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CLINICAL PRESENTATION AND TREATMENT OF GASTROINTESTINAL STROMAL TUMORS

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Aims and background: **Gastrointestinal stromal tumors (GISTs), although rare, are the most common mesenchymal neoplasms affecting the gastrointestinal tract. We present our experience in the treatment of localized and metastatic disease and a review of literature.**
Patients and methods: **Nine patients were observed from April 2002 to July 2004. Eight tumors were in the gastric area and 1 was in the small bowel. In 5 cases, complete surgical removal was performed, and none of these patients underwent adjuvant therapy. The remaining 4 cases, with locally advanced or recurrent disease, were treated with imatinib.**
Results: **The patients with localized disease treated only by surgery did not relapse. In the patients with locally advanced or metastatic disease treated by imatinib, we observed 3 partial responses, and one case was not assessable because he had no measurable disease. In 2 of 3 responders, it was possible to perform a new radical surgery.**
Conclusions: **Our series is too small to draw any conclusion. According to our review of the literature, surgery remains the standard treatment for non-metastatic GISTs. Imatinib mesylate represents a major breakthrough in the treatment of advanced GISTs and is the first effective systemic therapy for the disease.**

Key words: gastrointestinal stromal tumors, treatment.

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract that are believed to originate from a neoplastic transformation of the intestinal pacemaker cells (interstitial cells of Cajal) normally found in the bowel wall, or their precursors[1,2]. The identification of these tumors has been facilitated by the recent application of CD117 immunohistochemistry which identifies the *c-kit* proto-oncogene product, overexpressed in nearly all GISTs, and distinguishes this type of neoplasm from leiomyomas or leiomyosarcomas.

Although relatively rare, GISTs, make up the largest subset of mesenchymal tumors of the gastrointestinal tract and are reported to comprise about 5% of all sarcomas[3-5]. The estimated annual incidence is 10-20 cases per million, of which 20-30% are malignant, although, following the recent clearer definition of the diagnostic criteria for GISTs, it may be necessary to revise these estimates[6,7].

GISTs occur in both sexes with similar frequency, but several reported data have shown a preponderance in males, generally after the 4th decade, with most studies finding a mean age at diagnosis of about 60 years. They are occasionally found in young adults, although extremely rarely in children[6,8].

Such tumors may occur anywhere in the gastrointestinal tract but are most commonly found in the stomach (40-70%) and small intestine (20-40%). Only 5-15% are found in the colon and rectum, about 5% in the esophagus and in the omentum, and rarely in the mesentery or retroperitoneum[3,6,7,9-11].

The most common symptoms reported are vague upper abdominal pain, gastrointestinal hemorrhage due to tumor bleeding, at times associated with anemia, and the presence of an abdominal mass. GISTs may also cause altered bowel function, bowel obstruction or perforation, dysphagia, and fever.

The clinical prediagnostic workup of GISTs is the same as for other gastrointestinal malignant disorders, although many small GISTs are discovered by chance during endoscopy or laparotomy performed for other reasons, such as submucosal or subserosal nodules, or during imaging examinations.

Surgery has been and continues to be the treatment of choice for GISTs. The tumor may present with a pseudocapsule and should be removed *en bloc* without a wide resection margin. Regional lymphadenectomy should be avoided since GISTs seldom spread to the lymph nodes[12-14]. There are no data to support the use of radiotherapy, and no effective chemotherapy for GISTs existed until the introduction of imatinib mesylate, a potent inhibitor of two cell-surface protein tyrosine kinases, the platelet-derived growth factor receptor and the stemcell factor receptor (*c-kit*). Activation of *c-kit*, often in association with mutation of the *c-kit* proto-oncogene, is believed to be present in all cases of GISTs. High rates of objective response have been achieved in phase I and phase II studies of imatinib thera-

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py for such tumors at a recommended dose of 400 mg *per os* daily.

Patients and methods

Nine patients affected by GISTs were observed in our Institute between April 2002 and July 2004. A GIST was defined as a mesenchymal tumor with immunohistochemical positivity for CD 117, the proto-oncogene protein of *c-kit*. In addition, immunohistochemical staging for CD34, desmin and the S100 protein was performed, and tumor resection margins and tumor histological subtype were determined. Tumors were considered malignant if they had more than five mitoses per 50 high power fields (>5 x 50/HPF).

