Gastrointestinal Stromal Tumors: Epidemiology and Treatment Outcomes

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Abstract

Introduction: Numerous studies have investigated the prevalence, incidence and clinical manifestations of gastrointestinal stromal tumors (GISTs). However, little is known about GISTs in Iran. This pioneer study focuses on description of 36 patients with GISTs in Iran.

Methods: A database was created for 36 patients suffering from GIST who were treated in Loghman Medical Center and Tehran Cancer Institute in Tehran, Iran. Information on age, sex, clinical manifestations, treatment and outcomes were recorded and analyzed using SPSS version 13.

Results: Patients had an average age of 60 years; and 16 of them were males. The disease was most commonly manifested by abdominal mass, weight loss, and anemia. Twenty one patients had a mass smaller than 10cm; and in 33 patients KIT test was positive. In the follow-up, 5 patients experienced relapse and 3 succumbed due to advanced cancer.

Conclusion: Primary results showed that GISTs might have different manifestations and incidence in Iran compared to other parts of the world. We hope that this study could serve as a starting point for the better understanding and classification of this disease in Iran and for development of improved management strategies.

Keywords: gastrointestinal stromal tumors (gist), surgery, Iran

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Introduction

Mesenchymal tumors of the gastrointestinal tract demonstrate variable biologic behavior with latency on one end and rapidly progressive malignancy on the other. They are classified into three groups: 1) gastrointestinal stromal tumors (GISTs) that are the topic of this work; 2) neoplasms derived from smooth muscle including leiomyoma and leiomyosarcoma ; 3) the least prevalent schwannomas [1].

The term GIST was first used by Mazur and Clark to describe non-epithelial tumors that lack microscopic features of smooth muscle cells or neurons [2]. GISTs are the leading type of mesanchymal tumors of the GI tact with an incidence of 14.5 per million [3]. Hirota et al showed that GISTs share some histological characteristics with interstitial cells of Cajal. They are in fact "pacemakers" that regulate peristalsis of the GI tract. GISTs can arise for any tissue with Cajal cells including stomach, small intestine, colon, rectum, omentum, oral cavity, biliary tree, and liver. GISTs are often diagnosed during the fifth to seventh decades of life [5]. Our understanding of the molecular biology of GISTs has expanded dramatically in the past years. These entire tumors express KIT gene (CD117), and they commonly express CD34. These markers are found in hematopoietic stem cells and malignancies like CML (chronic myelogenous leukemia). KIT is frequently activated by mutation, and hereditary expression occurs rarely [6]. GISTs have been diagnosed with increasing frequency since the discovery of KIT in 1992. Before such discovery, the differentiation between stromal tumors, smooth muscle neoplasms and schwannomas was cumbersome. A diagnosis of GIST was suggested when the neoplasm lacked smooth muscle (actin and desmin) or neurolemma markers (S100). This led to errors since a large subgroup of stromal tumors also express these markers [7]. Patient survival was clearly improved since FDA approved Imatinib in 2002 [8]. Imatinib is a specific protein kinase inhibitor that was initially used for the treatment of CML and whose therapeutic

effects in GISTs were discovered subsequently. Prior to the use of Imatinib, the response to chemotherapy was about 5% with a relapse rate of 9 to 20 months on average [9].

Patients with stromal tumors often have nonspecific symptoms like bloating and early satiety. GISTs are vascularized tumors that present with bleeding in half the cases. Others present with palpable mass or obstruction (35%) and pain [20]. Rarely the tumor is diagnosed incidentally [10]. In the GI tract, stomach is the leading site of stromal tumors (60-70%) followed by small intestine (20-30%, especially ileum), colorectal region (5%) and esophagus (5%) [11]. The majority of stromal tumors are benign and only 10 to 30% become malignant. Malignant transformation is diagnosed based on the number of mitoses in histological preparations [12]. Factors suggested to increase the risk of malignancy are extragastric location, size larger than 5cm, central necrosis, invasion to adjacent organs and distant metastasis. However, these factors are not agreed upon by all researchers. Frequent sites of metastasis are liver, peritoneum, lung, bone and lymph nodes [13].

Methods

A retrospective cohort study was conducted on 36 patients with GIST treated in Loghman Medical Center and Tehran Cancer Institute between 2000 and 2007. The study was approved by Medical Ethics Committee in Tehran University of Medical Sciences. A database was designed and information on age, sex, clinical manifestations, treatment and outcome was recorded. In the clinical manifestations, symptoms, extent of the tumor on diagnosis, and anatomical location of the tumor were registered. In terms of treatment, data were collected regarding type of surgical resection, adjuvant therapies, locoregional relapse and distant metastases. Appropriate descriptive statistics was applied and data on tumor characteristics, type and outcome of treatment, and specific tumor markers (KIT) were analyzed using SPSS. Patients were followed for end pints of relapse or decease.

