Am J Digest Dis 2017;4(5):40-47
www.ajdd.us /ISSN:2329-6992/AJDD0066766

Original Article

Neoadjuvant imatinib for gastrointestinal stromal tumor: community hospital experience

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Received October 8, 2017; Accepted October 20, 2017; Epub November 1, 2017; Published November 15, 2017

Abstract: Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. GISTs are characterized by the expression of the transmembrane receptor tyrosine kinase (KIT), which is defined by the CD117 antigen and is the product of the c-kit proto-oncogene. Surgical resection was the standard of care for GIST prior to the use of tyrosine kinase inhibitors such as imatinib. However, tyrosine kinase inhibitors have now provided effective treatment for unresectable, recurrent or metastatic GISTs and have been shown to increase the median survival of those with GISTs over two-fold. Aims: The primary aim of this study was to retrospectively evaluate the response of GISTs to neoadjuvant imatinib. The secondary aim was to determine if specific characteristics of GISTs are associated with imatinib treatment response including location, size of tumor, and mitotic index. Methods: Retrospective chart review was conducted on all patients who were diagnosed with locally advanced GIST between 2010 and 2014, received neoadjuvant imatinib and cross sectional imaging performed before and after treatment with imatinib. Using the Choi criteria for assessing response to TK inhibitor therapy, patients were classified as having complete or partial response to therapy, stable disease, or progressive disease. Mitotic index, size and location were noted for each case. Results: Ten patients met the inclusion criteria for the study. Following treatment with imatinib, 1 patient had a complete response, 8 patients had partial response, 1 patient had stable disease, and no patients had further progression. Five of the 10 cases (50%) became more surgically favorable after imatinib treatment. Mitotic index obtained from specimens at time of diagnosis, pre-treatment size and NIH modified criteria were not predictive of post treatment response. Conclusions: Neoadjuvant imatinib showed a significantly higher response than previously reported, with 90% of patients achieving either complete or partial response. Fifty percent of cases led to smaller and less morbid surgical resection with neoadjuvant imatinib.

Keywords: GIST, gastrointestinal stromal tumor, imatinib mesylate

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors with near-universal expression of the CD117 antigen previously classified as benign or malignant smooth muscle tumors. GISTs originate from the neoplastic transformation of the intestinal pacemaker cell, the interstitial cell of Cajal [1, 2]. GISTs can occur throughout the GI tract. Extra-gastrointestinal stromal tumors are noted in the mesentery, retroperitoneum and omentum. Significant percentage of GISTs exhibit metastases and infiltration, mostly intra-abdominal within the peritoneal cavity and to the liver [2]. GISTs are characterized by expression of the transmembrane receptor tyrosine kinase KIT, which is defined by the CD117 antigen and is the product of the c-kit proto-oncogene. The vague clinical presentation of GIST causes diagnostic delay. Most common symptoms include hematemesis, melena, nausea, vomiting, and abdominal pain/discomfort. Dysphagia and intestinal obstruction can occur based on the site of the tumor [3-6]. Diagnosis of GIST may occur incidentally during upper endoscopy

Table 1. Clinical characteristics of patients

Age in years [median, (25-75% interquartile range)]	67.5 (63.5 - 77.3)
Gender [n, (%)]	
Male	3 (30)
Female	7 (70)
Method of diagnosis [n, (%)]	
Forceps	4 (40)
Endoscopic ultrasound	5 (50)
Interventional radiology	1 (10)
Location of GIST [n, (%)]	
Gastric body	4 (40)
Gastric cardia	2 (20)
Gastric antrum	1 (10)
Duodenum	1 (10)
Esophagus	1 (10)
Peritoneum	1 (10)
Duration of treatment in months [median, (25-75% interquartile range)]	4.5 (3-13)
Tumor diameter in cm [median, (25-75% interquartile range)]	
Pre-imatinib	7.8 (5.1 - 12.5)
Post-imatinib	5.4 (3.2 – 7)
Tumor density in HU [median, (25-75% interquartile range)]	
Pre-imatinib	52.93 (39.77 - 76.54)
Post-imatinib	43.53 (37.89 - 46.01)