Staging and therapeutic choices were based on CT of the abdomen and, in all the cases with gastric GISTs, on endoscopy for biopsy specimens and echoendoscopy.

For patients undergoing surgery, resection was considered complete if all gross disease was resected at the initial exploratory procedure with reported negative margins. The level of response to treatment with imatinib mesylate was evaluated on the basis of radiological measurement of the tumor. Radiographic tumor size was defined as the length in centimetres of the greatest diameter, according to the RECIST criteria. A complete radiographic response was defined as a failure to identify a lesion that had been present on previous radiographic images.

Results

Between April 2002 and July 2004, 9 patients, 4 men and 5 women, affected by GISTs were observed in our Institute. Mean age was 64.5 years (range, 51-75). Eight tumors were in the gastric area and 1 was in the small bowel.

In 5 cases, 4 of the gastric GISTs and the small bowel tumor, complete surgical removal was performed. Of the 4 gastric GISTs, partial gastrectomy according to Billroth II was performed in 1 case. In the other 3 patients, a partial wedge gastrectomy was performed, one under videolaparoscopic control. In the remaining GISTs, small bowel resection was performed on the involved ansa. None of these 5 patients underwent adjuvant therapy with imatinib mesylate; so far, none of them has shown disease relapse (Table 1).

Of the 4 patients treated with imatinib mesylate, 2 presented local recurrence and the other 2 showed metastatic disease from the beginning. The 2 cases with localregional relapse were successfully treated with imatinib mesylate and then with radical surgery. Both patients are still alive and show no signs or symptoms of the disease. The 2 cases with metastatic disease underwent imatinib therapy. In only one of these patients was it possible to make an evaluation; he did not respond to a dose of 400 mg of imatinib but obtained CR with 800 mg. The second patient was not assessable because he had no measurable disease. The treatment was well tolerated, giving rise only to slight nausea and periorbital edema (Table 2).

Discussion

GISTs are the most common mesenchymal neoplasm affecting the gastrointestinal tract. The term GIST was first used by Mazur and Clark in 1983 to describe gastrointestinal non-epithelial neoplasms with neither the immunohistochemical features of Schwann cells nor the ultrastructural characteristics of smooth-muscle cells. The discovery of gain-of-function mutations in the c-*kit* proto-oncogene in GISTs by Hirota and colleagues in 1998 was of crucial importance in terms of the genesis and classification of these tumors[15]. This finding led to the development of rational molecularly targeted therapy of GISTs with the kit-receptor tyrosine-kinase inhibitor, imatinib mesylate (formerly known as STI571). With the identification of the tyrosine kinase inhibitor

Table 1 - Characteristic of the 5 cases treated by surgery alone

Sex	Age (yr)	Localization	Size (cm)	Mitotic index	Surgical procedure	Follow-up (mo)	Relapse
M	65	Stomach	8	<5 x 50/HPF	Partial gastrectomy, Billroth II	38	No
F	66	Stomach	17	>5 x 50/HPF	Partial gastric wedge resection	36	No
M	73	Small bowel	20	<5 x 50/HPF	Small bowel resection	30	No
F	75	Stomach	4	<5 x 50/HPF	Partial gastric wedge resection VLS	24	No
M	75	Stomach	8	<5 x 50/HPF	Partial gastric wedge resection	10	No

Table 2 - Characteristic of the 4 cases treated with imatinib mesylate

Sex	Age (yr)	Localization	Mitotic index	Dose of imatinib/day	Response	Follow-up (mo)	Surgery after response to imatinib	Relapse
F	64	Stomach	>5 x 50/HPF	400	PR, then surgery	57	Yes	NED
F	56	Stomach	>5 x 50/HPF	400	PR, then surgery	51	Yes	NED
M	51	Stomach, liver	<5 x 50/HPF	400-800	CR at 800 mg	45	No	NED
F	61	Stomach, liver, peritoneum	<5 x 50/HPF	400	NE	6	Not applicable	NE

PR, partial response; CR, complete response; NE, not evaluable; NED, no evidence of disease.

imatinib mesylate as an effective therapeutic agent, it has become increasingly important in the clinical treatment of GISTs to distinguish these neoplasms from other mesenchymal tumors such as leiomyomas, leiomyosarcomas, and schwannomas.

