RESEARCH COMMUNICATION

Neoadjuvant and Adjuvant Therapy with Imatinib for Locally Advanced Gastrointestinal Stromal Tumors in Eastern Indian Patients

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Abstract

Background: Imatinib mesylate is able to at least modify the course of gastrointestinal stromal tumours (GISTs). Neoadjuvant use for locally advanced lesions is evolving as a new treatment paradigm in this hitherto universally fatal disease. Methods and Results: The study patients with locally advanced GIST received neoadjuvant and adjuvant imatinib mesylate. Response was noted as per the RECIST protocol and overall progression free survival was reported. Of 19 patients (mean age 38.5 years, range 26 yrs to 64 yrs) studied, 13 achieved partial response (PR) and 6 a stationary disease (SD) on preoperative imatinib. Histopathological evaluation and grading of responses revealed only moderate and low grade pathological response after imatinib. R0 resection was possible in 13/19 and R1 in 6/19. Imatinib was well tolerated and adverse reactions were minimal. Post operative complications of surgery were not out of the ordinary for a surgical series featuring extensive abdominal surgery. Conclusion: Preoperative imatinib in locally advanced GIST seems to be a reasonable option for locally advanced GIST patients and enough downstaging to allow a resection with microscopically negative margins can be expected in a fairly good proportion of patients.

Keywords: GIST - neoadjuvant imatinib - locally advanced - recurrent

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Introduction

Gastrointestinal stromal tumours (GISTs) are rare neoplasms that originate from the cells of Cajal located in the myenteric plexus of gut wall. These neoplasms account for 0.1%–3% of all gastrointestinal tumours (Kindblom et al., 1998; Miettinen et al., 2002; Rossi et al., 2003). The peak incidence of GIST is commonly observed after the fourth decade of life, with an equal male to female ratio. These tumors usually present late and are often discovered incidentally (Sturgeon et al., 2003). Surgical resection is currently the "gold standard" in the management of GISTs. Complete resection with negative margins, albeit not always achievable, remains the main goal of surgery. Historically the prognosis after surgical treatment of locally advanced and metastatic disease has been dismal. Imatinib mesylate (IM), an inhibitor of tyrosine kinase has been able, at least, to modify the course of this hitherto universally fatal disease. Fortunately by the year 2002, results of some trials had documented that imatinib is effective and safe in patients with unresectable and/or metastatic GIST (Hassan et al., 2006; Joensuu et al., 2001). Since it may potentially offer benefits in the treatment of these tumors, its role in neoadjuvant setting also has been explored by retrospective clinical studies (Hassan et al., 2006). The most obvious benefit is to increase the likelihood of complete gross resection of the tumor and, as a result, the likelihood to minimize the sacrifice of normal tissue by avoiding a radical excision (Hou et al., 2009). In the present prospective report, we studied patients with locally advanced GIST, for possible complete surgical resection after neoadjuvant imatinib mesylate (IM) and followed in the postoperative period with adjuvant therapy.

Materials and Methods

The present prospective study was conducted in the department of surgical oncology at Chittaranjan Memorial National Cancer Institute (CNCI), Kolkata, India from Jan 2005 to July 2010. The institutional review board approved the study. Informed consent was obtained from all the participating patients. The patients with locally advanced gastrointestinal stromal tumors (GIST) without any evidence of metastasis were studied. Patient data included age, sex, and presentation status. Presentation status reflects the extent of disease and the history of prior treatment when the patient was first seen at our institution. The histologic diagnosis of all patients was confirmed at the department of pathology of the authors' institute. The pathological diagnosis of all referred patients

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was reviewed as per the policy of authors' institute. All tumors were considered histologically malignant. All patients received imatinib mesylate in the neoadjuvant and adjuvant setting. Response to neoadjuvant imatinib was noted in all patients.

Imatinib mesylate protocol

Patients were administered 400 mg of Imatinib in 100 mg capsules, taken orally once daily with food for a minimum of 12 weeks. The administration of each dose and any adverse events were recorded for each patient as per 'Common toxicity criteria. Version 2.0; Bethesda (MD) [National Cancer Institute 1999]. In patients attaining suboptimal response, neoadjuvant therapy was continued for a total of six months. Imatinib was stopped not more than one week (Range 5-7 days) prior to the planned day of the surgery. Surgical exploration was undertaken in all patients who achieved a response or stable disease (SD). Surgical exploration would be withheld only in case a patient developed progressive disease (PD). Post operatively imatinib was planned for a period of two years or till the time the patient shows response, whichever of the two is less.

