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Letters to the Editor

Gastrointestinal stromal tumors (GIST): New treatment expectations

Key words: Gastrointestinal stromal tumors. Imatinib. c-kit receptor. Neoadjuvant therapy.

Dear Editor,

Gastrointestinal stromal tumors (GIST) have been known for over twenty years, but until ten years ago they were a heterogeneous group of neoplasms which included leiomyomas, leiomyosarcomas, leiomyoblastomas and schwannomas. They represent approximately 0.5-3 % of all primary tumors of the gastrointestinal tract, only 5 % of visceral sarcomas, but 80 % of malignant tumors originated in the mesenchymal tract (1). The belief that these tumors are the "benign" form of the gastrointestinal neoplasms is widespread. However, the most commonly used classification –Fletcher, 2002 (2), based on the tumor size and the mitotic count by 50 high power fields– divided GIST in very low, low, medium and high risk of *malignancy*.

A review of the available literature showed that both medium and high risk-malignancy tumors are able to induce distant metastasis. Over the last ten years, eleven patients were diagnosed and operated in our hospital. Three of them died from metastatic disease: One of them presented a high risk GIST. Half of the four whose tumors were classified as medium-risk died due to the neoplasms. All remaining patients are currently asymptomatic and only one of them, with a medium risk-tumor originated in the small bowel, is still being treated with 400 mg of imatinib per day.

Table I. Fletcher's criteria of prognosis

	Size (cm)	*Mitotic count (per 50 HPF*)*
Very low risk	< 2	< 5
Low risk	2-5	< 5
Medium risk	< 5	6-10
	5-10	< 5
High risk	> 5	> 5
	> 10	Any mitotic rate
	Any size	> 10

*HPF: High power fields.

A new marker, which happens to be independent of KIT mutations and PDGFRα, has been recently discovered. It is a chloride channel protein denominated DOG1. It seems to have the same diagnostic sensitivity as other mutations that have been employed until now. DOG1 is especially useful in highly-suspected GIST with negative KIT staining (3,4). However, there was negativity for these two immunohistochemical markers (DOG1 and KIT) in 2.6 % of the gastrointestinal tumors (3). In these cases, the protein kinase C theta (PKCtheta) could be used since it seems to be expressed in all GIST (5). Those two mutations (DOG1 and PKCtheta) are gaining importance for diagnosing GIST after a negative KIT, since an accurate diagnosis is crucial for a satisfactory treatment with imatinib.

The treatment of choice for primary disease is complete surgical resection (R0). The spread via the lymphatic system is not probable, therefore, it is not necessary to leave wide margins of resection or perform an extended lymphadenectomy. Sometimes it could be necessary to perform complex interventions (Mile's abdominoperineal amputation, Whipple intervention) due to the tumor location (6,7). The fragmentation of the tumor may cause tumor implants, thus the most important aspect during the surgery is trying to avoid this situation (1). It would be equivalent to a R2 resection (6).

Instrumental manipulation could increase the risk of peritoneal dissemination. This is the reason why most authors accept

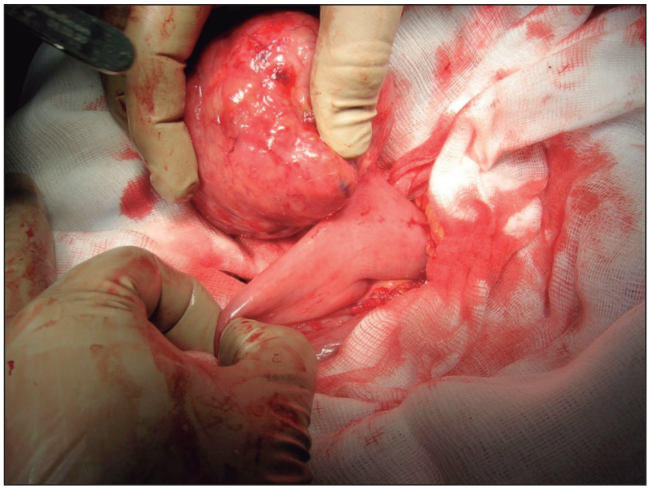

Fig.1. GIST located in the antimesenteric side of the first jejunal loop.

laparoscopic resection only if the tumor size is minor than 5 cm. Nevertheless, in tumors located in the gastroesophageal junction, antro-pyloric area, or the posterior gastric wall, laparoscopic resection is under discussion provided their complexity (6).

GIST are resistant to conventional chemotherapy, and radiotherapy is completely ineffective. Intraperitoneal chemotherapy or radioablation (for liver tumors) was attempted, but the results were disappointing. Nonetheless, hepatic arterial chemoembolization was successful for the treatment of liver metastases secondary to GIST. A study with 110 patients conducted in the United States demonstrated an increase of global survival rate in patients who underwent this kind of intervention (7).

Results are very different since Imatinib was introduced in the postoperative period. Imatinib as an adjuvant therapy significantly improves recurrence-free survival (8). After numerous trials, Imatinib was recommended in a dose of 400 mg/day for tumors with exon 11 mutation and 800 mg/day for those with exon 9 mutation, respectively (4). The use of imatinib as a neoadjuvant therapy is being considered in patients that may be operated subsequently (10).

Resistance to Imatinib therapy is defined as a negative response after 3-6 months of treatment. GIST with exon 9 mutation or PDGFR-gene are more likely to present stronger resistance. In these cases, Sunitinib malate may be used (Sutent®, Pfizer, New York, USA) as second-line therapy (11).

Sunitinib has obtained the best results after Imatinib, but there are other options under study. Everolimus, HSP90 and flavopiridol are some of them. Phase I/II studies are yielding better results for the combined treatment with everolimus (mTOR inhibitor) and a tyrosine kinase inhibitor, especially as a third-line therapy (12). In GIST resistant to imatinib and sunitinib, the use of sorafenib, dasatinib, motesanib and nilotinib is being studied (13).

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