Six months neoadjuvant Imatinib improves resectability potential of gastric stromal tumors in Egyptian patients

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Abstract

Objectives: Local excision with negative margins is the preferred approach for treating gastric stromal tumors. Adjuvant imatinib is essential for advanced cases, but data are not enough to recommend its use before operation to increase resectability. Current study aims at probing this concept in Egyptian patients.

Patients &Methods: The study included 16 patients, presenting with gastric GISTs and were candidates for emergency or elective surgery. Patients were enrolled in 2 groups: A proposed for planned surgery and B: harbouring c-kit +ve tumors. Each B patient received imatinib (400 mg /day) for 6 months before operation. Clinical and radiological evaluation was at day 100. Chi-square test checked size changes, and p at < .02535 was considered significant.

Results: All patients had abdominal discomfort, while 62.5 % had epigastric pain, and 12.5% had hematemesis. Tumor size ranged from 8.4 to 20 cm. 2/3 located in upper stomach. Five patients (31.3%) harbored lesions with low risk malignancy, 8 (50%) moderate and 3 (18.8%) high. Wedge gastrectomy was the commonest operation done (81.25%) while partial gastrectomy was done in the rest, reporting no recurrence for 6 months. Not determined in group A patients, c-kit status was strongly positive in all members of group B, in 2 of them treatment was suspended due to poor response.

Conclusion: Imatinib has an acceptable safety profile and would be considered as a neoadjuvant therapy in gastric GISTs. Until developing clear guidelines, 6 months intake may increase noticeably their resectability potential and may improve prognosis.

Introduction

Gastrointestinal stromal tumors (GISTs) were not recognized as a distinct entity, until their origin from the interstitial cells of Cajal - or their predecessors - was established. These turn into epithelioid, undifferentiated cells branded by over expression of the tyrosine kinase receptor KIT (CD117) (1, 2). GISTs span a wide clinical spectrum from benign to highly malignant or even metastasizing (3), and harbor the potential risk of local and distant recurrence and are difficult to cure (4,5) . The only treatment for metastatic disease is surgery, while chemo and radiation treatments have proven ineffective. (4). While minority of GISTs affects the small intestine, colon, rectum and mesentery, estimates demonstrate their prevalence in the stomach (60%) particularly in elderly males reaching zenith at the age of 60 years (6,7,8), though occasionally touching children. Requiring immediate surgery, bleeding is the commonest presentation of gastric stromal tumors (50%) and is usually associated with ulceration into the lumen (9). Other patients present by abdominal pain, palpable mass, obstructive symptoms or minor bleeding episodes (6). Endoscopy possibly will disclose the gastric tumor as a submucosal mass, and CT (or MRI) scans may give diagnostic suggestions, but firm diagnosis is only sure by pathologic study of biopsy or resected specimens. Being sensitive, rapid and reliable (10), it is preferable to keep CT scans to measure response to adjuvant therapy if used after operation. It is difficult for surgeons to select the suitable procedure to pursue, and as late as 2001 local resection was considered adequate (11), The rapid recurrence that follows was attributed to removing the inhibition exerted by the primary tumor on its remote metastases via circulating angiostatin(12,13). Currently, achieving negative surgical margins on frozen section examination is mandatory (14) and this entails segmental resection, at times amounting to subtotal gastrectomy and omentectomy as in perforation, bleeding or when a tumor ruptures (9, 15). Being of no profit lymphadenectomy is not required, and adjuvant therapy with the KIT tyrosine kinase inhibitor imatinib remains essential for high risk or metastasising tumors , as it significantly prolongs survival(16-17). Very recently much attention has been focused on using this drug as a neoadjuvant therapy (18), but earlier reports included diminutive formal analysis for data concerning success rates that might have been caused by this approach. Notwithstanding this, and being impressed by the amazing pathological response it induces, particularly on tumor volume (19), the need to launch this new discipline on Egyptian patients was recognized.