Efficacy and response evaluation

Response assessment was performed according to the RECIST protocol. Responses were classified as follows: Complete Response (CR) - disappearance of all target lesions, confirmed at 4 weeks; Partial Response (PR) - at least 30% decrease in the sum of the longest diameters of all measurable lesions, taking as reference the baseline study, confirmed at 4 weeks; Stable Disease (SD) - neither PR nor PD criteria are met, taking as reference the smallest sum of longest diameter recorded since treatment started; and Progressive Disease (PD) - at least 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of longest diameter recorded since treatment started or appearance of new lesions[Therasse et al 2000]. Failure of the patient to turn up for evaluation was also categorized as PD. All patients underwent CT imaging before and every three months after starting IM therapy. On imaging, tumor size was recorded as the largest diameter in any dimension of the primary tumor and was stratified as ≤5 cm, 5 to 10 cm, or >10 cm. The response of the tumor to imatinib mesylate was evaluated after twelve weeks, and thereafter four weekly for further twelve weeks in case the tumor shrinkage was suboptimal for measurement.

Surgical management protocol

Standard surgical approach consisted of a midline laparotomy. Complete resection of gross disease, with as limited adjacent organ removal as possible, was the goal. Complete omentectomy was performed in cases with evidence of limited peritoneal disease. Resections were classified as R0 when margins were microscopically free of tumor, R1 when positive microscopically in grossly complete resection and R2 when gross residual disease was left behind. R0 and R1 resections were considered complete resections for study purposes. Post operative complications were recorded for all operated patients.

Pathologic classification of the response

Assessment of pathologic responses was performed on all surgical specimens. Depending upon the percentage of nonvital tissue present in the specimen, responses were codified as follows (percentage of nonvital tissue is put parenthesis): high (≥90%), moderate (50%–90%), low (10%–50%), no response (0%–10%) (National Cancer Institute, 1999).

Exclusion criteria

The patients presenting with resectable disease and the patients with metastasis to liver or to extra-peritoneal sites were excluded from the study. Patients, with extensive intra-peritoneal disease and malignant ascites with or without liver metastasis, were also excluded from the study.

Follow up

Follow up protocol of patients was planned prospectively, with complete staging every 3 months for two years or as dictated by clinical situation; every four to six months thereafter or as dictated by the clinical situation for next two years and thereafter yearly.

Results

Table 1 shows data for the nineteen patients (16 females and three males), mean age 38.5years, range 26 yrs to 74 yrs, presented with locally advanced disease. Overall, small intestine was the commonest site of disease (6/19; 32%). Thirteen had tumours arising from following organs: stomach in three, recto-sigmoid region in two, rectum in five and retro-peritoneum in three patients.

Response to imatinib therapy:

Mean tumor diameter on CT scan was 11.8±4.6 cm

Table 1. Demographic Data of 19 Locally Advanced GIST Patients Treated with Preoperative Imatinib Mesylate

Characteristics	Primary n=19
Mean Age(yrs)	37.5±3.5
Gender(M:F)	3:16
Location:	
Stomach	3
Duodenum	0
Jejunum	1
Ileum	5
Recto-sigmoid	2
Rectum	5
retroperitoneum	3
Tumor size:	
Mean/Median (cm)	11.8± 4.6
Range (cm)	8-16.4
Response(RECIST):	
Complete	0
Partial	13
Stable disease	6
Progressive disease	0
R0 resection	14
R1 resection	5
R2 resection	0

(range 8cm to 16.5cms). No patient achieved complete response (CR) or progressive disease (PD) as per RECIST. Thirteen (13/19) achieved partial response and six (6/19) had disease stabilization on neoadjuvant imatinib.

