# Imatinib Mesylate Therapy in Advanced Gastrointestinal Stromal Tumors: Experience from a Single Institute

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Gastrointestinal stromal tumors (GIST) are rare soft tissue sarcomas arising primarily from mesenchymal tissue in the gastrointestinal tract and abdomen. Since there is no effective treatment in the advanced stages, the outcome is poor in such patients. Recently, imatinib mesylate, a selective tyrosine kinase inhibitor, has shown a promising effect in GIST. Hence, we report our experience on the management of advanced GIST with imatinib therapy. A total of 14 patients were enrolled in this study, including 10 males and four females (median age, 51 years). The results showed that the small intestine was the most frequent site of primary lesion, while the liver was the most frequently metastasized organ. Most of the patients experienced tolerable side effects with imatinib therapy, including edema of periorbital area and/or legs and abdominal pain. Only two mortalities were noted during follow-up. The patients clinically benefited from imatinib therapy, with one patient having a complete response, three having a partial response, and seven having stable disease. The results demonstrate promising effects of imatinib in advanced GIST.

**Key Words:** gastrointestinal stromal tumor, imatinib, sarcoma
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Gastrointestinal stromal tumors (GIST) are rare soft tissue sarcomas arising primarily from mesenchymal tissue in the gastrointestinal tract and abdomen [1,2]. They account for only 1% of all tumors in the gastrointestinal system, but are the most common mesenchymal malignancies of the gastrointestinal tract [3,4]. Because the tumor has a heterogeneous histologic picture, which is composed mostly of spindle cells but sometimes with epithelioid features, these tumors were previously often classified as leiomyomas and leiomyosarcomas, or even neurogenic tumors [1,2,5]. Recently, the definition of GIST has evolved to be a mesenchymal tumor with overexpression of a transmembrane receptor tyrosine kinase stem cell factor receptor (KIT, CD117) protein and it is now known as a discrete neoplastic entity [6–8].

Surgery has so far been the only effective treatment for GIST because the tumor has generally shown resistance to chemotherapy and radiation therapy [9,10]. Without effective management, patients with metastatic and/or advanced disease have poor outcomes [7]. Moreover, surgical intervention alone is always inadequate, with many patients eventually having a relapse after tumor resection [2]. Recently, imatinib mesylate, a selective inhibitor that suppresses

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the activity of tyrosine kinase, showed a potential effect on GIST with expression of CD117 [9,11]. This launched a novel target therapy in GIST patients of advanced status with promising results [12–14]. Here, we report our experience of managing metastatic GIST with imatinib therapy.

## Materials and Methods

Between 2001 and June 2005, a total of 14 GIST patients with advanced/metastatic lesions were treated with imatinib at Kaohsiung Medical University Hospital and were enrolled in this study. All GISTs were diagnosed by histology and positive CD117 stain. The advanced/metastatic lesions were confirmed by re-biopsy and/or imaging study. Patients were prescribed oral imatinib 400 mg once daily. Clinical presentation, response, and side effects were reviewed from the medical records.

Response to therapy was evaluated by follow-up computed tomography (CT) or magnetic resonance imaging, and a complete response (CR) was defined as there being no evidence of disease for 1 month; a partial response (PR) as a decrease in tumor size by ≥ 50% in the sum of the products of the bi-perpendicular diameters without new sites of disease; a progression as a 25% increase in the sum of the products of the bi-perpendicular diameters or any new sites of disease; and stable disease (SD) as less than 50% response or 25% progression. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) for Windows and the Kaplan–Meier method was used for survival analysis.

## Results

Among the 14 patients, the small intestine was the most frequent site of primary lesion, followed by the stomach, colon, and omentum (Table). Eight patients had metastatic lesions on diagnosis, while six patients had metastatic lesions after initial surgical resection, with an interval of 2–25 months. The liver was the most frequently metastasized site, followed by the peritoneum (Table). All patients underwent surgical intervention as the primary treatment. Even in patients with initial metastasis, surgery for tumor removal and diagnosis was also performed.

**Table.** Clinical characteristics of patients ($n = 14$)

| Characteristic | *n* |
|---|---|
| Median age (range), yr | 51 (36–72) |
| Male/female | 10/4 |
| Primary lesions | |
| Stomach | 5 |
| Small intestine | 6 |
| Colon | 1 |
| Omentum | 2 |
| Metastatic sites | |
| Liver | 8 |
| Peritoneum | 7 |
| Spleen/pancreas invasion | 1 |
| Pleural invasion | 1 |
| Side effects of imatinib therapy | |
| Edema of periorbital area and/or legs | 9 |
| Abdominal pain | 8 |
| Gastrointestinal disturbance | 3 |

The patients took imatinib treatment at a dosage of 400 mg daily for 2–44 months (median, 21 months). However, one patient had poor drug compliance and in another the dosage was increased to 600 mg daily due to the absence of any response. Four patients had also received other therapies for the metastatic lesions before imatinib treatment, including three who had received local radiotherapy without response. One patient initially had a metastatic liver lesion and underwent transarterial chemoembolization therapy before surgical intervention. According to the National Cancer Institute Common Toxicity Criteria, patients suffered from tolerable side effects, including edema of the periorbital area and/or legs, muscle cramping, and gastrointestinal disturbance without any severe (grade 3 or 4) side effects.

