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Safety of Regular-Dose Imatinib Therapy in Patients with Gastrointestinal Stromal Tumors Undergoing Dialysis

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Keywords
Imatinib · Hemodialysis · Gastrointestinal stromal tumors

Abstract
The number of cancer patients undergoing dialysis has been increasing, and the number of these patients on chemotherapy is also increasing. Imatinib is an effective and safe therapy for KIT-positive gastrointestinal stromal tumors (GIST), but the efficacy and safety of imatinib in dialysis patients remain unclear. Because clinical trials have not been conducted in this population, more investigations are required. We report on a 75-year-old Japanese man undergoing dialysis who presented with massive tarry stool from a duodenal GIST. The duodenal GIST was 14 cm in diameter with multiple liver and bone metastases. The patient underwent an urgent pancreaticoduodenectomy to achieve hemostasis. After surgery, he was administered imatinib 400 mg/day. No severe adverse event including myelosuppression, congestive heart failure, liver functional impairment, intestinal pneumonia, or Steven-Johnson syndrome occurred, and the liver metastasis remained stable for 4 months. During chemotherapy, hemodialysis continued three times per week without adverse events. We suggest that regular-dose imatinib is an effective and safe treatment in patients with GIST undergo-

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ing dialysis. In addition, we present a literature review of the effectiveness and safety of imatinib treatment in dialysis patients.

Introduction

Approximately 6% of patients undergoing dialysis have malignancies [1], and the number of these patients undergoing chemotherapy continues to increase. Chemotherapy in dialysis patients is challenging because excretion of the drug differs between dialysis and non-dialysis patients. Drugs that are excreted by dialysis may show reduced efficacy, while drugs that are not excreted may cause adverse events.

Imatinib is an effective and safe therapy for KIT-positive gastrointestinal stromal tumors (GIST) [2–5]. However, the efficacy and safety of imatinib treatment in dialysis patients remain unclear because clinical trials have not been conducted in this population. Further information is required on dialysis patients treated with imatinib.

We report a patient with duodenal GIST undergoing dialysis who was treated with regular-dose imatinib and remained stable with no adverse events for 4 months. We also present a literature review of the efficacy and safety of imatinib treatment in patients with GIST undergoing dialysis.

Case Presentation

In a 75-year-old Japanese man, a large duodenal tumor was identified on computed tomography (CT) in 2008 and was suspected as GIST on endoscopic ultrasonography. However, the patient refused further investigation and underwent a follow-up visit. He also had chronic kidney disease, due to type 2 diabetes, and began a course of hemodialysis three times weekly in 2014.

A large-volume and painless tarry stool with hemorrhagic shock occurred in April 2014. A complete blood count showed a hemoglobin level of 6.3 g/dl, and the patient required transfusion of 32 units of packed red blood cells to recover a general condition. Contrast agent-enhanced CT scans revealed a duodenal tumor 14 cm in diameter, with multiple liver and bone metastases. The patient underwent an urgent upper endoscopy, which showed a 3.5-cm submucosal tumor with stigmata of recent hemorrhage in the bulb of the duodenum. Endoscopic hemostasis was not conducted due to the large exposed vessel, and an urgent pancreaticoduodenectomy was performed to achieve hemostasis. The resected tumor showed a GIST composed of spindle-shaped cells with positive staining for KIT and CD34 and negative staining for S-100; the mitotic count was 12 per 50 high-power fields, and the MIB-1 labeling index was 10% (fig. 1).

After surgery, the patient was treated with imatinib at a dose of 400 mg daily (orally). Myelosuppression did not occur during treatment. Complete blood counts showed a white blood cell count in the range of 36–69 × 10^2/l, a hemoglobin level range of 8.9-10.2 g/dl, and a platelet count range of 162–265 × 10^3/l. No congestive heart failure occurred. Hemodialysis continued three times per week without adverse events. Furthermore, no severe adverse event, including liver functional impairment, intestinal pneumonia, or Stevens-Johnson syndrome occurred. However, mild adverse events including fatigue and edema were observed, and his metastases remained stable for 4 months. Finally, imatinib treatment was discontinued because of progression of the disease and worsening performance status in January

2015. The patient died of duodenal perforation induced by residual tumor progression in February 2015, 6 years after the initial diagnosis and 5 months after chemotherapy for GIST.