Patients and Methods

This prospective study was completed at Cairo University Hospitals and also in the private practice, from May 2007 through January 2009. It included 16 patients (13 males, 3 females, their age ranged from 38 to 72 years (mean = 60), presenting with suspected gastric stromal tumors and were candidates for emergency (n=3) or elective (n=13) surgery. Investigations included endoscopy, endosonography and endoscopic biopsy, while extra luminal spread and lymph node status were assessed by CT, but one patient required percutaneous drainage of abdominal sepsis as a preliminary step. Meticulous analysis of patients' symptoms made the diagnosis straightforward in most cases, and preoperatively all tumors were amenable to surgical resection To improve compliance, it was important to clarify

to each individual patient what GIST is, and to assure him that his illness may be controllable, and to provide him with full idea about the treatment protocol, and to have his signature on a written consent. Subsequently patients were enrolled in 2 groups: A (n= 6: projected to planned surgery alone) and B (n= 7: harbouring tumors with c-kit +ve biopsy specimens). Each Group B patient received imatinib (400 mg /day orally) for 6 months before operation. Clinical and radiological evaluation of drug effect was at day 100, and the Chi-square test was used to check the significance of size reduction induced by treatment. A value at p <0 .02535 was considered significant. Two patients had poor response to the drug and were shifted to classical management as in members of group A. Imatinib –associated side effects were not identified in this series.

Results

Clinically all patients presented having abdominal discomfort, while only 62.5% had epigastric pain, and 12.5% had hematemesis. Mean tumor size was 13.2 cm (8.4-20), mostly located in the upper stomach (68.8%). About one third of the patients (31.3%) harbored lesions with low risk malignancy, 50% moderate and 18.8% high. The c- kit status was strongly positive in the 7 patients who received neoadjuvant imatinib. Preoperative imatinib for 6 months succeeded in reducing tumor size by 29%, and subsequently increasing resectability rate (Fig.1). Having no operative mortality, wedge gastrectomy was the most common procedure (81.25%) while partial gastrectomy (proximal in 12.5% and distal in 6.25 %) was performed in 3 (Table I). Within the following 6 months there was no evidence of recurrences. In 2 patients the response to the drug was poor and treatment suspended.

Discussion

Currently most clinicians working on GISTs recommend attempting complete or near complete surgical resection of gastric lesions. Low grade tumors have excellent prognosis and resection may be curative, while recurrence is the rule in high grade ones. For the latter postoperative imatinib was suggested even if resection is incomplete (17). Only little is known about using this drug prior to surgery (18, 19), and the present trial was thought for to study this modality in Egyptian patients. In mind it was clear that gastric lesions in particular show themselves by large sizes and resection may be difficult or incomplete, creating an ideal situation for making use of preoperative imatinib to increase resectability potential. Likewise a comprehensible study performed by Florien in 2007, demonstrated appreciable reduction of tumor diameter in a linear fashion following preoperative imatinib therapy, monitoring at the same time concomitant exponential reduction in volume, regarding the latter more sensitive to disclose tumor response than diameter (20-22). Hohenberger et al. recently reported 18 patients manipulated in this way and concluded that even partial response reflects better outcome than in progressive disease (23). In the present study the efficacy of imatinib on the tumor size was adequately disclosed on CT, showing a 29% reduction -with or without cystic changes- and histological examination detected residual (or no) tumor cells, scant vascularity and scattered inflammatory cells. The c- kit immunohistochemistry in tumor cells in the 7 patients receiving pre-treatment was strongly positive (4 were highly malignant), while in 2 patients poor response dictated treatment suspension. In no case the remission was complete, same was observed by Langer et al in 2003 (24). Due to this achievement, we advocate regularly following the neoadjuvant policy in dealing with gastric GISTs, but a universal decision to switch to this new regimen needs further studies. In fact we share Raut (25) his viewpoint in that it is very early to do so now, and even to adequately determine the dose of the drug, optimal duration of treatment and to select the best time of surgical intervention. We propose the latter to be immediately after maximal drug effect but before possible disease progression caused by secondary mutations (26). Till more dose-response studies become on hand, surgeons who want to adopt this regimen should use the lowest effective dose for the shortest possible duration; 400 mg daily for 6 months is most likely the optimum. Escalation or doubling the dose has no effect as tolerance is not known. Should no evidence of response in the first month appear clinically or in the CT, then treatment must be stopped, and resection is arranged for. Moreover it is reasonable to notify patients receiving the drug about probable side effects and one should be aware about the disadvantage using the drug in type 2 diabetics receiving insulin (27), and also in patients with splenomegaly (28). The true worry in this regimen is the possibility of developing resistance to imatinib ascribed to secondary mutations (28)., as happens in myeloid leukemia , a bother to expect in metastasizing cases intended to receive post operative therapy. Testing for this mutation in resected material (30) is a missing item in this work.