There were two deaths during treatment, one due to internal tumor bleeding after imatinib and the other due to pneumonia. The 2-year cumulative survival rate of patients during the follow-up period was 0.84 (Figure). Most of the patients ($n = 7$) showed SD, with one CR, three PR, and one progressive disease.

## Discussion

GIST consistently shows a resistant character to chemo- and radiotherapy with poor outcomes in patients with unresectable and/or advanced status [2]. With

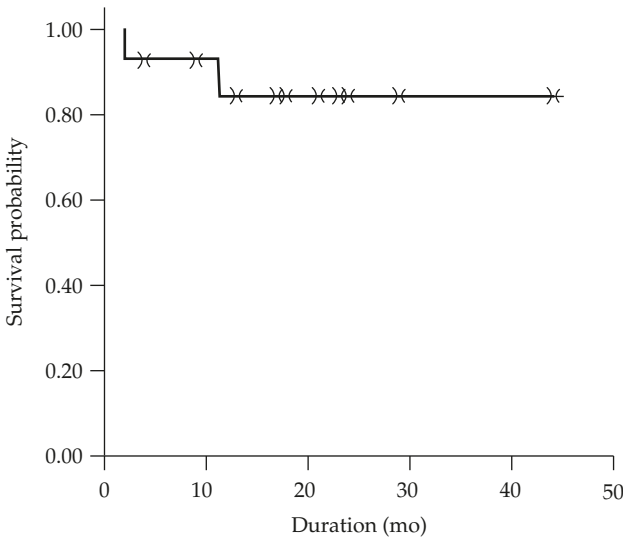


**Figure.** *Cumulative survival rate of patients.*

overexpression of the c-kit antigen in GIST, imatinib therapy demonstrates a promising effect on these patients [4,6]. It makes GIST a discrete neoplastic entity not only in terms of pathologic diagnosis [7,8], but also in management [9,11]. We present our experience of 14 GIST patients of advanced status and the outcomes of imatinib therapy. Although there was a male predominance in this study, the median age was similar to other reports [9,12]. The most frequently involved organ is the stomach, which accounts for 60–70% of patients. However, in our study, more than half of the cases occurred in the small intestine. This discrepancy might be due to the small number of patients in our series.

Although there were two deaths in this study, the other patients showed clinical benefits from imatinib therapy. After administration of imatinib, most of the patients ($n = 11$) had CR, PR, and/or SD, while only one patient had progressive disease. Our data, similar to other reports [11–14], support the significant benefit of imatinib therapy in patients with advanced GIST. The side effects were also mild and tolerable without significant hematologic toxicity in routine dosage and no intractable side effects. Compared to results before the era of imatinib therapy when the 5-year survival rate after surgical resection was only 28–43% [2,15] and the median survival of recurrent GIST after resection was 15 months [16], our results demonstrate a promising development in the treatment of advanced GIST. However, long-term follow-up is warranted for a clear conclusion.

The most frequently metastasized site was the liver, followed by the peritoneum, which was similar to other reports [2]. Many patients suffered from recurrent disease after initial resection of the tumor, even after follow-up of 25 months. This stresses the importance of regular follow-up even after total tumor resection. Though the response was promising, some of our patients still had advanced disease in the diagnosis. Novel, multimodal protocols, including neoadjuvant imatinib or resection of residual tumor after imatinib, warrant further survey [14,16].

Furthermore, there are improvements in the management and diagnosis of GISTs. Since a few GISTs may not express CD117, making the diagnosis difficult, mutation survey, including KIT and platelet-derived growth factor receptor α, is essential for accurate diagnosis [8,17]. Mutation survey can also help in the prediction of treatment response [17,18]. High-technique methods, such as multidetector CT, are useful in detecting the exophytic component and in evaluating the extent of disease [19]. These developments provide us with more information regarding the treatment of GISTs.

In summary, we have reported our experience of using imatinib for patients with advanced GIST. Most of the patients benefited clinically from imatinib therapy with tolerable side effects. However, long-term follow-up is warranted for a clear conclusion.

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# Imatinib Mesylate 對於晚期基質細胞腫瘤的治療：單一機構之經驗

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胃腸道基質細胞腫瘤是一種由胃腸道及腹腔之間質組織而來的罕見的軟組織肉瘤。因為對於晚期之病患無有效之治療方法，其預後一般均不佳。近來由於選擇性的 tyrosine 激脢抑制藥物，imatinib mesylate，顯示對基質細胞腫瘤有不錯的療效，因此提出我們對於晚期基質細胞腫瘤的病患使用 imatinib 治療的經驗。一共有十四位病患：包括十名男性及四名女性，其中位數年齡為五十一歲。小腸是最常見的原發部位，而肝臟是最常見的轉移部位。大多數的病患在治療中均有可忍受的副作用；包括水腫 (眼周圍或下肢水腫) 及腹痛。病患有不錯的累積存活率，只有兩位病患在治療中死亡。病患對於 imatinib 治療有不錯的療效：包括一位病患達到完全反應；七位是穩定疾病及三位部份反應。這結果顯示 imatinib 對於晚期之胃腸道基質細胞腫瘤有很好的療效。

**關鍵詞**：胃腸道基質細胞腫瘤，imatinib，惡性肉瘤
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