Results

There were 16 males (45%) and 20 females (55%) aged 42 to 85 years (mean: 60 years) in the study. Age average and distribution were equal in both sexes.

Our patients presented most commonly with abdominal mass, anemia, weight loss and malnutrition. Less frequently, patients presented with right upper quadrant abdominal pain, small intestinal obstruction, upper GI bleeding, acute abdomen or an incidental finding in CT or exploratory laparotomy (Table 1).

Table 1: *Frequency of presenting symptoms according to sex*

Presentation	Male	Female	Total
abdominal mass	2	4	6
weight loss and malnutrition	2	4	6
Anemia	2	4	6
small intestinal obstruction	2	3	5
upper GI bleeding	1	2	3
right upper quadrant abdominal pain	-	3	3
acute abdomen	2	1	3
incidental finding in CT or exploratory laparotomy	1	1	2
Indigestion and constipation	1	1	2
Total	**13**	**23**	**36**

The time between the onset of symptoms and referral to a medical center ranged from a few hours to two years. Twenty eight patients had local disease, 5 had locoregional extension and 3 had distant metastasis. Only 3 patients received chemotherapy by Imatinib alone due to advanced disease and hepatic metastases. The remaining 33 underwent laparotomy during which the following findings were reported: small intestinal tumor in 16 patients (48.5%); gastric wall tumor in 15 (45.5%); colon tumor in 2 (6%); and 21 patients (59%) had a tumor less than 10 centimeters. Mean and median of tumor size were 5.8 and 5.2 cm respectively (range: 3-34cm).

Gastrectomy was performed for 8 patients, and 3 patients received a Roux-en-Y gastrojejunostomy. In none of the 9 patients whose lymph nodes were excised due to enlargement during surgery was a metastasis discovered. Immunohistochemical studies for KIT were performed in all patients. 33 were positive for KIT (91%). The rest received a diagnosis of GIST based on typical microscopic findings and after other Mesenchymal tumors were ruled out.

Among the 33 patients who underwent surgery, 1 was deceased due to pneumonia during hospitalization. Patients were followed by CT scanning and serial clinical examinations at months 3, 6, 12, and 24. One patient died due to unrelated causes and 5 others did not return for the follow-up. Two patients with metastasis at the time of presentation and 1 patient with small intestinal involvement died due to their advanced disease.

From the 26 patients who remained in the study, 5 (21%) experienced postoperative relapse. Time before relapse averaged 15 months (range: 4-24 months). Three relapses occurred in the peritoneum, 1 in small intestine and 1 in stomach. Small intestinal relapse was managed by a second surgery and the others received only Imatinib.

Discussion

About 5000 new cases of GISTs with an average age of 63 years are diagnosed in America each year [9]. Lack of randomization in our study makes it impossible to judge age and sex distribution of the disease. However, using non-parametric tests (WilCoxon), no significant difference was noted with other studies.

GIST patients frequently present with an enlarging abdominal mass or obstruction. Nonetheless, it is not unusual to find the tumor incidentally during surgery or endoscopy for other reasons. These tumors can have different biologic behaviors from slow growing to rapidly spreading [14]. Nearly half the patients have signs of distant metastasis at the time of diagnosis [15]. In two third of the cases of metastasis liver is involved in the form of a solitary lesion. Extra-abdominal metastasis or lymph node involvement occurs rarely. In our study, however, only 3 patients (8.5%) presented with distant metastasis (one with multiple metastases and 2 with a single hepatic metastasis). This difference can be a result of the paucity of the sample and the referral center bias and should be addressed in larger studies. In patients whose tumor is excised thoroughly, the risk of relapse with or without adjuvant therapy is 40% and 17-24% respectively [3]. Average survival after relapse is between 9 to12 months (3). One third of relapses are local and half of them in the form of metastasis. In our study 21% (5 patients) experienced relapse on average 15 months (4 - 24 months) following surgery, which is similar to other studies. We did not start all our patients on Imatinib. Recurrent tumors were found in peritoneum (3 patients), small intestine (1 patient) and stomach (1 patient). Malignant pattern may be seen in 10 to 30% of stromal tumors [11] in the form of higher locoregional relapse, peritoneal invasion, and liver metastasis [16]. The risk of malignant transformation and prognosis is related to tumor size, amount of mitoses, fibrosis and involvement of lymph nodes [16]. These factors, however, are not uniformly accepted [12].

