



CLINICAL RESEARCH

Advanced gastrointestinal stromal tumor patients with complete response after treatment with imatinib mesylate

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Abstract

AIM: Most gastrointestinal stromal tumors (GISTs) express constitutively activated mutant isoforms of kit kinase or platelet-derived growth factor receptor alpha (PDGFRA), which are potential therapeutic targets for imatinib mesylate (Glivec). Partial response occurred in almost two thirds of GIST patients treated with Glivec. However, complete response (CR) after Glivec therapy was sporadically reported. Here we illustrated advanced GIST patients with CR after Glivec treatment.

METHODS: Between January 2001 and June 2005, 42 advanced GIST patients were treated with Glivec. Patients were administered 400 mg of Glivec in 100-mg capsules, taken orally daily with food. The response of the tumor to Glivec was evaluated after one month, three months, and every three months thereafter or whenever medical need was indicated. Each tumor of patients was investigated for mutations of kit or PDGFRA.

RESULTS: The median follow-up time of the 42 advanced GIST patients treated with Glivec was 16.9 months (range, 1.0 - 47.0 months). Overall, 3 patients had complete response CR (7.1%), 26 partial response (67.8%), 5 stationary disease (11.9%), and 3 progressive disease (11.9%). The median duration of Glivec administration for the three patients was 36 months (range, 23-36 months). The median time to CR after Glivec treatment was 20 months (range, 9-26 months). Deletion and insertion mutations of c-kit exon 11 and insertion mutation of c-kit exon 9 were found in two cases and one case, respectively.

CONCLUSION: Complete response (CR) can be achieved in selected advanced GIST patients treated with Glivec. The median time to CR after Glivec treatment was 20 months. Deletion and insertion mutations of kit exon 11 and insertion mutation of kit exon 9 contribute to the genetic features in these selected cases.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are soft-tissue sarcomas primarily arising from mesenchymal tissue in the gastrointestinal (GI) tract and abdomen. They are rare neoplasms, estimated to represent 0.1 to 3% of all GI tract tumors^[1]. However, GISTs are the most common mesenchymal malignancy of the GI tract with precise incidence unknown^[2]. GISTs appear to be related to the interstitial cells of Cajal of the mesenteric plexus^[3]. These cells are considered GI pacemaker cells, from the interface between the autonomic innervation of the bowel wall and its smooth muscle^[4,5]. GISTs express the cell-surface transmembrane receptor kit with a tyrosin kinase activity and is the protein product of the kit proto-oncogene. There are frequent gain-of-function mutations of kit in GISTs. These mutations result in constitutive activation of kit signaling, which leads to uncontrolled cell proliferation and resistance to apoptosis. It has been recently reported that kit activation occurs in all cases of GISTs, regardless of the mutation status of kit.

Surgical resection remains the mainstay of therapy for GIST. However, recurrence is common; the 5-year survival rates after complete resection range from 40 to 65%^[6-10]. Unresectable or metastatic GIST is a fatal disease that resists conventional chemotherapy. In a recently reported series, the response rate to doxorubicin therapy was less than 5%^[11]. The effectiveness of radiation therapy for unresectable or metastatic GIST has not been proved. The median length of survival for patients with a metastatic GIST is approximately 20 months, and 9 to 12 months for patients with local recurrence^[3]. Before the development of Glivec, the outlook for patients with advanced GIST was extremely poor. A significantly large number of patients with initial resection of GIST eventually experience

Imatinib mesylate (formerly STI571, now referred to as Gleevec in the United States and Glivec in Europe [Novartis]) selectively inhibits certain protein tyrosin kinases: intracellular ABL kinase, chimeric BCR-ABL fusion oncoprotein of chronic myeloid leukemia, transmembrane receptor kit, and platelet-derived growth factor (PDGRF) receptors^[12-15]. Glivec induced a sustained objective response in more than half of patients with advanced GISTs^[16]. However, complete response (CR) induced by Glivec on GIST patients has been sporadically reported. We report herein our experience on three GIST patient treated with Glivec achieving complete response.