At present, GISTs are defined as spindle-cell, epithelioid, or occasionally pleiomorphic mesenchymal tumors of the gastrointestinal tract that express the kit protein[6,7]. The kit protein is often detected clinically by immunohistochemical assays for the CD117 antigen, an epitope of the kit-receptor tyrosine kinase. GISTs characteristically stain strongly for the CD117 antigen, whereas smooth-muscle neoplasms (leiomyoma and leiomyosarcoma), neurogenic tumors (schwannomas), and desmoid fibromatoses typically do not show this positive expression of CD117[6,7,11]. In addition to CD117, GISTs commonly exhibit positive staining for CD34, a sialylated transmembrane glycoprotein, but less commonly for SMA and S100 (neural cell marker), which are expressed typically by leiomyosarcomas and schwannomas, respectively[7,16]. Thus, CD117 immunostaining is an important method for diagnostic distinction.

There is no consensus within surgical and pathological communities regarding the grading or classification of GISTs. Malignant potential is not always predicted by conventional histologic factors. Because of this, some investigators have suggested that the terms benign and malignant GIST be replaced by low, intermediate, or high risk for malignant behavior[17,18]. Several factors independently predict the prognosis of GISTs following resection. The most important and easily applicable histologic criteria for prediction are tumor size (maximum diameter in cm), and mitotic rate[11,18-20]. A rate of ≤5 mitoses per 50 HPF is commonly used as a limit for a tumor of expected benign behavior, and according to a large study, this can discriminate between benign and malignant gastric tumors, but not between benign and malignant small intestinal tumors[11]. Low-grade tumors (mitotic index <10 per 50 HPF) also lead to a better outcome than high-grade tumors (mitotic index >10 per 50 HPF). Tumors of 2 cm in diameter are generally expected to behave in a benign fashion. Tumors of <5 cm in diameter are associated with a better survival rate than those of 5-10 cm, which in turn have a better prognosis than those of >10 cm. Degree of cellularity and atypia have also been suggested as useful criteria, but their reproducibility is more problematic. Finally, GISTs found in the stomach are associated with better survival than those located in the small intestine. Limited survival information is available for GISTs found in other locations. Age has also been suggested as an independent prognostic factor, but studies published up till now have not reported figures regarding cancer deaths[9]. Many others factors have also been investigated. Karyotypic or genetic markers such as deletions in chromosome 9p[21] or gain of function mutations in exon 11 of the *c-kit* gene have been correlated with malignant behavior in some studies[22-25] but still require further validation.

A peculiar feature of GISTs is that most recurrences are solely intra-abdominal. Macroscopic extra-abdominal metastases are uncommon even in advanced disease, and they rarely occur in the absence of intra-abdominal relapse. This feature contrasts with true leiomyosarcomas of the abdomen and gastrointestinal tract, which commonly give rise to pulmonary metastases[8,15]. About 40-80% of GISTs recur despite histopathologically complete tumor resection. Most recurrences take place within 5 years of the primary diagnosis[9], but in the slowly proliferating subset of GISTs, metastases may appear more than 10 years after the primary diagnosis. The most common sites of metastases are the peritoneum and the liver[3,8], whereas regional lymph node metastases are extremely rare[3,13]. In one review of 60 patients with recurrent GISTs, local recurrence occurred in 76% of patients, half of whom had synchronous liver metastases, 15% liver metastases, and 7% peritoneal metastases[26]. None had extra-abdominal metastases at the first relapse. Peritoneal metastases are most probably a result of tumor cell seeding from the primary tumor directly into the peritoneal cavity. Similarly, liver metastases most probably result from hematogenous seeding into the portal vein.