Discussion

We administered regular-dose imatinib in a patient with multiple metastases from GIST undergoing dialysis. The patient remained stable without any adverse event associated with imatinib for 4 months. To our knowledge, this is the first literature review and third case report of imatinib treatment for GIST in patients undergoing dialysis.

Chemotherapy in dialysis patients continues to increase [6]. Several cytotoxic drug therapies have been reported in patients with major gastrointestinal tract malignancies undergoing dialysis. Dialysis patients with esophageal cancer have been administered 5-fluorouracil and cisplatin [7–9] and dialysis patients with gastric cancer have been administered tegafur-uracil, docetaxel, and irinotecan [10, 13]. Dialysis patients with colon cancer have been treated with tegafur-uracil, irinotecan, and oxaliplatin [14–24]. In these cases, most cytotoxic drugs were used safely without dose modification, but irinotecan caused severe myelosuppression and resulted in death [15, 18]. Selection of a chemotherapeutic agent is an important issue in dialysis patients. However, available data on molecular-specific therapies in dialysis patients are limited, and treatment-related issues are unclear.

Table 1 lists previous reports of imatinib treatment in patients with GIST undergoing dialysis. Pappas et al. [25] reported a 44-year-old woman with rectal GIST and liver metastasis undergoing dialysis for 1 year. She had undergone surgery for rectal GIST 7 years earlier. Six years later, she was diagnosed with liver metastasis of the resected rectal GIST and received regular-dose imatinib for the liver metastasis. No severe adverse events associated with imatinib occurred, and the liver metastasis remained in partial remission for 12 months. Wada et al. [26] reported a 69-year-old Japanese man with peritoneal GIST undergoing dialysis for 9 years. The main lesion of the peritoneum GIST was resected, and he received regular-dose imatinib for residual disease. No severe adverse event occurred, and the residual disease remained in partial remission for 20 months.

In our case and the previous cases, no severe adverse events were associated with imatinib. Imatinib is metabolized by cytochrome P450 isoenzymes in the gut wall and liver [27]. A previous study evaluated the pharmacokinetics of both imatinib and its metabolite CGP74588 in dialysis patients and reported that the pharmacokinetics of dialysis patients were similar to those of non-dialysis patients [25]. The clinical importance of these data was supported by our results, and we also consider that dialysis patients can be treated safely with imatinib. However, our case showed grade 2 fatigue and grade 2 edema during chemotherapy. These findings have been reported as warning signs of congestive heart failure [28]. Heart failure was not observed in our case due to strict water management, but physicians should pay careful attention to patients with these findings.

Previous studies reported good clinical outcomes, with no recurrence after 12–20 months [25, 26]. The effects of imatinib are dose-dependent [29]. Imatinib treatment without dose reduction may contribute to good responses in patients undergoing dialysis as well as those without dialysis. In our case, overall survival was shorter than that in previous reports [25, 26], but the difference may be due to the clinical stage at the time of initiation of imatinib treatment. Our case had poor prognostic factors, such as a lesion size larger than 11.1 cm, wall invasion, and hepatic metastasis [30]. We consider that early imatinib treatment is important in patients with GIST undergoing dialysis.

Conclusions

In conclusion, regular-dose imatinib was an effective and safe treatment in a patient with GIST undergoing dialysis. We believe that physicians should perform early imatinib treatment without dose reduction.

Statement of Ethics

There are no ethical conflicts to declare.

Disclosure Statement

The authors declare no conflicts of interest.