MATERIALS AND METHODS

Patients

During January 2001 to May 2005, 42 histologically confirmed, unresectable or metastatic GIST patients expressing CD117 (a marker of kit-receptor tyrosine kinase) and CD34 treated at Department of Surgery, Chang Gung Memorial Hospital, Taiwan were enrolled in this study. Metastatic disease was defined as that occurring at structures noncontiguous with the primary tumor site. Criteria for inclusion were as follows: at least one measurable tumor; adequate hepatic, renal, and cardiac function; an adequate platelet count; and an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less. Patients could have previously received chemotherapeutic regimens (the last chemotherapy treatment must have been at least four weeks before the study entry) and undergone radiotherapy, or surgery, or both. R0 resection means curative resection without microscopic evidence of tumor. R2 resection means resection with macroscopic evidence of tumor. The study was approved by the Local Institutional Review Board of Chang Gung Memorial Hospital and written informed consent for drug administration and the analysis of tumor-associated genetic alteration was obtained from each patient.

Study design

A prospective, non-randomized, and single center trial was conducted to evaluate the role of Glivec in inducing objective response in GIST patients. Patients were administered 400 mg of Glivec in 100-mg capsules, taken orally daily with food. Patients had regular physical examinations and evaluations of performance status, body weight, complete blood count, and serum chemistry. The administration of each dose and any adverse events were recorded for each patient. Standard computed tomography (CT) was performed on each patient every three months to assess patient response. Standard [18F] fluoro-2-deoxy-D-glucose positron-emission tomography (PET) scanning was performed on selected patients to complement standard CT and assess changes in the metabolic profiles of the tumors.

Efficacy and safety evaluation

The response of the tumor to Glivec was evaluated after one month, three months, and every three months thereafter or whenever medical need was indicated. Assessments were performed according to the standard Southwest Oncology Group (SWOG) criteria and based solely

on CT or PET^[17]. Responses were classified as follows: complete response (CR) (disappearance of all disease that could be measured and evaluated); partial response (PR) (> 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions, the absence of progression, and the absence of new lesions); stationary disease (SD) (a response that did not qualify as a complete response, a partial response, or disease progression); and disease progression (DP) [> 50% increase or an increase of 10 cm (whichever was smaller) in the sum of the products of the perpendicular diameter of all measurable lesions, worsening of a lesion that could be evaluated, the reappearance of any lesion or the presence of a new lesion, or failure of the patients to return for evaluation because of disease progression]. Toxic effects were recorded in accordance with the National Cancer Institute Common Toxicity Criteria^[18].

Analysis of KIT and PDGFRA mutations

Sections were prepared from formalin-fixed, paraffin-embedded pretreatment specimens trimmed to enrich tumor cells. Polymerase chain reaction amplification of genomic DNA for KIT and PDGFRA was performed and amplification was analyzed for mutations as previously described^[19].

RESULTS

Age and sex

The investigation comprised one male patient and two female patients with ages ranging from 45 to 56 years (median: 51 years) (Table 1). All three patients had grade 0 ECOG status.

Tumor location, size, and treatment

Table 1 summarizes the size and location of each tumor. One patient underwent laparotomy with excisional biopsy and the other two had curative segmental resection of jejunal GIST previously. Tumors of all three patients displayed strong positive kit staining with the tumor size ranging from 10 cm to 20 cm (median: 10 cm). The interval between diagnosis of GIST and tumor recurrence ranged from 0 to 15 months (median 7 months). All three patients displayed peritoneal carcinomatosis and two had liver metastasis.

Treatment

All three patients were administered 400 mg Glivec after diagnosis of metastasis was made. The duration of Glivec administration ranged from 24 to 36 months (median: 36 months). The side effect of Glivec treatment was grade II to III edema.

Genetic investigations of tumors from GIST

The sequencing analysis of the tumor from the three patients exhibited mutation in c-kit gene. Two displayed deletion and insertion mutation in exon 11 and one insertion mutation in exon 9 (Figures 1, 2, and 3).

Time to response and follow-up outcome

Since 2000, Glivec has been administered to advanced GIST patients. Forty-two patients with advanced stages

Table 1 Clinicopathological and mutational status of three advanced and metastatic GIST patients treated with imatinib mesylate with CR

Patient	1	2	3
Age (yr)	57	45	51
Gender	F	M	F
ECOG	Grade 0	Grade 0	Grade 0
Tumor origin	Jejunum	Stomach	Jejunum
Tumor size (cm)	20	10	10
Previous treatment	Operation	Laparotomy and excisional biopsy	Operation
Resection	R0	R2	R0
Site of tumor recurrence	Liver, locoregional, and peritoneum	Liver, peritoneum, and retroperitoneum	Peritoneum
Interval between previous treatment and recurrence (mo)	15	0	18
Glivec dose/duration (mo)	400/36	400/23	400/36
Side effect	Grade II edema	Grade III edema	Grade II edema
Mutation status	Deletion and insertion mutation at codons 563-572 in exon 11	Deletion and insertion mutation at codons 556-557 in exon 11	Insertion AY at codons 502-503 in exon 9
Time to CR (mo)	20	9	26
CT	CR	CR	CR
PET	CR without activity	CR without activity	CR without activity
Duration of response (mo)	16	14	10
Overall survival (mo)	40	24	54
Status	Free of disease	Free of disease	Free of disease

