Imatinib in Gastrointestinal Stromal Tumors
CA Bakshi, RA Jain, PSRK Sastry, AR Sainani, SH Advani

Abstract
Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of gastrointestinal tract. The tumors express the cell surface transmembrane receptor KIT that has a tyrosine kinase activity and is a protein product of KIT protooncogene. These tumors occur in the whole of Gastrointestinal tract. Treatment includes surgical resection for localized tumors. For metastatic disease treatment options include systemic chemotherapy, radiation therapy, with a response rate of less than 10%. Presently Imatinib; a tyrosine kinase inhibitor has shown promising result with response rates upto 59-69% in phase II results in metastatic setting; and ongoing phase II & phase III trials in adjuvant setting will help to establish its role as an adjuvant to surgery.

We have treated eleven patients of metastatic GIST with Imatinib and we hereby present these cases.

INTRODUCTION

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasms of gastrointestinal tract.1 The fundamental pathogenetic feature of these tumors is activation of the KIT signalling pathway. KIT is a transmembrane tyrosine kinase and is a protein product of KIT protooncogene.2 These tumors uniformly express the cell surface transmembrane receptor KIT (C-kit), as KIT activation occurs in GIST regardless of mutational status of KIT.3

GIST may occur anywhere in gastrointestinal tract. It may arise from omentum, mesentery and the retroperitoneum. Mitotic rate, tumor size and site are three more important prognostic factors.1 Surgical resection is the treatment of choice in localized tumors. Incomplete surgical resection or metastatic disease signifies a poor prognosis. Metastatic disease shows poor response to conventional chemotherapeutic drugs. In recently reported series, response rate to Doxorubicin was less than 5%.4-5 Imatinib mesylate is a selective inhibitor of intracellular ABL kinase, the chimeric BCR - ABL fusion protein expressed in chronic myeloid leukemia, transmembrane receptor kit and platelet-derived growth factor receptor.6-9 Recently Imatinib has become the first line therapy for both chronic myeloid leukemia and metastatic GIST.

We hereby report initial experience in eleven patients with GIST showing good response to Imatinib.

CASE REPORTS

No.1:

Mr. P.S, a 36-year-old healthy young male presented to us on the 23rd of July 1998 with a history of excessive belching and abdominal discomfort since six months. The abdominal discomfort increased on consuming food. He was noticed to have a firm lump in the left hypochondriac region and was advised an MRI Abdomen. The MR scanning revealed a gastric neoplasm without any locoregional spread. His chest X-ray was normal. He underwent a partial gastrectomy with gastrojejunostomy. The postoperative CT scan was normal. The histopathological examination of the specimen showed a low-grade Leiomyosarcoma with positive cut margins. A C-kit expression could not be ascertained. The patient was started on chemotherapy with Ifosfamide and Adriamycin. The patient was reassessed after 3 cycles in January 1999, CT scan showed a progressive disease with multiple liver and splenic metastases with retroperitoneal deposits. Further chemotherapy was withheld and the patient was kept under observation thereafter and was given symptomatic treatment only. The patient continued to have a growing disease and had large palpable masses in the abdomen with multiple cutaneous and subcutaneous nodules. A CT scan of the abdomen done in June 2001, showed an increase in the size of the liver and splenic metastases as compared to the previous scans and large omental deposits (Fig. 1).

In view of these findings, he was started on oral Imatinib mesylate 600mg daily from 23rd June 2001. The patient
received Imatinib for three months. On reassessment, the patient had improved symptomatically and the palpable masses had reduced rapidly. At the time of follow up on 29.07.2002, the patient was in excellent general condition with a performance score of 100% and has no hepato-splenomegaly or palpable masses in the abdomen, CT scan of the abdomen showed significant reduction in the abdominal masses and hepatic and splenic lesions (Fig. 2). Recent MRI done in June 2003 shows almost 90% regressions in tumor size.

No. 2:

Mrs. G.P, a 58 years old lady, came to us with mass in abdomen since 1 month in November 2002. USG abdomen revealed a large mass in abdomen with normal liver and spleen. She underwent exploratory laparotomy with excision of tumor on 19/11/2002. Her pathology report showed high-grade malignant stromal tumor of small bowel with infiltration in iliac wall. Immunohistochemistry revealed reactivity with S 100 and C-kit. After the surgery, she was kept under observation. In Feb 2003, her sonography of the abdomen, revealed multiple metastasis in right lobe of liver, largest measuring 27 x 35 mm. On 27/3/2003, she was started on oral Imatinib, 600mg per day. Her sonography of the abdomen done in December 2003 shows stable disease. She continues to be in good general health.