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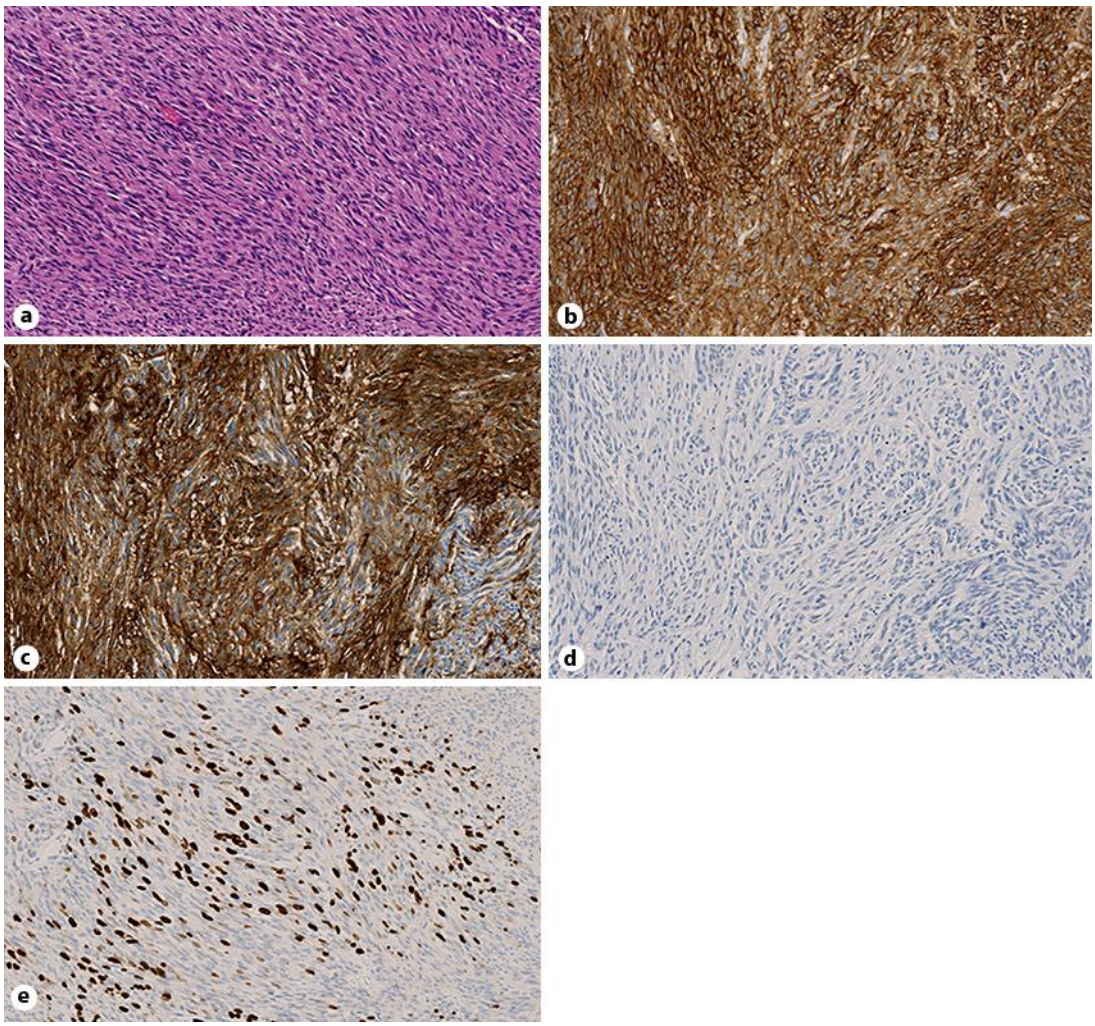

Fig. 1. The resected tumor: composed of spindle-shaped cells, hematoxylin and eosin stain, ×20 (**a**); positive for KIT, ×20 (**b**); positive for CD34, ×20 (**c**); negative for S-100, ×20 (**d**); and with a MIB-1 labeling index of 10%, ×20 (**e**).

Table 1. Review of the literature on imatinib treatment in patients with GIST undergoing dialysis

	Our case	Case 1	Case 2
First author [Ref.]	Niikura	Pappas [25]	Wada [26]
Patient	75-year-old man	44-year-old woman	69-year-old man
Hemodialysis period, years	0.8	1	9
Tumor location	Duodenum	Rectum	Peritoneum
Tumor size, cm	14.5	Not reported	11.2
Staging	Multiple liver and bone metastases	Multiple liver metastases	No metastasis
Imatinib dose, mg/day	400	400	400
Timing of administration	After hemodialysis	Not reported	Not reported
Response [31]	Stable disease	Partial response	Partial response
Overall survival, months	5	Not reported	Not reported
Adverse events[1]	Grade 2 fatigue and grade 2 edema	No major adverse events	No major adverse events

[1] Adverse events of imatinib treatment were evaluated using the Japan Clinical Oncology Group Common Terminology Criteria for Adverse Events version 4.0, Japan Clinical Oncology Group (http://www.jcog.jp/doctor/tool/ctcaev4.html, accessed July 29, 2013). ALT = Alanine aminotransferase; AST = aspartate aminotransferase.