The neo-adjuvant treatment in Gastrointestinal Stromal Tumor

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Abstract

Gastrointestinal Stromal Tumor (GIST) is a rare intra-abdominal tumor, characterized by a specific histological and immunohistochemical pattern. These tumors affect with higher frequency stomach and small bowel and occur at a median age of 60 years with a slight male predominance. An early stage of GIST often don't cause any symptoms, so most GISTs are diagnosed in later stages of the disease. We report a case of GIST diagnosed only with clinical data and positron emission tomography (PET). We demonstrate the usefulness of neo-adjuvant treatment with Imatinib mesylate, a newly developed tyrosine kinase receptor inhibitor. The neoadjuvant treatment with Imatinib reduced the mass size and vascularization, making possible a surgical approach.

Key Words: GIST, Imatinib mesylate, Neo-adjuvant treatment.

Case Report

A man (68 years old) was admitted into our Department for hematemesis, melena and anaemia (red blood cells $3.93x10^{12}$/L, white blood cells $9.5x10^{9}$/L, packed cell volume 28.9%, haemoglobin 8.7 g/dl, mean cell volume 73.5 Fl) Serum parameters and coagulation were within normal limits, with mild reduction of serum protein (6 g/dl) and serum iron (22 mg/dl). Esophago-gastroduodenal endoscopy (EGDS) (8/3/03) showed an ulcerated and bleeding lesion of 4 cm size in the fundus, under cardias region. At ecoendoscopy (10/3/05) we appreciated an anechogenic and hyperechogenic lesion of the fundus, originating from muscolaris propria, of 4 cm size, without node of celiac tripod. The patient submitted a PET showing a focal gastric lesion with a high radiodrug uptake (18F-FDG: 18-Fluoro-Deoxy-Glucose) at gastric fundus and body. PET examination gave evidence of a focal gastric lesion with high metabolic activity. At Computed Tomography (TC) examination with contrast we appreciated a large mass, of 42 mm size, protruding into gastric lumen, at gastroesophageal angle and lesser curve gastric. Mesenteric and celiac lymph nodes were absent. Being impossible to make a pre-surgical biopsy, for the high risk of bleeding, diagnostic hypothesis of GIST based on clinical and laboratory data and PET result. Usually GIST causes intermittent episodes of acute crampy abdominal pain, associated with intussusception, followed by chronic bleeding with iron deficiency anaemia, weight loss, pain, gastric outlet obstruction. Symptoms, when occur, tend to be vague and non specific (1).

In date 18/04/05 the patient gave its consent form for a neo-adjuvant therapy with Imatinib (400 mg/die) and refused surgery. This drug is a newly developed tyrosine kinase receptor inhibitor. Approximately 90% of GIST contains activating mutations in tyrosine kinase receptor (c-kit). The c-kit protein is a cell membrane receptor tyrosine kinase that binds the growth factor called stem cell factor (SCF). SCF is also known as mast cell growth factor, steel factor (SLF) and c-kit ligand. A prisoner dilemma strategy was preferred: when a doubt exists, the choice of a maximal benefit with minor risk is chosen. In this case being surgery a risk, histologic pattern and the positivity of CD117 was unknown. Fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to be highly sensitive to assess disease status in patients with GIST. In the last visit performed at March 2008, the patient appeared in good health.

The administration of Imatinib went on for 7 months since April 2005, with poor adverse effects (cramps and difficulty of hands fine movements). Follow up consisted of weekly visits and haemogram and then every 15 days. Considering that after 20 days of therapy with irongluconate, haematologic pattern improved, it was stopped. In July 2005, patient submitted an EGDS, showing a submucosa lesion, of 30 mm size, covered by smooth mucosa, with a small ulcer in the apex. Ecoendoscopy confirmed data of EGDS, with the histological diagnosis of GIST. PET revealed a focal area with a fewer radiodrug uptake that previous exam. In date 03/11/05 patient underwent a laparoscopic wedge resection of gastric fundus. Operatory piece was a gastric segment of 6 cm size, with an intramural lesion of 3 cm, and a histological diagnosis of gastric stromal cancer with advanced sclero-ialinosis.

Discussion

GIST is a rare intra-abdominal tumor accounting for no more than 3% of gastrointestinal malignancies, characterized by a specific histological and immunohistochemical pattern. These tumors affects with higher frequency stomach and small bowel and occur at a median age of 60 years with a slight male predominance (2). Molecular events of GIST are known: mutations of KIT (which encodes the KIT protein) o PDGFRA (which encodes the A chain of the PDGF receptor) protooncogenes.