No. 3:

Mr. M.G. is 53-year-old gentleman presented to us in October 1998 with complaints of epigastric pain, high-grade fever and shoulder pain since six weeks of duration. He was investigated for these complaints. Sonography of the abdomen revealed presence of sub-diaphragmatic mass arising from gastric fundus. CT scan confirmed that mass was infiltrating the diaphragm and lower surface of left lung. He underwent surgery on 22nd October 1998, excision of mass was done along with partial gastrectomy, splenectomy, and partial diaphragmectomy. Histopathology was reported as Leiomyosarcoma. He was alright for two and half years. In January 2001, CT scan abdomen revealed 5x3 cm lesion in left upper abdomen, which was excised. On 30th March 2001, CT scan showed recurrence in left parietal wall with lesion in liver. The FNAC confirmed Leiomyosarcoma. He underwent hepatic metastatectomy. His MRI abdomen in August 2001 revealed 8 x 3 x 5 cm mass in the left hypochondrium adherent to left lateral abdominal wall. He was then started on Imatinib (600mg) daily, in August 2001 and continued till May 2002 with stable disease as seen on CT scan. In November 2002, progression of the disease was noticed in the CT scan with a large well-defined mass along the lateral abdominal wall of 8.5 x 3 cms (Fig. 3). He was re-operated and partial excision of mass was done. Histopathology was reported as high grade GIST, expressing C-Kit, CD34 and Vimentin. He was restarted on Imatinib on 15/12/2002.

Since then he is on regular follow up. His CT scan abdomen done in January 2004 showed a very small lesion in left sub diaphragmatic region thus showing an excellent...
response. (Fig. 4)

No. 4:

Mr. D.K, 33-year-old gentleman presented in Jan. 2001 with bleeding per rectum. USG abdomen done revealed mass in jejunoileal loop. He underwent resection anastomosis in Feb. 2001. Histopathology revealed GIST with C-kit expression. He was alright for one and half year and was under regular follow up. On 23/9/2002, USG Abdomen and pelvis revealed multiple hepatic metastases. CT scan abdomen showed lesion of 5.7 x 3.4 x 4.6 cm in right lobe and 1.8 x 1.2 x 1.7 cm in left lobe and ill-defined mass in pelvis (Fig. 5). In September 2002, he was started on Imatinib 600mg/day. CT scan on 11/03/2003 reveals regression in size of hepatic lesions. On 11/09/2003, CT scan abdomen and pelvis showed total disappearance of pelvic mass and regression in size of hepatic metastasis. (Fig. 6). Patient is advised to continue Imatinib (600 mg / day).

No. 5:

Mr. D. Kh., 52-year-old male presented to us in July 1996 with retention of urine. He was detected to have a mass in retrovesical region. He underwent surgery in form of prostatectomy. Histology showed Leiomyosarcoma. C-kit expression was not ascertained. In Oct. 2000, CT scan revealed metastatic deposits in liver with enlarged right internal iliac nodes. He received 3 cycles of Ifosphamide and Adriamycin. CT scan abdomen done on 31/12/2001 revealed multiple metastatic deposits in liver with enlarged iliac lymph nodes (Fig. 7). He was started on Imatinib 400mg / day. Patient continued Imatinib till June 2002 with reduction in liver metastasis. Due to financial problems, he stopped Imatinib in June 2002. He has restarted Imatinib in April 2003. Imaging studies done in September 2003 (Fig. 8) did not show any increase in liver metastasis inspite of patient being off the Imatinib

No. 6:

Mr. R. V., 50 year old patient presented in 1998 with history low grade fever and fatigue. He was detected to have a
pallor. Investigations showed Hemoglobin 7gm%, normal sigmoidscopy, Barium Meal revealed irregularity in the small bowel. He underwent exploratory laparotomy in July 1998. Mass was detected in jejunum and mesentery. Eleven inches of jejunum was resected along with the lesion. The histopathology report was suggestive of leiomyoma expressing C-Kit. Patient received no adjuvant therapy. Repeat USG in March 1999 showed mass lesion in mesentery, which was gradually increasing in size, for which he was reoperated in Dec. 2000. After three months he developed a recurrence with sonography showing multiple masses in the abdomen for which he underwent a Laparotomy and resection of multiple masses. He received adjuvant therapy in with 6 cycles of Doxorubicin and Etoposide till July 2001. Ultrasonography abdomen in July 2001 revealed liver metastasis. In Dec 2001, he was started on Imatinib (600mg / day) in view of increase in liver metastasis. Initially he developed ascites and pleural effusion; which was treated with diuretics. Imatinib was continued. In July 2002, there was 60% regression in the hepatic lesions with central necrosis. At present, he has shown good symptomatic relief with oral Imatinib being continued for last 2 years.

No. 7:

Mrs. A. S 48 year old lady came in July 1999 with pain in left subcapsular region and abdomen. Her CT scan abdomen showed large heterogeneously enhancing soft tissue mass seen in the left side of upper abdomen extending into spleen. She underwent excision of the tumor with partial gastrectomy on 21/07/99. Histopathology revealed gastrointestinal stromal tumor, low-grade leiomyoma with c-kit strongly positive. Her CT scan abdomen in April 2000 showed recurrence of tumor in spleen. She underwent splenectomy. On 20/08/01 CT scan of abdomen revealed two well defined peripherally enhancing lesions seen in the liver 3.1x1.5 cms and 1.6x1.8 cms respectively (Fig.9). FNAC of that lesion confirmed Leiomyosarcoma expressing C-kit. She was started on Imatinib (600 mg / day). In October 2002, lesions further show 50% regression regressed in size, 1.5x1.6 and 0.6 x 0.5 cms respectively. In May 2003, lesions were of same size (Fig. 10). Patient is continued on Imatinib and is doing very well. She did not experience any major side effects with Imatinib.

No. 8:

Mr. C. K. is a 77-year-old man who presented to us in April 2001, with pain in abdomen. His USG abdomen revealed presence of multiple lesions in liver. Trucut biopsy from liver lesions revealed metastasis of gastrointestinal tumor with C-kit expression. He did not take any treatment for one year till July 2002. CT scan done on 10th July 2002 revealed ulceroproliferative growth of the stomach involving gastric fundus with multiple hypodense nodular lesions involving both the lobes of liver. He was started on Imatinib (400mg per day). His follow up CT scan on 8th Oct. 2002 revealed regression of lesion along the anterior wall of stomach and liver lesions remaining same in size. He was continued on Imatinib. CT scan done on 14th Oct. 2003 shows further
reduction in size of gastric mass with no interval changes in hepatic metastatic deposits. He continues to have 100% performance score on Imatinib. He did not experience much side effects with Imatinib except grade I or II vomiting and periorbital edema.

No. 9: Mr. A. P. 40 year old man presented to us in April 2002, with history of malena, loss of appetite and weakness since 3 months. On examination, he had pallor; there was no lymphadenopathy or organomegaly. Upper gastrointestinal endoscopy showed a large ulceroproliferative tumor in the second part of duodenum. Histopathology was reported as low grade GIST, with tumor cells expressing Vimentin, C-kit and CD34. His CT scan abdomen revealed a large mass involving duodenum and pancreatic head, with hepatomegaly and multiple space occupying lesions in liver. He was started on Imatinib 600mg daily on 28/05/2003. His repeat Endoscopy done on 01/09/2003 was completely normal. However, CT scan abdomen revealed same 8 x 6 cm mass in the abdomen with multiple liver space-occupying lesion. PET scan was performed which revealed that there were no foci of hyper metabolism to indicate the presence of tumor. Thus, the tumor, which was visible on CT scan probably, consists of necrotic tumor cells.

His follow up CT scan done on 17/12/2003 revealed abdominal mass slightly reduced in size as compared to previous one. Patient tolerated Imatinib very well. He did not experience any side effects except lightening of skin color. He is continued on Imatinib.

