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Original Article

Resection Combined with Imatinib Therapy for Liver Metastases of Gastrointestinal Stromal Tumors

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Abstract

Purpose. To evaluate the effectiveness of resecting liver metastases of gastrointestinal stromal tumors (GISTs), when performed in conjunction with imatinib treatment.

Methods. Forty-one patients with pathologically diagnosed GIST and liver metastases were randomly assigned to an operation group (neoadjuvant therapy + resection + adjuvant therapy with imatinib) or a nonoperation group (imatinib alone). Patients were monitored for up to 36 months, and survival was analyzed.

Results. We monitored 39 patients throughout the 36-month follow-up period, recording 1- and 3-year survival rates of 100% and 89.5% in the operation group and 85% and 60% in the nonoperation group, respectively. There was a significant difference in overall survival between the operation and nonoperation groups ($P = 0.03$). Furthermore, resection improved the survival of patients who responded poorly to 6 months of preoperative imatinib treatment, compared with that of their counterparts in the nonoperation group ($P = 0.04$).

Conclusion. These findings suggest that surgical intervention in combination with imatinib treatment is more effective than imatinib alone against GIST liver metastases, with minimal complications and side effects.

Key words Gastrointestinal stromal tumor · Surgery · Neoadjuvant therapy · Tyrosine kinase inhibitor · Imatinib

Introduction

Gastrointestinal stromal tumors (GISTs) constitute the most common sarcomas found in the gastrointestinal tract. Primary GISTs are generally resected,[1] but recurrent tumors develop in approximately 50% of cases, even after R_0 resection, the majority of which metastasize to the liver.[2] Unfortunately, the rate of objective antitumor response to traditional chemotherapy agents has been estimated as only 0%–4%.[3,4] Moreover, radiotherapy seems to have little effect on GISTs.[5]

Molecular targeted therapy, such as imatinib, is now regarded as primary treatment for GISTs. The mechanism of imatinib is derived from selective inhibition of the uncontrollably activated KIT receptor, tyrosine kinase, whereby imatinib blocks the kinase activity of KIT, arrests proliferation, and causes apoptosis of GIST cells. One of the original indications for the use of imatinib was unresectable and/or metastatic GISTs. However, tyrosine kinase inhibitors are not radical treatments but control tumor progress for a limited time. Some patients may develop secondary resistance to the medication over 1 or more years. So many researchers believe that we must evaluate the effects of combining surgical resection and molecular targeted therapy for GISTs, to increase the rates of complete surgical resection or preserve organ functions,[6] especially for liver metastases.[7,8] Thus, we studied the effects of neoadjuvant therapy + surgical resection + adjuvant therapy with imatinib (NSA) against GIST liver metastases, to investigate the hypothesis that this combination will provide results superior to those of imatinib alone. To test the hypothesis, we designed a clinical research study to compare the effects of NSA on patients with GIST liver metastases to those obtained using imatinib alone.

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Patients and Methods

Patients

To find out whether NSA is more effective than imatinib alone for patients with GIST liver metastases, 41 patients treated for GIST between January 2005 and December 2005 were enrolled in this study. The selection criteria were as follows. Patients were aged from 18 to 79 years old. They had undergone R_0 surgical resection of primary tumors before, established by immunohistochemical staining as c-kit (CD117) expression-positive and histologically diagnosed as GIST after the operation. They had recurrent tumors and liver metastases after resection of the primary tumor, meaning that they had at least one measurable metastatic liver tumor that had not been treated with radiotherapy or embolization, but no detectable extrahepatic tumors. For each patient, the proportion of liver tissues encroached by GIST was <50%, and the Child–Pugh classification of liver function was A, which indicated that the tumors were potentially resectable. Patients were not pregnant or breast-feeding, and they were free of serious underlying disorders, such as diabetes, chronic liver disease, chronic kidney disease, or active infection.

The trial was conducted in accordance with the guidelines for Good Clinical Practice and the provisions of the Declaration of Helsinki in 1995, as revised in Edinburgh 2000, and approved by the medical ethics committees of Sichuan University West China Hospital. Written informed consent was obtained from all patients before randomization.

Methods

The 41 patients were randomized into two groups using the random digit table method, assigning 20 to the operation group and 21 to the nonoperation group. The operation group received imatinib treatment for 6 months preoperatively, and it was continued for 2–4 weeks after surgical resection of GIST liver metastases. The surgical plan and extent of liver resection were decided according to individual conditions such as the position, size, and number of metastatic GISTs, and the tumor response to preoperative imatinib treatment. Surgical exploration consisted of inspection of the peritoneal cavity to exclude extrahepatic involvement, and histological examination of frozen sections for any suspicious lesions. Patients in the nonoperation group received imatinib alone. In both groups, the imatinib capsules were taken orally and daily after breakfast or lunch. To avoid interference from other substances, patients were not given medication that could affect the concentration of imatinib in blood during the medication period.