Operative findings and Extent of surgery:

Unexpected findings like metastasis to liver at the time of the surgical exploration were not seen in any of patients. Overall, in fifteen patients, operative findings were consistent with the preoperative imaging findings. In the remaining four patients preoperative imaging had missed the involvement of additional structures like, contiguous involvement of the ascending colon by a small intestine tumor in one; involvement of one ovary each in two; and involvement of the bladder in one patient. R0 resection was achieved in 14 patients and the remaining 5 patients had R1 resection. Removal of adjacent involved organ, either partially or wholly in order to achieve complete R0 resection, was required in three patients: in one patient ovary was removed; in another, a cuff of urinary bladder was excised; in third en- bloc distal pancreatectomy was needed. Three out of 5 patients who underwent R1 resection, needed en bloc excision of contiguous organs in order to have grossly complete excision: one patient with predominantly small intestinal tumour required en bloc sigmoid colectomy; another required right hemicolectomy for small intestinal lesion and the third patient with gastric lesion needed segmental transverse colectomy.

Correlation with histopathology

Correlation of responses according to RECIST and histopathological examination revealed that out of thirteen patients who showed clinically partial response (PR) to neoadjuvant imatinib, only nine had moderate pathologic response and remaining six had low pathologic response. Of the six patients, who had stabilization of disease (SD), four patients had moderate pathologic response and two patients had low pathologic response.

Post operative complications

Three had postoperative complications. Two of them had wound infection, one had fever. Median surgical blood loss for the entire group was 325 ml. Intraoperative blood transfusion was not required in any patient although preoperative packed cell transfusion was given in three patients with anemia. There was no instance of postoperative hemorrhage or re-operative surgery for postoperative complication. The median length of postoperative hospital stay was 10.5 (range 6- 19) days. There was no surgical mortality.

Tolerability of imatinib mesylate

Imatinib was a well tolerated drug in this series with severe toxicity like neutropenia occurring in only one patient. Five patients developed edema, three had anorexia, and two reported constitutional symptoms. The patients received preoperative imatinib for a median of 140 (range 84 to 168) days and the median time of imatinib discontinuation prior to planned surgery was five days (range 2 to 7 days).The median time for starting postoperative imatinib was 18.9 days (range 15 days to 28 days). In two patients postoperative imatinib was delayed; in one patient due to a surgical complication and in another patient, due to a delay in follow up visit.

Follow up

At the time of analysis, no patient had developed progression of the disease and there are no deaths so far; Seventeen patients completed the planned two years of adjuvant imatinib; remaining two patients have not yet completed and are continuing on adjuvant therapy.

Discussion

Imatinib mesylate, a selective inhibitor of the tyrosine kinase, KIT, Bcr/Abl, PDGFRA, and PDGFRB, revolutionized the care of patients with GIST and created a new paradigm in targeted cancer chemotherapy (Heinrich et al., 2003). As neoadjuvant or adjuvant therapy, however, the role of imatinib in the treatment of GIST remains under investigation. Eisenberg et al. (2009), in their report of early results of phase II trial of neoadjuvant/ adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST), observe that most of the information about the combined use of imatinib and surgical resection has been based on retrospective data collected from small reports with the exception of the American College of Surgeons Oncology Group (ACOSOG) postoperative adjuvant studies and Radiation Therapy Oncology Group Protocol 0132. However, in addition to the observation made by Eisenberg et al. (2009), two more prospective studies, one by Rutkowski et al. (2006) and another, more recently, by Fiore et al. (2009), also report neoadjuvant imatinib therapy in a series of metastatic GIST. Rutkowski et al. (2006) emphasize that the surgical removal of residual disease during imatinib treatment may allow for complete remission in selected GIST patients after response to therapy, theoretically prolonging the durable remission, but it is necessary to continue imatinib for its maintenance. Recently, as pointed out earlier, Fiore et al (2009), have reported a series of 15 patients and have suggested the use preoperative imatinib in unresectable or locally advanced GIST, as a useful tool both to improve resectability and reduce surgical morbidity. Same authors (Fiore et al., 2009) have stressed that preoperative imatinib should, therefore, always be considered before embarking on a major surgical procedure in these patients. Presently, the consensus based on reports in the literature (Ng et al., 1992; Oh et al., 2006; Rutkowski et al., 2006; Eisenberg et al., 2009, Fiore et al., 2009) regarding the treatment recommendations for patients with primary GIST, is an expeditious and complete surgical resection. Thus surgery, as the first treatment modality, remains the "gold standard" at present, even after the noted clinical success of the tyrosine kinase inhibitors for GIST. However, the potential benefit of downsizing imatinib therapy in the GIST patients, as well as, of the continuation adjuvant therapy after surgical resection has not been systematically studied in large randomized trials. In addition to the obvious potential advantages of enhanced progression free