No. 10: Mr. S. T. 46-year-old male patient, presented first to us with distention of abdomen in Nov. 1999. He underwent surgery in the form of partial gastrectomy and excision of the tumor. He was alright for two years, but developed abdominal wall recurrence in July 2001, for which he again underwent surgery. Histopathology reported as gastrointestinal stromal tumor of the stomach of intermediate grade with overexpression of C-Kit. His CT scan abdomen done in Oct. 2002 revealed soft tissue nodular density along the superomedial aspect of the spleen. He was advised to take oral Imatinib. He started oral Imatinib 600mg daily since Jan. 2003. His CT scan abdomen in June 2003 shows that there was considerable regression in the size of the mass. In Dec. 2003, his repeat CT scan abdomen was completely normal without any evidence of the disease. He is continued on oral Imatinib.

No. 11: Mrs. B.T. a 58 years old lady came to us on 12th May 2000, with pain in abdomen since one month. CT scan abdomen revealed a mass in it upper abdomen measuring 12 x 8 cm.

She underwent surgery with partial gastrectomy and splenectomy on 24/5/2000. Histopathology examination revealed Leiomyosarcoma of stomach intermediate grade. C-Kit was strongly positive. She was all right for two years. CT scan abdomen done on 20/6/2002 revealed 4 x 4 cm mass in the iliac region. She underwent 2nd surgery on 26/6/02 with removal of mass. After three months, she developed recurrence in lymph node at porta hepatis. She was started on chemotherapy with Ifosfamide and Etoposide but had progressive disease. Her USG abdomen on 15/11/02 revealed increase in size of node. She received 2 more courses of chemotherapy with VAD (Vincristine, Adriamycin and DTIC) with no response. She was started on Imatinib in Jan 2003. Her CT scan abdomen before starting Imatinib revealed tumor mass near lesser curvature of stomach along with another tumor mass in lumbar region. In July 2003, after six months of Imatinib, her CT scan abdomen revealed total disappearance of tumor with complete response. During last follow up in December 2003, sonography of abdomen continued to show complete regression of abdominal mass.

Summary of all eleven patients with relevant clinical features are given in Table 1. Response to Imatinib is summarized in Table 2.

**DISCUSSION**

Gastrointestinal stromal tumor (GIST) can arise anywhere in Gastrointestinal tract, 50-60% of GIST occurs in stomach, 20-30% in small intestine, 10% in large intestine, 5% in esophagus and 5% anywhere in abdominal cavity. GIST as

<table>
<thead>
<tr>
<th>Case No / Initials</th>
<th>Age / Sex</th>
<th>Date Of Diagnosis</th>
<th>Site of the Disease</th>
<th>Prior Chemo</th>
<th>Response To Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 / P.S.</td>
<td>36/M</td>
<td>23/7/98</td>
<td>Stomach</td>
<td>Ifosphamide + Cisplatin +</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>2 / G.P.</td>
<td>58/F</td>
<td>19/11/02</td>
<td>Small intestine</td>
<td>Nil</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>3. / M. G.</td>
<td>53/M</td>
<td>10/98</td>
<td>Stomach</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 / D. K.</td>
<td>33/M</td>
<td>1/01</td>
<td>Jejunum</td>
<td>Nil</td>
<td>-</td>
</tr>
<tr>
<td>5 / D.Kh.</td>
<td>52/M</td>
<td>7/96</td>
<td>Prostate</td>
<td>Holoxan &amp; Adriamycin</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>6 / R.V.</td>
<td>50/M</td>
<td>7/98</td>
<td>Jejunum</td>
<td>Adriamycin, Etoposide</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>7 / A.S</td>
<td>48/F</td>
<td>7/99</td>
<td>Stomach</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8 / K.C.</td>
<td>77/M</td>
<td>04/01</td>
<td>Stomach</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9 / A. P.</td>
<td>40/M</td>
<td>04/02</td>
<td>Duodenum</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10 / S. T.</td>
<td>46/M</td>
<td>11/99</td>
<td>Stomach</td>
<td>Ifosphamide, Etoposide, Vincristine, Adriamycin, Dactinomycin</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>11 / B.T.</td>
<td>58/F</td>
<td>12/5/00</td>
<td>Stomach</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
known to be resistant to chemotherapy, for our patients had received prior chemotherapy with no response. GISTs are heterogenous histologically, being most often composed of spindle cells but sometimes having epitheloid features. These possibly arise from progenitors related to interstitial cells of cajal and uniformly express C-kit gene product receptor.1 This receptor, the product of proto-oncogene C-kit, can be detected by immunohistochemical staining for CD117 which appears to be most specific diagnostic criterion for GIST.11 The proto-oncogene C-kit encodes a tyrosine kinase receptor located on the long arm of chromosome 4.12 Imatinib mesylate selectively inhibits the enzymatic activity of kit tyrosine kinase.13 It competes with ATP for its kinase-binding site, and prevents the kinase from transferring phosphate from ATP to tyrosine residues of the substrates. This action inhibits downstream signaling from the kinase, which switches the balance towards apoptosis leading to reduction in the tumoral metabolism and growth.