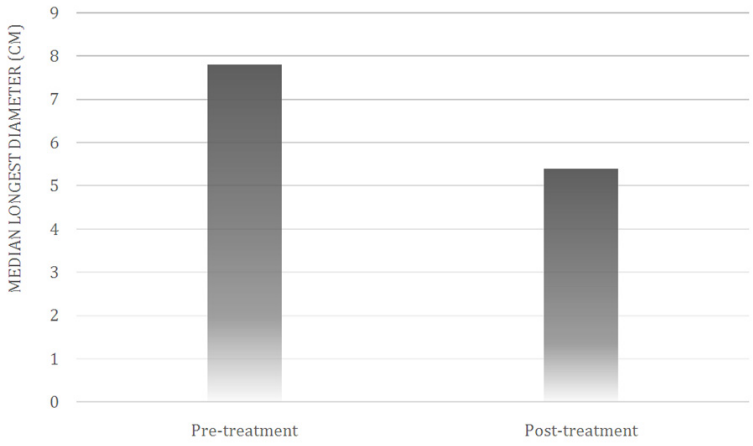

Figure 1. Pre- and post-treatment tumor sizes.

or barium study. Complete surgical resection with negative margins is the standard of care for treatment of GISTs. GISTs were previously known for being unresponsive to chemotherapy, and until the introduction of the KIT inhibitor imatinib, there had been no effective therapy for advanced, metastatic disease. Introduction of imatinib has provided an effective treatment for unresectable, recurrent or metastatic GISTs [7-9]. Imatinib as adjuvant therapy and its dosing are well studied in multiple trials whereas there is limited data on indications and efficacy of imatinib as neoadjuvant therapy. The purpose of the study was to evaluate the response of GIST to neoadjuvant imatinib and to determine if any criteria obtained in the diagnosis were prognostic of response to imatinib.

Methods

Retrospective review of patients who met the following selection criteria was conducted: [1] diagnosis of locally advanced GIST via forceps, endoscopic ultrasound (EUS) fine needle aspiration (FNA)/core biopsy or interventional radiology (IR) core biopsy between 2010-2014, [2] received neoadjuvant imatinib, [3] cross sectional imaging performed before and after treatment with imatinib. Patients who received the diagnosis of GIST during the study period were identified using the natural language search function by the pathology department.

Table 2. Tyrosine kinase inhibitor therapy assessment

Response	Choi criteria	RECIST criteria
Complete response (CR)	A. Disappearance of all lesions B. No new lesions	A. Same
Partial response (PR)	A. Decrease in size of 10% or more or a decrease in tumor density (HU) of 15% or more on CT imaging B. No new lesions present C. No obvious progression of non-measurable disease	A. At least 30% decrease in sum of diameter of target lesions
Stable disease	A. Does not meet criteria for CR, PR, or progression B. No symptomatic deterioration attributed to tumor progression	A. Does not meet criteria for CR, PR, or progression
Progressive disease	A. Increase in tumor size 10% or more AND does not meet criteria of partial response by HU on CT B. New lesions C. New intra tumoral nodules or increase in size of existing intra tumoral nodules	A. At least 20% increase in the sum of the diameter of target lesions, along with an absolute increase of at least 5 mm B. New lesions

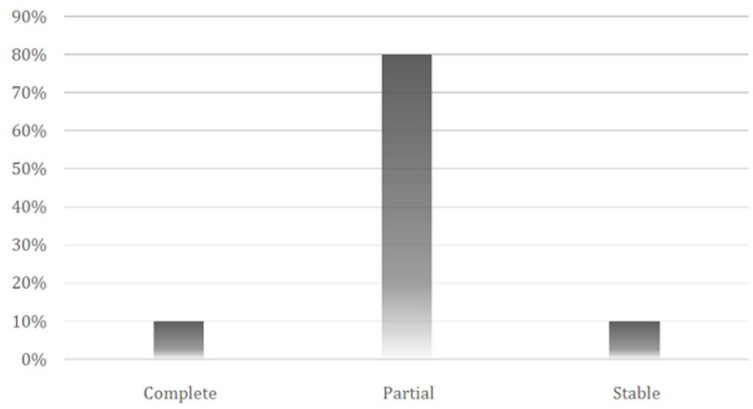

Figure 2. Treatment response based on Choi criteria.

Statistics

Analyses were performed using Stata version 10 (College Station, TX). Number of fine needle aspiration passes, tumor sizes, and tumor densities were described as median and interquartile ranges (IQR). Correlation between pre-treatment diameter/mitotic index and tumor response was tested using ANOVA (analysis of variance). Two-sided *P* value of <0.05 was considered to be significant.