ECOG: Eastern Cooperative Oncology Group; mo: months; CR: complete response; CT: computed tomography; PET: positron emission tomography.

of the disease were given 400 mg Glivec per day. The median follow-up duration was 16.9 months (range, 1.0-47.0 months). Overall, 3 (7.1%) patients had complete response (CR), 26 (67.8%) partial response, 5 (11.9%) stationary disease, 3 progressive disease, and 3 (7.2%) patients were unavailable to evaluate. The time to CR after Glivec treatment ranged from 9 to 26 months (median, 20 months) as illustrated by CT first and confirmed by PET without any metabolic activity (Figures 1, 2 and 3). The median follow-up period of the three advanced GIST patients treated with Glivec with CR was 40 months (range, 24 - 54 months).

DISCUSSION

Before the introduction of Glivec, poor responses to radiation and chemotherapy made surgery the only realistic treatment to cure the primary lesion^[3,10,20-22]. A substantial number of patients with initial resection of GISTs eventually experience recurrence. There has been no effective treatment for advanced GISTs and the outlook for patients is extremely poor.

Therapeutic responses to targeted inhibition of activated tyrosine kinases have been demonstrated for certain types of leukemia, sarcoma, and breast cancer^[19]. The mechanisms of kinase activation vary considerably among these cancers, but there is little information available in literature about the influence of these mechanisms on drug response^[19]. The GISTs, in particular, present a variety of genomic mutations across two different receptor tyrosine kinase genes. The KIT or PDGFRA mutation in

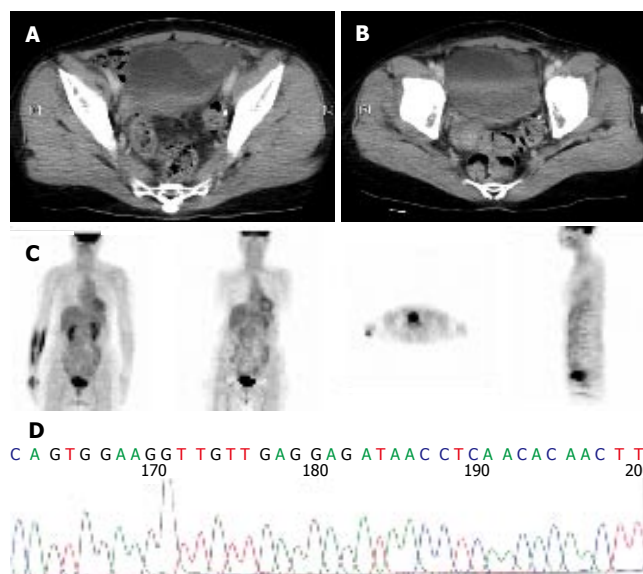


Figure 1 (A) Abdominal CT showing a tumor located near the urinary bladder (arrow); (B) abdominal CT showing complete response without tumor at the same level as Figure 1A; (C) [18F] fluoro-2-deoxy-D-glucose positron-emission tomography (PET) scanning PET revealing no tumor with metabolic activity in the whole body; (D) Direct sequencing analysis of DNA from patient 1 showed deletion and insertion mutation at codons 563-572 in exon 11 (arrow).

Asian clinically advanced small bowel GIST patients was examined in this study. The kit kinase oncoproteins were intrinsically sensitive to Glivec, accounting for the excellent overall clinical response to Glivec, and coincident with results obtained by Heinrich *et al*^[19]. Similar to the report by Demetri's *et al*^[16], the CR and PR rates for Glivec in this