Demetri et al in a phase II, trial studied 147 patients with GIST, with Imatinib 400mg or 600mg daily. In their series 53.7 percent had partial response, and 27.9 % had stable disease. 13% of patients progressed on treatment. No patient had complete response to the treatment.14 In another phase I trial, conducted by EORTC, 36 patients were studied. They observed response rate of 69% and progression was seen in 11% of the patients.15

In our analysis, four patients showed complete response to the treatment within six months of starting treatment whereas six had Partial Response and one stable disease. Response could be documented as early as within three months of starting the treatment with Imatinib. None of our patients showed resistance to Imatinib. Two of our patients (No.1 and No.5) could take Imatinib intermittently only due to financial reasons. We could not see any progression of disease during drug free interval. This observation suggests prolonged effect of Imatinib in inhibiting the C-Kit activity.

All our patients had undergone surgery prior to any other treatment. Also four of them had received prior chemotherapy with no response. In two patients, Imatinib was started as the first line of treatment. Overall Imatinib was tolerated well by our patients. One uniform side effect of Imatinib was lightening of skin color. Other minor side effects included nausea and edema feet. One patient developed retention of fluid leading to ascites and pleural effusion, which was treated with diuretics.

At present, all our patients are in excellent general health with performance status of 100% and are able to perform their duties without any problems.

We conclude that targeted therapy with Imatinib has been found to be effective in GIST. It is warranted to do randomized studies for use of Imatinib as an adjuvant treatment of GIST.

### References


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**Announcement**

**LECTURESHP (2005)**

1. Unichem Lectureship in Gastroenterology (2005)
2. Dr. Yodh Memorial and Gwalior Conference Training Fellowship (2005)
4. Shree Krishnaji Govind and Mrs. Pramalabai Bhave Memorial Lectureship in Asthma and Bronchitis (2005)

**LECTURESHP (2004)**

Dr. Coelho Memorial Lectureship in Experimental Medicine (2006)

The selected candidate has to deliver his/her lecture at the Annual Conference of API 2006.

All the above lectureships need prescribed application forms which are available from the API Office. The completed application forms for the above Lectureship should reach to Dr. Sandhya Kamath, Hon. General Secretary of API, Launder Mansion, 3rd Floor, 21, Maharshi Karve Road, Opp. Charni Road Station (E), Mumbai - 400 004 not later than 31st July, 2004.

**II. ORATIONS**

Suggestions are invited from members for the following assignments so as to reach Dr. Sandhya Kamath, Hon. General Secretary not than 31st July, 2004.

5. Hoechst Senior Lectureship in Diabetes (2006)
6. Dr. PJ Mehta Oration (2006)
7. Dr. GS Sainani Oration (2006)
8. Dr. Shurvir Singh Trust Visiting Professorship (2005)

There are no prescribed nomination/application forms for the above orations but, persons are selected from the recommendations received from members of the Association. The recommendations for the above assignments must be accompanied with reasons for recommending a particular person showing the value of his/her research and eight copies each of three of his/her best publications. All relevant papers in connection with the suggestions, such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer. The recipient of the above awards (except Dr. Shurvir Singh Trust Visiting Professorship) should deliver a lecture pertaining to his/her work at the Annual Conference in January, 2006. As regards Dr. Shurvir Singh Trust Professorship the selected candidate should visit a medical institution as directed by the Hon. Secretary of API during the year 2005.

A person who has received oration in the past is not eligible for any oration.

All lectureships, orations (except the Sarabhai Oration) and awards are open to eminent persons from the discipline of medicine and allied subjects such as Pharmacology, Biochemistry, Pathology and Physiology. The orator in the discipline of medicine should preferably be a member of API.

The members of the Governing Body of API and the Members of the Faculty Council of ICP are not eligible to received any award.

Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai - 400 011.  Dr. Sandhya Kamath

Tel. : (022) 56663224  Tel./Fax : (022) 2492 0263  Hon. General Secretary