Results

29 patients received the diagnosis of GIST during the study period. The total number of patients who met the inclusion criteria was 10. Median age was 67.5 years (25-75% interquartile range 63.5-77.3). There were 7 females (70%) and 3 males (30%) (**Table 1**). Method of diagnosis included forceps biopsy (4), EUS (5), IR (1). Median number of FNA passes (for EUS cases) to obtain the diagnosis was 6. Locations of the tumor were: gastric body (4), gastric cardia (2), antrum (1), duodenum (1), esophagus (1), and peritoneum (1). Dose of imatinib was 400 mg per day and the median duration of treatment was 4.5 months. Median of the longest diameters of the tumors pre- and post-imatinib were 7.8 cm and 5.4 cm, respectively (**Figure 1**). Median tumor density pre- and post-treatment were 52.93 HU (Hounsfield Unit) and 43.53 HU, respectively.

Following is the result based on Choi modified CT response criteria [42] (see **Table 2** for Choi criteria): complete response (1, 10%), partial response (8, 80%), stable (1, 10%), progression (0) (**Figure 2**). Mitotic index obtained from specimens at the time of diagnosis ranged from 0-8 per 10 hpf, and there was no correlation between mitotic index and tumor response ($p = 0.6948$). Pre-treatment size was not predictive of post-treatment response ($p = 0.2952$). Likewise, the NIH modified criteria were not predictive of post-treatment response ($p = 0.0767$). Clinical factors such as age ($p = 0.9637$) and gender ($p = 0.5447$) did not predict post-treatment response to imatinib.

Five cases (50%) became more surgically favorable diseases post-treatment (3 cases that would have needed partial gastrectomy be-

Table 3. Modified consensus classification for selecting patients with GISTs for adjuvant therapy

Risk category	Tumor size (cm)	Mitotic index (per 50 High power fields)	Primary tumor site
Very low risk	< 2.0	≤ 5	Any
Low risk	2.1-5.0	≤ 5	Any
Intermediate risk	2.1-5.0	> 5	Gastric
	< 5.0	6-10	Any
	5.1-10.0	≤ 5	Gastric
High risk	Any	Any	Tumor rupture
	> 10	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	2.1-5.0	> 5	Non-gastric
	5.1-10.0	≤ 5	Non-gastric

came wedge resection, 1 case that would have needed multi-organ resection changed to a single organ resection, 1 case that would have needed multi-organ resection resulted in complete resolution). Of the 10 patients, two patients refused surgery, one patient was thought to be a poor surgical candidate due to other comorbidities, and one patient was deemed to have unresectable disease. Remaining 6 patients' ultimate post-surgical outcome and length of follow-up are listed in **Table 4**. Side effects to imatinib are listed in **Table 5**.

Discussion

GISTs are the most common nonepithelial, mesenchymal neoplasms of gastrointestinal (GI) tract [1, 2]. They constitute only 1% of primary GI malignant tumors [3, 4]. GIST can occur in any part of GI tract, most common sites being stomach (60-70%) and proximal small intestine (20-25%) followed by colon/rectum (5%) and esophagus (< 5%) [4]. The term "gastrointestinal stromal tumors" was coined by Mazur et al [5] in 1983 to collectively refer to a group of mesenchymal tumors of neurogenic or myogenic differentiation which lacked the immunohistochemical features of Schwann cells and did not have the ultrastructural characteristics of smooth muscle cells. These tumors were distinguished from other histopathological subtypes of mesenchymal tumors in 1998 after the discovery of c-KIT proto-oncogene mutations [6]. There is usually no predilection but some series suggest a slight male predominance in their middle age or older age. The median age at diagnosis is 63 years [7].

Majority of the patients with GIST are symptomatic (70%) and the symptoms depend on the site of the tumor. Small percentage of tumors are detected incidentally during endoscopy, barium study or on cross sectional imaging. GI bleed, abdominal discomfort, abdominal pain, intestinal obstruction are the most common presenting symptoms [8-10]. Surgical emergency could arise in patients with peritoneal bleeding secondary to ruptured GIST. Vague symptoms, such as early satiety, nausea, vomiting, weight loss, are also noted. Site specific symptoms include dysphagia in the esophagus, intussusception in small intestine and biliary obstruction around the ampulla of Vater [8, 9]. Large GISTs have a tendency to develop paraneoplastic hypothyroidism caused by inactivating enzyme iodothyronine deiodinase (D3) within the tumor [11]. GISTs metastasize frequently to the peritoneum, omentum, mesentery, and liver but rarely to regional lymph nodes [8, 9, 12].