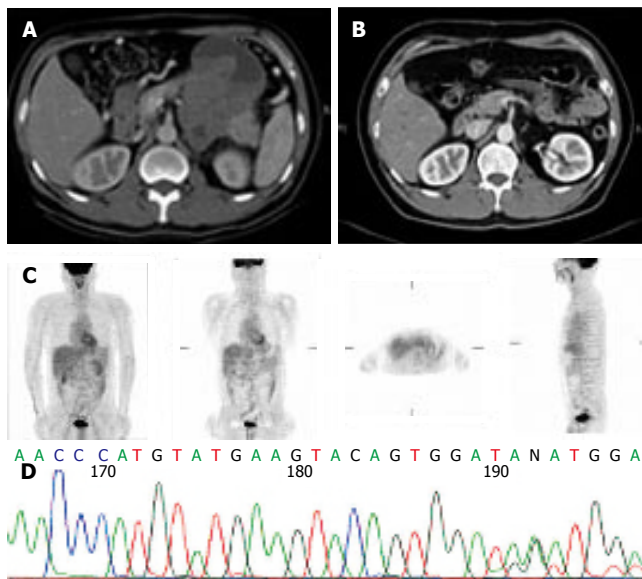


Figure 2 (A) Abdominal CT showing a huge retroperitoneal tumor invading the pancreas (arrow); (B) abdominal CT showing complete response without tumor at the same level as Figure 2A; (C) PET showing no tumor with metabolic activity in the whole body; (D) direct sequencing analysis of DNA from patient 2 showed deletion and insertion mutation at codons 556-557 in exon 11 (arrow).

study was 68.0%. Glivec induced a sustained objective response in more than half of the patients with advanced GISTs^[16]. However, CR induced by Glivec on GIST patients was sporadically reported. In US Intergroup S0033 phase III study on 751 metastatic or unresectable GIST patients receiving 400 or 800 mg Glivec per day^[23], CR rate was 3%. Moreover, in the EORTC 62005 phase III study, the CR rate was 4.76% for 923 metastatic or unresectable receiving 400 or 800 mg Glivec per day. Contrast to the aforementioned two studies, the CR rate in this study was 7%. The experience on CR after Glivec treatment for advanced or metastatic GIST patients in this study may justify the use of Glivec as neoadjuvant or adjuvant treatment in the future. FDG PET has been proven to be highly sensitive in detecting early response^[24]. Stroobants *et al.*^[24] demonstrated that the CR rate increased to 52.3% (11/21), however, discrepancy was noted between the CT and PET results. In this study, CR was diagnosed according to SWOG criteria by CT scan first. PET scan was used to confirm its metabolic activity by FDG uptake on PET scan thereafter.

Regarding further use of Glivec for GIST patients with CR after Glivec treatment, no consensus was made. A recently reported randomized trial has shown that Glivec interruption after 1 year is associated with a high risk of relapse, even for patients with CR^[25]. So, Glivec might be administered in the three patients until intolerance or patient refusal. The further use of Glivec for GIST patients with CR after Glivec treatment needs investigation.

In conclusion, CR can be achieved in selected patients with advanced GIST treated with Glivec. Deletion and insertion mutations of kit exon 11 and insertion mutation of kit exon 9 contribute to the genetic features in these selected cases.

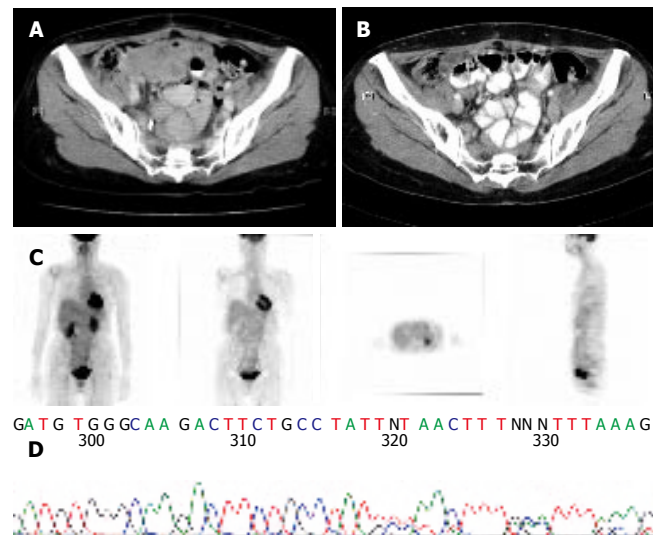


Figure 3 (A) Abdominal CT showing a tumor located near the ileum (arrow); (B) abdominal CT revealing complete response without tumor at the same level as Figure 3A; (C) PET showing no tumor with metabolic activity in the whole body; (D) direct sequencing analysis of DNA from patient 3 showed insertion AY at codons 502-503 in exon 9 (arrow).

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