CASE REPORT

Hepatectomy for liver metastasis from gastrointestinal stromal tumor in the era of imatinib mesylate: a case series study

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Received: 30 January 2017 / Accepted: 23 March 2017 / Published online: 31 March 2017
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Abstract The prognosis of metastatic gastrointestinal stromal tumor (GIST) has improved since the introduction of imatinib mesylate; however, acquired resistance has been reported, so alternative treatment option is needed. We evaluated the efficacy of hepatectomy for metastatic GIST. Six patients with liver metastases from GIST underwent hepatectomy. Four were treated with imatinib mesylate before hepatectomy, and all the patients were treated with imatinib mesylate after hepatectomy. Patients were followed-up for a mean duration of 113.5 months after hepatectomy. Complete resection was accomplished in four patients, with incomplete resection performed in the remaining two patients due to peritoneal dissemination. One patient with incomplete resection died 10 months after surgery. One patient with complete resection has survived without disease progression since initial hepatectomy. The remaining four patients with progressive disease during imatinib mesylate treatment developed tumor recurrence and three of them underwent a second hepatectomy. These three patients underwent complete resection during repeat surgery. In total, three patients died during the follow-up period, all of whom had tumors of small intestine origin. Primary tumor site (small intestine vs. others) was identified as a risk factor of mortality ($P=0.02$). Although not statistically significant, there was a trend toward better outcomes in patients with exon 11 mutations. Surgical

resection for metastatic GIST was shown to be effective and needed to achieve a better prognosis. Repeat hepatectomy demonstrated efficacy in selected patients. Hepatectomy should be considered based on tumor characteristics such as primary tumor site and c-KIT mutation status.

Keywords Gastrointestinal stromal tumor · Metastatic GIST · Imatinib mesylate · Hepatectomy

Introduction

During the era prior to imatinib mesylate (IM), recurrence occurred in 40% of patients who underwent complete resection of primary lesions and patients with metastatic gastrointestinal stromal tumors (GIST) had a median survival of 19 months [1].

IM has demonstrated clinical benefit in approximately 80% of patients with metastatic GIST, with a reported 2-year survival rate of 75–80% [2, 3]. However, acquired resistance to IM has been reported with prolonged use, with a reported median progression-free survival of 24 months [2]. There is a lack of consensus regarding treatment recommendations for patients with metastatic GIST that develop acquired resistance; therefore, there are three treatment options as follows: surgery, high-dose IM, and sunitinib malate [4–9].

The present case series reports six patients of hepatectomy for metastatic GIST, including five patients with acquired resistance to IM.

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Materials and methods

From February 2002 to July 2008, six patients underwent hepatectomy with or without other metastasectomy for liver metastases from GIST at Hokkaido University Hospital.

Cumulative survival is presented with Kaplan–Meier curves, and differences in survival between groups were analyzed using the log-rank test. Overall survival was defined as the time from initial hepatectomy to death. *P* values <0.05 were considered statistically significant.

Case presentation

Case 1

A 21-year-old male underwent total gastrectomy with diagnosis of submucosal tumor of stomach. Metastatic liver tumors were developed 10 years and 10 months after total gastrectomy, and the diagnosis was metastatic GIST. He received IM 5 years and 9 months, and partial response was achieved. Right lobectomy and two partial resections were performed. C-KIT mutation analysis showed wild-type. IM was re-started, and the patient has lived 6 years and 8 months after hepatectomy without recurrence.

Case 2

A 62-year-old male underwent small bowel resection due to perforation of small intestine. The pathological diagnosis was GIST of small intestine origin. The patient did not receive adjuvant therapy, and 5 years and 5 months later peritoneal dissemination developed. Metastasectomy was performed and adjuvant IM was started. Acquired resistance to IM developed 4 years and 1 months later, and right hemicolectomy was performed. IM was re-started after surgery but discontinued due to side effect. 6 months after hemicolectomy, liver metastases and peritoneum dissemination developed and the patient underwent five of the partial resections of the liver. Complete resection could not be achieved due to peritoneum dissemination. C-KIT mutation analysis showed wild-type. Low-dose IM (200 mg) was started, but recurrence progressed. The patient died 5 years 5 months after first recurrence.

Case 3

A 43-year-old male was found to have GIST of small intestine origin, and underwent small bowel resection. Adjuvant IM was started. One year and 2 months after surgery, acquired resistance occurred and liver metastasis was developed. The patient underwent partial resection of the liver, and high-dose IM (600 mg) was started. However,

liver metastases developed again and the patient underwent posterior bisegmentectomy 2 years after first recurrence. C-KIT mutation analysis showed exon 9 mutation. Four months later, disease recurrence developed and the patient died 5 years and 1 month after first recurrence.

Case 4

A 46-year-old male with GIST of small intestine origin underwent small bowel resection. He did not receive IM, and liver metastasis and peritoneal dissemination developed 2 years and 8 months after first surgery. He underwent partial resection of the liver and metastasectomy. Adjuvant IM was started. 1 year and 11 months later, liver metastases developed again and the patient underwent second hepatectomy. C-KIT mutation analysis showed exon 9 mutation. The patient experienced recurrence after second hepatectomy, and died 7 years and 8 months after first recurrence.

Case 5

A 57-year-old male was diagnosed with leiomyosarcoma of the stomach and underwent total gastrectomy more than 20 years ago, the era before immunostainings, such as desmin, CD34, and c-KIT, were established. 6 years and 8 months later, the patient developed liver metastasis and underwent left hepatectomy. The diagnosis was liver metastasis of GIST, and c-KIT mutation analysis showed exon 11 mutation. The pathological review of the primary lesion was consistent with GIST (immunostaining not performed). The patient received adjuvant IM. Liver metastasis developed again and the patient underwent partial resection of the liver 2 years and 10 months after first hepatectomy. After second hepatectomy, recurrence has not developed, and the patient has lived 14 years and 10 months since first recurrence.