GISTs are greatly variable in size, ranging from few mm to more than 30 cm, usual size being between 5 to 8 cm. Macroscopically, they are seen as exophytic growths sometimes displacing adjacent organs in the abdominal cavity [13, 14]. Histological appearance may be spindle cell (70%), epithelioid cell (20%) or mixed type (10%). When compared to KIT-positive GISTs, KIT-negative GISTs are more likely to be epithelioid type and contain PDGFRA mutations; they appear to have higher proportion of primary lesions arising outside the gastrointestinal tract (20% omentum primaries and 20% from peritoneal surface in one series), which is more than the generally accepted number of < 10% [15]. The cells show less cytoplasmic eosinophilia unlike smooth muscle tumors. Most of the GISTs are positive for vimentin and CD34 (hematopoietic/mesenchymal precursor cell marker) on immunohistochemical staining, and some even stain for smooth muscle actin, which may be confused with smooth muscle tumors [16]. The differentiating and diagnostic criteria is positivity for CD117 antigen. However, 10-15% of GISTs may be negative for detectable KIT/PDGFRA muta-

Table 4. Long-term outcome of patients that had surgical resection

Type of surgery	Long-term surgical outcome	Follow up time
Laparoscopic hand assisted partial wedge gastrectomy	No recurrence	5.25 years
Laparoscopic-assisted partial gastrectomy	No recurrence	5.67 years
Pancreaticoduodenectomy	No recurrence	7.16 years
Gastric wedge resection	No recurrence	4.42 years
Sleeve gastrectomy	No recurrence	3.58 years
Gastric wedge resection	No recurrence	6.67 years

Table 5. Side effects to Imatinib.

Patient	Side effect
1	Tongue swelling
2	Slight swelling under eyes
3	Mouth sores/lower extremity swelling/skin eruptions
4	Rash, angioedema of lips, bloating
5	Emesis
6	Fatigue, peripheral edema, rash
7	Emesis
8	None
9	Diarrhea, loss of appetite
10	Blisters of bilateral hands

tions, hence negative for CD117 staining. Mutation absence cannot completely exclude the GIST diagnosis [16, 17]. It was discovered that KIT-negative tumors can also be diagnosed on immunostaining by expression of a calcium dependent, receptor activated chloride channel protein called DOG1, which is also highly specific for GIST. DOG1 expression are generally present in extra-gastrointestinal and metastatic GISTs [18, 19].

The diagnosis of GIST requires high degree of suspicion and familiarity with radiological appearance. Oral as well as IV contrast-enhanced CT (CECT) scan is the preferred imaging method to characterize the tumor, evaluate its extent, and the presence or absence of metastatic disease at the initial staging work up [18, 20]. It is also helpful for monitoring response to therapy and follow up surveillance. MRI may be the preferred modality in patients who cannot receive IV contrast and for GISTs at specific sites, such as rectum or liver to provide anatomic definition in evaluating for surgery. On CT scan, GIST appears as well-defined circumscribed mass with smooth contour [21]. On endoscopy, GIST appears as smooth submucosal lesions bulging into the lumen. Endoscopic ultrasonography (EUS) can assess depth of invasion and is useful in obtaining tissue sample with reported accuracy of preoperative diagnosis of EUS-FNA using immunohistochemical analysis for surgically resected GIST cases ranging from 91% to 100% [22]. High grade GISTs on EUS appear as irregular extra-luminal borders, heterogeneous echo patterns, presence of cystic spaces and echogenic foci [23]. Preoperative percutaneous biopsy is generally not recommended due to risk of tumor rupture or dissemination [24]. Positron emission tomography (PET) may be helpful in detecting small metastases otherwise undetected on CT scan and also differentiates malignant from benign tissue as receptor tyrosine kinase increases glucose transport protein signaling [13, 18]. PET is also used to assess tyrosine kinase inhibitor (TKI) therapy response. Routine use of PET for surveillance after resection is not recommended.

