly targeted therapy. The efforts belonging to the medical

oncologists, in order to treat GIST with conventional cytotoxic chemotherapy, were universally dismal. The rates of objective antitumor response to a variety of chemotherapy agents, for patients with GIST or abdominal leiomyosarcomas, were routinely reported as 0% to, at the best, less than 5%. Other investigators attempted to boost the benefits of chemotherapy by administrating the drugs via an intraperitoneal route. The combination of debulking surgery and intraperitoneal cisplatin and doxorubicin or mitoxantrone was demonstrated to be both technically feasible and safe (7). However, because few GISTs remain confined to the peritoneal surfaces, and because the majority of life-threatening complications of GIST arise from hepatic involvement or other bulky sites or omental disease, this has been viewed as less optimal result. Based on these disappointing results, conventional cytotoxic chemotherapy has been generally regarded as an overall failure in the GIST treatment (9).

In 1998, when Hirota et al. (10) published their observations about five patients with GIST, the treatment of gastrointestinal stromal tumor changed radically. Imatinib mesylate (Glivec®), formerly called STI-571, is an inhibitor of different tyrosinkinases, including Bcr-Abl, c-Kit and PDGF-R. Inhibition of Bcr-Abl underlies its activity in chronic myeloid leukemia (CML), whereas inhibition of c-Kit underlies activity in GISTs. So far, it is less clear, however, the drug has been demonstrated to be active in some cases of dermatofibrosarcoma protuberans, due to its action on the PDGF-R pathway (11).

Laboratory experiments testing imatinib in human GIST cell lines with defined activating c-Kit mutation, revealed dramatic evidence of anti-GIST activity from this agent. The addition of imatinib to GIST cell in culture rapidly and completely blocked the constitutive activation of c-Kit, arrested cell proliferation, and induced apoptosis in the tumor cells. By all criteria therefore, imatinib appeared to be a very promising and scientifically rational approach to the treatment of GIST (12).

Imatinib was approved by the *Food and Drugs Administration* (FDA) in May 2001 for the treatment of CML resistant of interferon therapy, and in February 2002 for the treatment of GISTs.

The results have been reported first by Joensu et al. (13): within a few weeks from starting daily oral administration of imatinib, the patient exhibited an objective clinical response that has been maintained for more than 18 months. A dramatic decrease in tumor activity was detected by PET. The biopsies demonstrated that the tumor has been largely replaced by myxoid degeneration and fibrosis within 4 weeks. Trials investigating the efficacy and safety of imatinib for GIST yielded dramatic results, that have permitted imatinib to be indicated as first line treatment of metastatic or unresectable malignant GISTs. As a consequence of this indication, current clinical approaches to the treatment of GISTs worldwide are being refined and clarified.

There is no standard dose for Imatinib, but, usually, doses range between 500 mg to 1000mg/day per os. Responses rate vary between 51% and 75% and the tumor control rate is more than 90%. The optimal dose of imatinib for the treatment of advanced GIST remains uncertain. Although there were no documented benefits to higher doses than 600 mg/day, the data of actual trials demonstrated that there were a few patients who regained disease control when crossed over from lower doses (400 mg daily) to the higher level. Therefore, some marginal benefit might be obtained from modest dose escalation of imatinib, in a subset of patients whose disease progress despite continous doses at lower therapeutic level of imatinib (14).

The major toxic reactions of imatinib are: mild fatigue, diarrhea, periorbitary oedema and intermittent muscle cramping. Significant gastrointestinal bleeding has been reported in a few patients and is possibly associated with a massive tumor necrosis (7).

Resistance to imatinib may be primary and may manifest as rapid progression of disease, despite imatinib dosing, although this appear in less than 20% of the patients. Alternatively, clonal evolution of GIST may be clinically detected, with the emergence of resistant disease after more than a year or two of durable response and disease control. Several mechanisms of resistance to imatinib in GIST have been described, and these are similar to the resistance mechanisms that have been demonstrated in CML (15).

Preliminary studies of GISTs suggest the following four mechanisms for drug failure, with parallels to imatinib resistance in CML: (a) acquisition of a secondary point mutation in c-Kit or PDGF-R that confers drug resistance; (b)

genomic amplification of c-Kit and resultant kinase overexpression; (c) activation of an alternate, yet unknown, receptor tyrosinkinase, with loss of c-Kit oncoprotein expression; (d) functional resistance in tumor expressing kinase, that are imatinib-sensitive in vitro (eg, exon 9 and c-Kit wild type) (8, 15).

There are interesting data regarding the site of c-Kit mutation and the likelihood of response to imatinib and other tyrosinkinase receptor inhibitors (16). The most common site of mutation is exon 11, followed by exon 9. Exon 11 mutations have the best response rate and the longest time to progression on imatinib therapy (17).

Fortunately, there is progress made in the development of new kinase-targeted small molecule inhibitors, that provides hope in the growing battle against imatinib resistance.

Sunatinib, a new multi-target tyrosinkinase receptor inhibitor has shown some activity in patients with GIST progressing after Imatinib. Eight percent of the patients in a phase II study had partial remission, and 37% of patients had stable disease for more than 6 months. An interesting observation was that patients with exon 9 mutations or wild type KIT, that is- those less likely to respond to imatinib, responded to sunitinib better than patients whose initial mutation was in exon 11. These data suggest that sunitinib is not an effective inhibitor of secondary resistant mutations which occur in relapsing patients with primary exon 11 mutations (18).

From the studies presented in this review, it is clear that these tumors do not constitute a single uniform entity, but rather, they represent a group of distinct closely related neoplasms (19).

Optimal clinical management of GIST requires a coordinated team effort of experienced medical and surgical oncologists, gastroenterologists, as well as pathologists and radiologists.

In less than half a decade, GISTs have emerged from historical anonymity to become an important focal point in trials of targeted therapeutics. However, it is also clear that new therapeutic methods will continue to be needed, in order to improve the outcome for malignant solid tumors following the GIST model. ❑

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