After the discovery that GIST characteristically express the kit protein, a transmembrane tyrosine kinase receptor for a stem cell factor, a specific tyrosine kinase inhibitor, imatinib mesylate, has been introduced in clinical practice with partial response rate as high in advanced GISTs. (Blanke CD, 2001)

The diagnosis of GIST relies on histological arguments (proliferation of spindle-shaped cells in 70% of cases, of epithelioid cells in 20%; histological variants are rare and sometimes misleading) and on immunohistochemical arguments (expression of KIT in 95%, usually associated with CD34 expression in 60%-70% of cases). The demonstration of mutations in target genes is required only in cases that are histologically suggestive but KIT-negative (2). A series of histopathological criteria have been reported to predict the malignant potential of these tumors but their conclusions varied. It was reported that the prognosis of the GIST correlated well with mitotic count, tumor size, tumor cellularity, tumor necrosis, anatomical location, invasive growth and expression of Ki-67 and PCNA index (3,4). The best immunostaining method for identifying GIST is to test for expression of KIT, also called CD117. KIT, a 145-kDa transmembrane glycoprotein, is the normal cellular homologue of the viral oncoprotein v Kit (5). KIT is also normally expressed by a few other types of cells in the body such as melanocytes in the skin, mast cells, and hematopoietic stem cells involved in making new blood cells (this is where “stem cell factor” got its name). It is a member of

the receptor tyrosine kinase subclass III family that includes receptors for platelet-derived growth factor (PDGF), macrophagecolony stimulating factor, and flt3. Nevertheless, there are tumors that are both KIT and PDGFR mutation negative, suggesting that additional, yet unidentified, abnormalities may contribute to GIST tumorigenesis (6).

Another immunohistochemical marker often found to be positive in GIST is CD34, a protein normally expressed by hematopoietic precursor cells (stem cells that generate new blood cells) and some interstitial cells of Cajal. Prior to the discovery of KIT, CD34 positivity was the best available indicator of a GIST diagnosis, but it was not very specific. It is now believed that GISTs originate from gastrointestinal pacemaker cells known as interstitial cells of Cajal, that control gut motility or from a precursor of these cells. The identification of mutations mostly in exon 11 and to a lesser extent in exons 9 and 13 of the c-kit protooncogene coding for c-kit (CD117) in many GISTs, has resulted in a better understanding of their oncogenic mechanisms. An early stage of GIST often do not cause any symptoms. Most GISTs are diagnosed in later stages of the disease. Larger tumors may cause symptoms that are generally related to the increased mass being accommodated in the abdominal cavity, and such symptoms would not necessarily be different from those other types of tumors. These symptoms include digestive discomfort, sensations of abdominal fullness, or abdominal pain. Some patients experience vomiting or diarrhea. Bowel obstruction may occur. Sometimes GISTs perforate the stomach or gut lining and bleed into the GI tract, resulting in black or tarry stools, or occasionally in vomiting of blood. Anemia may result from chronic bleeding, leading to fatigue. The patient may notice weight loss.

Many GISTs are found incidentally through medical imaging for other purposes or through surgery for other conditions. The management of the GIST (gastrointestinal stromal tumor) has significantly changed with the development and availability of Imatinib Mesylate, an agent with significant clinical benefit for patients with advanced GIST (7). Surgery has been the only effective treatment for both primary GIST and for respectable metastatic disease. Nevertheless, even after apparently curative surgical resection mare than 50% of patients relapse, either locally or with distant intra-abdominal disease (liver, peritoneum) (8). GIST is resistant to conventional cytotoxic chemotherapy (9). The development of an effective novel targeted therapy against GIST have been changed the approach to this tumor. Though the experience with imatinib is still limited, the majority of patients with irresectable GIST develop partial responses or stable disease (10,11). Imatinib at a dose of 400 mg/day is now the standard treatment of advanced GIST in which radical resection cannot be effected. Imatinib is an orally bioavailable 2-phenylaminopyrimidine derivative that potently and selectively inhibits KIT, Bcr-Abl, and platelet-derived growth factor receptor alpha (PDGF-R-alpha) and beta (PDGF-R- beta) protein-tyrosine kinases (12). Imatinib inhibits proliferation and promotes apoptosis in GIST cells by interrupting tyrosine kinase-mediated intracellular signaling. More than 80% of patients with metastatic or inoperable GIST have achieved a decrease in tumor burden of 50% or more (partial response) or had no disease progression in clinical studies of imatinib, for which at least 9 months of follow-up (Eisenberg BL et al. 2004). Rapid and dramatic

results have been documented, including a 52% reduction in tumor size and a complete metabolic response (i.e., absence of abnormal tumor uptake of [18F]fluorodeoxyglucose) demonstrated by positron emission tomography scanning after 4 weeks of imatinib (12). We have demonstrated positive effects of this drug in neo adjuvant regimen. The aim of the neoadjuvant treatment with Imatinib was the reduction of mass size and vascularization, making possible a surgical approach. The introduction of Imatinib mesylate, an inhibitor of tyrosine kinase activity of the c-kit proto-oncogene, has provided the first significant opportunity to treat this malignancy by means other that surgery. Responses obtained with imatinib are still short, while we have have obtained a prolonger response, that led to hopes of a curative treatment. As imatinib resistance in GIST occurs at a median of 18 to 26 months, further targeted therapies have been explored. Sunitinib, another tyrosine kinase inhibitor, seems to be useful especially in patients with exon 9 mutations of c-kit, who usually have a worse response to imatinib. This might indicate that more exactly targeted therapies in GIST might improve clinical outcomes in the future (13).

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