The clinical presentations of GISTs are highly variable according to their site and size. Many small GISTs are discovered incidentally during endoscopy or laparotomy performed for other reasons such as submucosal or subserosal nodules, or during imaging examinations. Symptomatic GISTs are usually larger in size. At presentation, the most common symptoms of GISTs are vague abdominal discomfort or pain, presence of a palpable abdominal mass, feeling of abdominal fullness, and secondary symptoms resulting from tumor bleeding and associated anemia. GISTs can also cause altered bowel function, bowel obstruction or perforation, dysphagia, and fever. Duodenal GISTs occasionally cause obstructive jaundice. GISTs are commonly discovered during emergency surgery for sudden perforation of the gastrointestinal tract and consequent intra-abdominal blood loss[27], and 15-50% of GISTs present with overtly metastatic disease[3,20,28].

Nevertheless, the most common symptoms seem to be gastrointestinal bleeding (20-50%) and vague upper abdominal pain/dyspepsia (50-70%)[3,25,29-31]. In a series of 55 patients evaluated at the Massachusetts General Hospital, for example, gastrointestinal bleeding and pain/dyspepsia were found in 26% and 14% of patients, respectively[32]. In the study, fewer than 10% had a palpable mass or perforation, and obstruction was only found in 3% of patients. However, in a series of 200 patients evaluated at the Sloan-Kettering Memorial Cancer Center, most patients presented with gastrointestinal bleeding[3].

In rare instances, GISTs occur as part of tumor syndromes. Carney's triad, described by the endocrine pathologist J. Aidan Carney of the Mayo Clinic, includes gastric GIST, paraganglioma and pulmonary chondroma (by definition, at least two of these tumors

seen in the same patient). Familial occurrence has been suggested for Carney's triad, but no detailed molecular genetic mechanism is known[33]. A pathogenetic correlation has also been suggested between neurofibromatosis type 1 (von Recklinhausen's disease) and GISTs because of the high frequency of non-random association of these diseases[34]. However, most GISTs are sporadic, and predisposing factors are unknown.

Radiological investigations occasionally pick up incidental cases. Imaging features usually offer information valuable to distinguish tumors of mesenchymal origin from lymphoma and epithelial neoplasms of the gastrointestinal tract. Nevertheless, the further differentiation of mesenchymal gastrointestinal neoplasms requires histological and immunochemical tests. Attempts to predict potential malignant behavior of GISTs from their imaging features have been unsuccessful. Image-guided tissue biopsy is also occasionally performed for selected cases.

Surgery remains the standard treatment for non-metastatic GISTs. As with other soft-tissue sarcomas, a true capsule does not exist, and the tumor should be removed *en bloc* with its pseudocapsule and, if possible, an adjacent margin of normal soft tissue or bowel, even though the optimum width of the tumor-free margin has still to be defined. In cases where contiguous organs are involved, *en bloc* resection has been recommended wherever feasible[35]. Local peritoneal tumor seeding is common, and a local peritonectomy should be performed if possible. Regional lymphadenectomy should be avoided since GISTs seldom spread to lymph nodes[13,14]. Tumor rupture, spontaneously or during surgery, may be associated with an increased risk of development of peritoneal implants and should be avoided[36].

Up to the year 2000, studies of GISTs included tumors that would not at that time have been classified as GISTs and data are therefore contaminated by these cases. However, the overall survival rates at 5 years range from 40% to 65% after complete resection[3,28,36-41], versus a median survival of 9-12 months for incomplete resection[32,39].

In two recent large series of malignant GISTs presenting combined data on 200 tumors from the Sloan-Kettering Memorial Cancer Center[3] and 191 tumors from the MD Anderson Cancer Center[36], overall 5-year survival was 35% and 28%, respectively. However, these patients, seen in two large oncologic hospitals, included many subjects referred for local failure or metastasis. The 5-year actuarial disease-free survival was much better, at 54% for patients whose tumors were completely resected[13].

Five-year survival after complete surgical resection varies considerably in published series involving patients with GISTs, as shown in Table 3[3,36,39-41].