The significance of the site of initial tumor has been debated and some authors believe that it plays a major role in the prognosis [17]. In the current study, considering the sample size, no association was discovered between primary tumor site and prognosis.

Surgery is the treatment of choice for GISTs and sarcomas in general and is the only option that provides definitive cure [18]. Radiotherapy and chemotherapy are only used as palliative measures in refractory cases. Selection of the type of surgical resection depends on primary tumor site and its growth pattern. Routine resection of lymph nodes is not recommended due to low incidence of lymph node involvement. None of our patients had lymph node involvement. Laparoscopic management of stromal tumors is shown to be associated with recurrence rates. Laparoscopic results are comparable to open techniques for tumors smaller than 5cm [19, 20].

Newer and more effective treatments were introduced in late 90's. Imatinib (STI-571, Gleevec or Glevic; Novartis) was the first tyrosine kinase inhibitor approved for human use [21]. It is an analog of phenylaminopyrimidinemethane-sulfonate, a signal transduction inhibitor. Imatinib is a potent competitive inhibitor of a number of tyrosine kinases including bcr-abl, PDGF-α and β, stem cell factor and KIT. It inhibits phosphorylation of the substrate and reduces signal transduction. It also induces apoptosis [22].

Treatment with tyrosine kinase inhibitors has changed the treatment of GISTs and improved patient survival. Not all patients were eligible for Imatinib treatment in our study; therefore, we cannot discuss its effect. A large study regarding the outcome of Imatinib treatment and resistance to it is being conducted in Iran at the moment whose results will be published in near future. Mutation in PDGFR (platelet derived growth factor receptor) occurs in 5 to 10 percent of stromal tumors and results in deletion of CD117. Mutations occur with decreasing frequency in exons 18, 12, and 14. Tumors with mutations in exons 12 and 14 are sensitive to Imatinib therapy [23]. Nine of our patients lacked CD117 marker that is comparable to other studies. Unfortunately, we were not able to assess mutations in PDGFR, α receptor. Recommended starting dose for Imatinib is 400mg daily. Adverse effects include nausea, edema, diarrhea, myalgia, fatigue, rash, headache and abdominal pain [24]. Imatinib therapy must continue until progression of the disease, development of resistance or patient incompliance [25]. Resistance eventually develops in the advanced disease; and it is seen in 42% of patients in 20 to 24 months after the start of treatment [25, 26]. About 21 to 20 percent of

patients are primarily resistant to Imatinib. Sunitinib is another FDA approved drug for use in case of resistance or intolerance to Imatinib [27].

Occasionally, patients have advanced local or metastatic disease that makes surgical resection impossible or too risky. In these cases, neoadjuvant therapy with Imatinib can shrink the tumor (76%) and can even make it resectable (25%) [28]. Three of patients received Imatinib from the beginning due to multiple metastases. In the six month follow-up, one of the patients died ; and the disease did not progress in the remaining two. Further research in controlled settings is required in this regard.

Specific treatment is currently recommended for the following cases:

In patients with metastatic GISTs, continuous Imatinib therapy is recommended until disease progression or development of resistance (increased Imatinib dose is recommended for mutations in exon 9 of KIT gene).

In cases of disease progression one can increase Imatinib dosage or use alternative drugs.

Neoadjuvant treatment with Imatinib is recommended for unresectable GISTs.

Adjuvant treatment with Imatinib is recommended after complete resection of stromal tumors, however, duration of treatment and patients who take the most benefit from such treatment are not clearly defined.

Adjuvant treatment with Imatinib can be considered for cases of incomplete resection in which a repeated procedure is not planned.

Imatinib should be considered in recurrent GIST.

Conclusion

Surgical resection with negative margins is the principal approach for patients with gastrointestinal stromal tumors and is associated with acceptable outcomes. Imatinib, a tyrosine kinase inhibitor, has revolutionized the management of GIST.

We recommend tyrosine kinase inhibitor therapy for all patients with GIST for at least 2 years after surgical resection.

The present study showed that clinical manifestations and incidence areas of GITS can be different in Iran compared to other countries. Response to surgery and chemotherapy is not yet clear in Iran. We strongly hope that this study could be useful for classification and understanding of this heterogeneous group of neoplasms and for development of appropriate therapeutic guidelines.

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