survival and overall survival in a GIST patient population, with a recurrence risk historically of up to 80%, the rationale for the neoadjuvant use of imatinib was that this approach might result in less short- and long-term surgical morbidity, and also result in organ preservation and function sparing (Ng et al., 1992; Oh et al., 2006; Eisenberg et al., 2009). Blay et al. (2005), Haller et al (2007) and Langer et al. (2003) stress the importance of complete surgical resection for cure in primary GISTs, and as such neoadjuvant downsizing imatinib therapy should be confined only to patients with unresectable tumour or tumours where a reduction in size may enable function-sparing surgery. The present report documents the early results of a single institutional study, the first of its kind in India; in that the study was prospectively designed with an objective to study the usefulness of imatinib in downstaging or downsizing locally advanced GISTs prior to a possible subsequent surgery. Recently, as mentioned above, the early results of RTOG 0132/ACRIN 6665 have been published by Eisenberg et al (2009. This phase II trial also has compared neoadjuvant imatinib mesylate in primary and recurrent GIST patients but, in contrast to the present study, almost all operable patients with primary GIST have been included in the study. Based on the conviction that primary extra-gastric GISTs are high risk tumors, the authors of the aforementioned phase II trial have favored the inclusion of operable tumors for study. We believe that upfront surgical treatment is still the best option available in unequivocally resectable GIST provided at least a grossly complete resection can be safely achieved with minimal sacrifice of involved adjacent organs. This dictum provided the underlying rationale of the present study.

The apparent delay in surgery, although refuted by Eisenberg et al. (2009), but still a moot point, due to the duration of imatinib induction does not appear to have had any adverse effects at least in our patients, who had locally advanced primary disease and no one showed disease progression during imatinib therapy. Although, no complete responses was observed in our study but still, three fourth (74%) patients had enough response to allow R0 resection. The fact that R0 resection could also be performed in patients who had only stabilization of the disease implies that the absence of measurable radiological shrinkage does not always mean that the tumor is viable. Correlation with pathological response has shown that four out six patients, who had stabilization of disease, did have moderate pathologic response and two patients had low pathologic response. We believe that a greater number of R1 resection in this group of patients had more to do with technical difficulty like adhesions after previous biopsy than with response to imatinib as two third patients did achieve partial response and the rest had stabilization of the disease. Scaife et al. (2003), Vermeil et al. (2004), observe that the imatinib therapy has dramatically improved progression- free and overall-survival in patients with metastasized/advanced GISTs; other authors have pointed out that a complete pathologic remission is rarely achieved (Scaife et al., 2003; Antonescu et al 2005, Bauer et al., 2005; Heinrich et al., 2005).Thus, surgical intervention should always be considered in neoadjuvant treated GISTs, preferably when the maximum effect of imatinib therapy has been achieved (Langer et al., 2003) .

Although RECIST was used to quantitate response in this study, in the last few years clinical experience has suggested that cytoreduction induced by imatinib may not be reflected by the strict use of RECIST criteria (Benjamin et al., 2007). However, all patients were subjected to surgical exploration in our study and as such insensitivity of the RECIST as compared to the Choi criteria did not seemingly influence the management of our patients. Choi response criteria incorporate tumour density and use small changes in tumour size on CT and are, as claimed by Benjamin et al. (2007), more sensitive and more precise than RECIST in assessing the response of GISTs to imatinib mesylate. However, as pointed out by Van den Abbeele et al. (2008), anatomic tumour response criteria are not as useful for sarcomas as they are for other tumour types and because sarcomas often show high metabolic activity related to intense glycolysis, positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (18FDG) can be utilized to more precisely evaluate these tumors and their response to therapy (Van den Abbeele et al 2008). In other studies, Van den Abbeele et al. (2001) and Demetri et al. (2002) observe that in patients with GIST treated with imatinib mesylate, responses seen on 18FDG-PET are closely related to clinical benefit while conventional objective response criteria based on tumor size, as measured by computed tomography (CT), lag weeks and months behind the 18FDG-PET imaging results. This has been indirectly borne out by the present study which shows that the number of partial responses in our patients is higher as compared to that of phase II RTOG 0132. In addition, this trial (Eisenberg et al., 2009) has given to understand that imatinib used for a maximum of 12 weeks preoperatively leads, in the majority of patients, to stabilization of disease. This apparent contrast of our results with those of phase II RTOG 0132 is explained by the fact that imatinib was continued for more than 12 weeks in majority of our patients (median 140 days) in case demonstrable shrinkage in the tumor mass was not seen by that time This is in agreement with observations of Van den Abbeele et al (2001) and Demetri et al (2002) regarding delayed observation of response by conventional CT imaging. Additionally, Asian patients may show a more favorable response to imatinib mesylate as compared to their western counterparts although this question has not been systematically or specifically studied at least in India. However, Yeh et al. (2006), report that imatinib not only significantly prolongs the postrecurrence and overall survival of Asian patients with advanced GISTs but also induces a sustained objective response in more than half of Asian patients with advanced small bowel GISTs. Many retrospective reports have also shown that neoadjuvant imatinib therapy of primarily inoperable GISTs commonly results in ''downsizing'' and enables curative surgical resection or function sparing surgery (Bümming et al., 2003; Katz et al., 2004, Liu et al., 2004; Lo et al., 2005; Loughrey et.al 2005; Salazar et al., 2006; Shah et al., 2005; Yeh et al., 2006].