Conclusion

In the wake of the recent thesis of neoadjuvant approach for malignancy, it might be relevant to think in making use of such function for imatinib treatment of gastric stromal tumors. Our findings at this juncture could be encouraging despite the small number of patients, absence of a control group and also in face of observably deficient earlier clinical trials. Until developing clear guidelines, 400 mg, daily before operation may be valid in increasing resectability potential. Six months treatment succeeded in reducing tumor size by 29%, but individual dose titration is not recommended. Absent early response means prompt switching to surgery.

Conflict of interest statement

No conflict of interest with other people or organizations. Study was neither done under grant nor funding.

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Tables

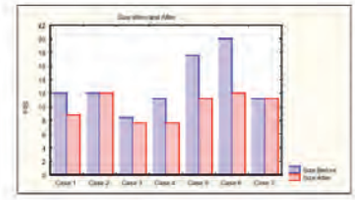
Table 1: Group B (n=7)
Patients & Tumors Characteristics + Management & Results

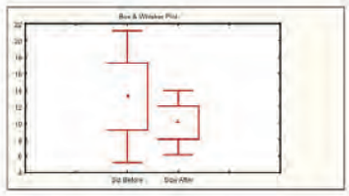
SN. *	Age Years	Location[ξ] &size(cm)	Indication for Neo-Imatinib	Residual size (RS) in cm	(RS) % of initial[γ]	Response Rate	Postoperative Histpathology	Post-ttt Op.procedure
1	61	D/12	Unresectable[α]	8.8	73.30	**26.7**	Hypocellularity + necrosis	WG
2	55	P/12	Unresectable	12 ^	--	--	--	
3	59	P/8.4	Unresectable	7.6	90.5	**9.5**[Ω]	Hypocellularity + necrosis+cycsts	WG
4	63	P/11.2	Unresectable	7.6	67.90	**32.1**	Hypocellularity + necrosis	WG
5	58	P/17.6	Large size	11.2	64.20	**35.8**	Hypocellularity + necrosis	PPG
6	60	P/20	Large size	12.0	60.00	**40.0**	Necrosis	PPG
7	48	P/11.2	Unresectable	11.2 ^	--	--	--	

*: All are males with histologically proven c-kit + ve gastric stromal tumors
α:Unresectability determined preoperatively by CT or MRI
Ω: Poor response. ^:No response - treatment suspended
γ: Average residual size % of the initial =71.18%

ξ: Location in stomach in D : distal - P : proximal
(%) Reduction in size= Mean Response rate : 28.82%
Type of gastrectomy: WG: Wedge PPG: proximal

Figures





Friedman ANOVA and Kendall Coeff. Of Concordance
ANOVA Chi Sqr. (N = 7, df = 1) = 5.000000 p < .02535
Coeff. Of Concordance = .71429 Aver. Rank r = .66667

	Average	Sum of	Mean	Std.Dev.
Siz Before	1.857143	13.00000	13.20000	4.072673
Size After	1.142857	8.00000	10.05714	1.992366

Observed vs. Expected Frequencies
Chi-Square = 7.613939 df = 6 p < .267776
NOTE: Unequal sums of obs. & exp. frequencies

	Size After	Size Before	A - B	(A-B)**2
Sum	70.40000	92.40000	-22.0000	7.613939

Fig 1. Analysis of Statistical Data