Case 6

A 67-year-old female underwent exploratory laparotomy due to bowel obstruction. GIST of mesentery origin was found, and the tumor was invaded to uterus. The patient underwent small bowel resection and extensive total hysterectomy. IM was started, but the treatment was discontinued due to non-compliance. Recurrence occurred in the liver and peritoneum 1 year and 2 months after first surgery. The patient underwent partial resection of the liver and metastasectomy, but could not achieve complete resection due to peritoneum dissemination. C-KIT mutation analysis showed exon 11 mutation. IM was started, and the patient has lived 10 years and 5 months after first recurrence, without disease progression.

Patient prognosis and associated risk factor

Clinical and pathological demographics are shown in Table 1. Survival after initial hepatectomy was significantly differed between primary tumor sites. Overall patient survival stratified by primary tumor site is shown in Fig. 1. Small intestine origin was associated with a worse prognosis ($P=0.02$). All patients whose primary tumor site was other than small intestine were alive with or without second metastasectomy. In contrast, all patients whose primary tumor sites were small intestine died despite complete resection.

Survival curves stratified by c-KIT mutations demonstrated no significant difference between the groups. Although not statistically significant, there was a trend toward better outcomes in patients with exon 11 mutations (Fig. 2).

Discussion

IM dramatically improved the prognosis of metastatic GIST, and has become the first-line treatment [2, 3]. However, a long-term follow-up study has shown that acquired resistance to IM may develop within 2 years, and treatment after acquired resistance represents a substantial clinical challenge [10].

Accordingly, the benefit of surgical resection for metastatic GIST is being re-evaluated.

In the present study, only one patient achieved partial response before hepatectomy, and other patients had acquired resistance or did not take IM. Among this population, small intestine origin was identified as a worse prognostic factor. Three patients died, and all had small intestine origin tumors. The remaining three patients who were alive after hepatectomy had stomach or mesentery origin tumors.

Fig. 1 Overall survival rate stratified by primary tumor site

Table 1 Clinical and pathological demographics of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	21	62	43	46	57	67
Sex	Male	Male	Male	Male	Male	Female
Primary tumor site	Stomach	Intestine	Intestine	Intestine	Stomach	Mesentery
Modified Fletcher classification	Unknown	High	High	High	Unknown	High
Time to DP	10 y 10 m	5 y 5 m	1 y 2 m	2 y 8 m	6 y 8 m	1 y 2 m
IM before hepatectomy	Yes	Yes	Yes	No	No	Yes
Disease control	PR	PD	PD	–	–	PD
IM after hepatectomy	Yes	Yes	Yes	Yes	Yes	Yes
c-KIT mutation	Wild	Wild	Exon 9	Exon 9	Exon 11	Exon 11
Ki-67 (%)	<1	9.5	8	13	26	<1
Prognosis	Alive	Death	Death	Death	Alive	Alive
Survival after recurrence	12 y 5 m	5 y 5 m	5 y 1 m	7 y 8 m	14 y 10 m	10 y 5 m

DP distant progression, IM imatinib mesylate, y years, m months, PR partial response, PD progressive disease

Fig. 2 Overall survival rate stratified by c-KIT mutation status

Some authors reported preoperative response to IM was strongly associated with improved outcomes, and those who achieved more than stable disease were good surgical candidates [4–7, 11–14]. Surgical indication for progressive disease is controversial. There are two forms of progressive disease: focal progression and general progression. Hasegawa reported surgical resection for focal progression might improve PFS when complete resection was performed [15]. On the other hand, surgical resection for general progression did not improve prognosis, because complete resection was not always feasible [13]. Therefore, surgical indication for acquired resistance should be focal progression cases, if complete resection is possible.

The other strategy is surgery before acquired resistance, because acquired resistance does occur in most of the cases. Some authors reported surgery before acquired resistance could achieve longer PFS and OS [4, 5, 14]. Park reported surgical resection achieved longer PFS and OS than IM alone in patients whose tumors were under control more than 6 months with IM (median PFS: 87.7 vs. 42.8%; median OS: not reached vs. 88.8 months) [14]. Best response to IM is achieved between 3.5 and 9 months [10], so surgical resection during this period could be effective treatment option.

There is no consensus for adjuvant IM after surgery for metastatic GIST. Because the efficacy of molecular targeted drugs, such as IM and sunitinib malate, depends on c-KIT mutation status, the analysis of c-KIT mutation allows the best treatment options to be selected for individual patients [8, 16–19]. Exon 9 mutation and wild-type could be candidates for sunitinib malate [18]. On the other hands, exon 11 mutation could be benefited from IM [16]. Although it is controversial whether IM for acquired resistance is effective, Sawaki reported rechallenge with IM improved OS in patients who failed IM and sunitinib [19]. Therefore, IM

might be effective even after surgery for acquired resistance cases. It is hard to determine the duration of adjuvant IM for metastatic GIST, and case accumulation is needed.

Based on these facts, future treatment direction against metastatic GIST could be preoperative IM for 3–9 months, while best response could be expected, and surgical resection if complete resection is feasible. And then, adjuvant therapy should be performed based on c-KIT mutation status.

Acquired resistance does occur: therefore, surgery may play an important role for metastatic GIST.

The results of the present study indicate patients with GIST of stomach or mesentery origin, either with wild-type c-KIT or exon 11 mutations or with disease controlled with IM may benefit from repeat surgical resection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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