The management of GIST depends upon the preoperative diagnosis, tumor location and size, extent of spread, and clinical presentation. Surgery is the initial treatment of choice in localized or potentially resectable GIST and with a size of ≥ 2 cm or with suspicious endoscopic features. Laparoscopic resection of gastric GISTs is safe and effective [25, 26]. However, imatinib therapy is preferred if the tumor is borderline resectable or if resection has the risk of organ disruption. GISTs less than 2 cm size require no resection if asymptomatic and should be monitored with endoscopic surveillance every 6-12 months until they grow or become symptomatic [27, 28]. Complete resection is possible in most of the GISTs [29, 30]. Adjuvant TKI therapy decreases recurrence rate within first year of therapy, approved for GISTs ≥ 3 cm size. Esophageal GISTs are hard

to manage due to the poor confinement of the tumor by the serosal layer, requiring open esophagectomy if tumor size ≥ 2 cm or located at GE junction [31, 32]. Surgery outcomes are poor in GISTs involving colon and rectum and carry worse prognosis compared to gastric GIST. Preoperative imatinib therapy improves surgical outcome in colon and rectal GISTs and large tumors of size ≥ 5 cm [33-35]. Lymphadenectomy is not necessary as GISTs have a low incidence of nodal metastases [20].

Imatinib mesylate is a TKI with activity against ABL, BCR-ABL, KIT, PDGFRA, and PDGFRB. Structure of imatinib mimics that of adenosine triphosphate (ATP) and binds competitively to ATP binding sites of tyrosine kinases. Its mode of action is through prevention of substrate phosphorylation and signaling, thereby inhibiting cellular proliferation and survival. The response to imatinib therapy is based on the presence and type of KIT/PDGFRA mutations. Most common mutation is in exon 11 of KIT juxtamembrane domain and have better response rates with overall survival. Exon 9 mutations occur in KIT extracellular domain, specific for intestinal GIST and are associated with poor response to imatinib. Exon 18 mutations seen in tyrosine kinase domain of PDGFRA, common in gastric GIST [36, 37]. Estimation of recurrence risk after the tumor resection is important in selection of patients while considering the adjuvant imatinib. All the GISTs are known to have malignant potential and the recurrence or metastasis predictors are tumor size, origin and mitotic rate [38] (**Table 3**, NIH modified criteria). Benefit of adjuvant imatinib therapy is well studied in multiple trials leading to FDA approval in 2008 for its usage in GISTs of at least 3 cm size and the most accepted daily oral dosage is 400 mg [36, 37, 39]. 800 mg daily doses are beneficial in patients with advanced GIST and exon 9 KIT mutations if tolerated.

Neoadjuvant TKI therapy is fairly new; small retrospective series and several case reports have been published since 2003 and no randomized trials were conducted thus far. It is found to be beneficial in patients with unresectable or borderline resectable primary tumor, a potentially resectable tumor that requires extensive organ disruption, a local recurrence of locally advanced disease, or a limited amount of potentially resectable metastatic disease [40]. The aim of therapy is reduction of tumor size and organ preservation. A baseline CECT scan is recommended before initiating the treatment. The optimal duration of therapy is not yet established. Imatinib can be continued to obtain maximal response (until no further improvement in 2 successive scans) in patients noted to have good initial response or until they appear to have downsized for a complete resection of the tumor. Response to therapy is assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) or the Choi criteria (**Table 2**). Imatinib can be stopped prior to surgery and resumed once oral intake is tolerated for 2 years after surgery at the same dose [41].

In this study, we report a small retrospective case series on the effect of neoadjuvant imatinib for GIST in a community hospital setting. Our local experience with neoadjuvant imatinib showed a significantly higher response than previously reported, with 90% of patients achieving either complete or partial response. Fifty percent of cases led to smaller and less morbid surgical resection with neoadjuvant imatinib. Mitotic index was difficult to obtain with sampling via EUS (mostly measurable when diagnosis made with forceps biopsy or IR-directed biopsy), but there was no clear correlation with response to imatinib when detected. Additionally, pre-treatment size did not predict post-treatment response. Limitation of this study is the small sample size and the retrospective nature. Further studies, ideally randomized controlled trials, are needed to verify the findings of our series.

Acknowledgements

This study was approved by the Kaiser Permanente Southern California (KPSC) Institutional Review Board.

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