Our study, although small in patient numbers,

demonstrated a fairly acceptable response to neoadjuvant imatinib in patients with locally advanced GIST, and two third of the patients could undergo a microscopically complete resection .The progression free survival (PFS- 100% at 30 months) results are quite favorable in comparison to historical controls with high risk GIST from our institutional records where median disease-free survival ranged from 6 to 23 months. This is in agreement with historical surgical series (Dematteo et al., 2000; Eisenberg et al., 2009). Andtbacka et al (2007), report only a single recurrence in eleven treated patients with a median follow-up of 19.5 months. Gronchi et al (2007), report on three patients after neoadjuvant imatinib with no recurrences after a median of 21months.

In addition to the above, the present series represents, however, one of the few prospective studies to address the question of neoadjuvant followed by adjuvant therapy in GIST. Evidently this clinical treatment paradigm is just beginning to be explored and awaits further evaluation. It is probable, however, as also maintained by Eisenberg et al (2009), that neoadjuvant downsizing therapy has no overall advantage for relapse-free survival as adjuvant therapy in intermediate and high-risk patients. The exception to this is the theoretical advantage of neoadjuvant administration in primary GIST patients where a responsive tumour might be downsized to allow for less morbid surgery with organ or function-sparing intent (Eisenberg et al., 2009). Additionally, there may be benefits, albeit theoretical, in terms of decreased seeding of tumor cells and decreased tumor bleeding at the time of resection. The ACOSOG phase II and III trials (Dematteo, 2008) of 1year of postoperative adjuvant imatinib in primary GIST suggest a demonstrative benefit particularly for patients with high risk GIST (>10cm). The phase II Z9000 study (median tumor size 13 cm) recently reported a recurrence-free survival of 94%, 73%, and 61% at 1, 2, and 3 years, respectively (Eisenberg et al., 2009). Our study (median tumor size 11.8 cm) compares favorably with the reported progression free survival at 2 years. There is no disease progression in any of our patients who has completed 2 years of imatinib after undergoing resection. Understandably this enhanced benefit is likely due to the effect of post-operative rather than that of neoadjuvant imatinib.

Yeh et al. (2006) and Eisenberg et al. (2009) demonstrated that imatinib is a remarkably safe and well-tolerated drug. Likewise, in the present study, severe toxicity like neutropenia occurred in only in one (5%) patient, while as edema, anorexia and constitutional symptoms were the commonly seen adverse effects.

The postoperative complications were not severe or extraordinary for a surgical series representing extensive abdominal surgery. The common complication was wound infection with minimal drug effects on wound disruption or anastomatic breakdown despite discontinuing imatinib only within five (range 2 to 7) days of surgery and restarting within a median of 19 days. Postoperative imatinib administration was delayed due to a surgical complication in only one patient. In conclusion the use of neoadjuvant imatinib in locally advanced GIST was studied and the short term results are reported. Keeping in view the small number of cases, no definite recommendations based on this study can be made; however, the approach seems feasible and the postoperative complications are acceptable.

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