There are still insufficient data about the usefulness of resecting recurrent disease or intra-abdominal metastases. In some studies, tumor-specific mortality and overall survival have not differed significantly between patients who underwent complete resection of recurrent disease and those who had partial resection or biopsy alone[26]. However, there is evidence that metastasectomy may improve survival in selected patients. Patients with well or moderately differentiated GISTs, with a disease-free interval between the diagnosis and detection of metastases of longer than 12 months, and isolated resectable liver metastases are more likely to benefit from metastasectomy than patients who have rapidly progressing or widespread GISTs[42,43].

Table 3 - Five-year survival of patients with GISTs following surgical resection

	No. of patients evaluated	No. of patients completely resected	5-year survival %
Akwari *et al.*[41] Mayo Clinic	108	52	50
Shiu *et al.*[40] MSKCC	38	20	65
McGrath *et al.*[39] MCV	51	30	63
Ng *et al.*[36] MDACC	191	99	48
DeMatteo *et al.*[3] MSKCC	200	80	54

MSKCC, Sloan-Kettering Memorial Cancer Center; MCV, Medical College of Virginia; MDACC, MD Anderson Cancer Center.

Until not long ago, the treatment for GISTs relied on surgical resection as the only therapeutic approach. In fact, conventional chemotherapy and external beam radiotherapy have not been successful in the past in the treatment of either recurrent or metastatic disease because of the chemoresistance of GISTs and limited radiation tolerance of intra-abdominal organs. The response rates to chemotherapy, including dacarbazine, mitomycin C, doxorubicin, and cisplatin, were less than 10%[44-46]. These chemotherapeutic strategies resulted in partial response rates of 0% to 15% and overall survival rates of 40% at 5 years. The introduction of imatinib-targeted therapy for KIT that expressed GISTs has substantially impacted the clinical treatment and prognosis of metastatic GISTs and has potentially influenced the role of surgery.

Imatinib mesylate is a competitive inhibitor of certain tyrosine kinases including the intracellular kinases ABL and BCR-ABL fusion protein present in some leukemias, kit, and the platelet-derived growth factor receptors[47]. Early reports indicate that this represents the first systemic therapy for GISTs with promising evidence of treatment response[48-50].

The first case report on the effect of imatinib mesylate therapy for GISTs was published by Joensuu *et al.*[48] The patient was reported to have a significant response to therapy, demonstrated by MRI and PET scanning as well as repeated fine-needle aspiration cytology. Subsequent series from the US-Finland GIST Study Group and the EORTC Soft Tissue and Bone Sarcoma Group evaluating the treatment response of metastatic GISTs to imatinib mesylate reported partial response rates of 59% and 69% based on radiographic

evaluation, in 86 and 36 patients, respectively[46,48,51]. Recent studies have confirmed the safety of 400 mg imatinib and the possibility of increasing the dose to 800 mg die if no response is obtained[52,53]. The most common side effects were anemia (92%), periorbital edema (84%), skin rashes (69%), and fatigue (76%)[54,55]. Some authors have outlined the relationship between molecular profile (mutations in codon 11) and better response to treatment with imatinib[56]. This was consistent with our results. Recently, a new tyrosine kinase inhibitor, SU11248, seems to achieve particular acivity in GISTs resistant to imatinib[57]. The role for imatinib mesylate in the neoadjuvant and adjuvant setting in the treatment for GISTs is still, however, to be fully investigated. Two trials are currently underway to explore the use of imatinib mesylate as an adjuvant therapy after complete primary tumor resection (ACOSOG Z9000 and Z9001). Trials investigating the use of imatinib mesylate in the neoadjuvant setting are currently in the formulative stages[58]. In our experience, the 2 cases undergoing surgery after a satisfactory response to imatinib are still alive and with no evidence of disease relapse.

In conclusion, it is important to distinguish GISTs from other mesenchymal tumors of the gastrointestinal tract because of differences in biologic behavior and treatment strategies. At present, surgery remains the standard treatment for nonmetastatic GISTs, whereas imatinib mesylate represents a major breakthrough in the treatment of advanced GISTs and is the first effective systemic therapy for the disease. Nevertheless, owing to the lack of long-term data, widespread use of imatinib mesylate outside approved indications or controlled trials must be avoided. Patients with GISTs should be considered for enrollment in one of the many ongoing clinical trials.

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