Prior to enrollment in the study, each patient had a baseline examination, including physical and neurological examinations, complete blood count, serum biochemistry workup, type-B ultrasound, abdomen-pelvic computed tomography (CT) scan, and chest radiograph. The number, location, size, and density of the tumors were recorded. During the study period, we evaluated quality of life, as well as cardiovascular, respiratory, digestive, urinary, and locomotor system function of each patient, monthly. At the same time, we also performed routine blood tests, serum biochemistry inspections, and type-B ultrasounds of the abdomen. Chest radiographs and abdomen-pelvic CT scans were performed every 3 months post treatment. Patients in the operation group also had chest radiographs and abdomen-pelvic CT scans done before and after surgery.

The primary trial outcome was overall survival, counted from the first dose of imatinib to the date of last follow-up examination or death. For patients with tumor progression, we gave therapeutic opinions based mainly on their progress and condition, to inform them and allow them to make voluntary choices. Reoperation was more beneficial for patients with limited tumor progress, whereas for patients with general tumor progress or unresectable lesions, escalating the imatinib dose to 600 mg/day was the preferred option. If the tumor response was poor or patients were intolerant of the imatinib dose escalation, a medication change to sunitinib was recommended.

Tumor response was based on CT images, and was evaluated by a radiologist and a surgeon. The criteria were considered with the combination of tumor size and tumor density as follows9: complete response, defined as the disappearance of all target tumors; partial response, defined as a decrease in tumor size >10% or a decrease in tumor density >15%; stable disease, defined as minor changes between partial response and progressive disease; and progressive disease, defined as increased tumor size >20% without any decrease in tumor density, or the appearance of new lesions not due to decreased tumor density. Complete response and partial response were regarded as good responses; the others were regarded as poor responses.

Statistical Analysis

All data were assessed for normality of distribution and equality of variance. Categorical data were compared using the chi-squared test. Rates of overall survival were estimated by the Kaplan–Meier method and compared by the log-rank test to evaluate the effects of surgical intervention for GIST liver metastases. Fixed-right censoring was used in the survival analysis. All data analysis was performed using the program SPSS 11.5 for

Windows (SPSS, Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

One patient from the operation group decided not to undergo surgery after treatment with imatinib, and one patient from the nonoperation group was ineligible because of his arbitrary decrement in imatinib dosage and discontinuous drug administration. To avoid differences in the distributions of survival times for the participating patients and the noncompleting ones, we did not adopt random censoring but kept only the 39 patients who completed the 36-month follow-up period. The baseline characteristics of the patients and their tumors were similar in the two groups (Table 1).

The follow-up finished in December 2008. During the study period, 12 patients died, all of tumor progression. In the operation group, no patients died in the first year, the survival rate after 3 years was 89.5%, and the mean survival time was 32.84 months. In the nonoperation group, the survival rates after 1 and 3 years were 85% and 60%, respectively, and the mean survival time was 24.55 months. The value of the log-rank test for the two different treatments was significant with a *P*-value of 0.03, showing that NSA yielded better survival than imatinib alone (Fig. 1).

After treatment with imatinib for 6 months, tumor response was evaluated based on CT findings, and the outcomes of good and poor responders were analyzed separately (Table 2). There were no differences in the overall survival rates of good responders between the two groups during the follow-up period (Fig. 2A), but a significant difference in the survival rates of poor responders was noted between the two groups (Fig. 2B). These results indicate that resection may help to prolong survival, especially for patients who respond poorly to imatinib.

All of the resected specimens of liver metastases were examined pathologically and definitively diagnosed as

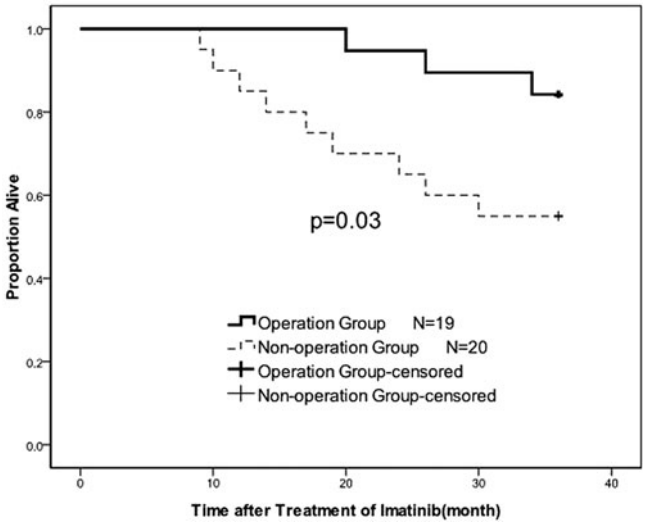

Fig. 1. Impact of surgical resection on gastrointestinal stromal tumor (GIST) liver metastases after imatinib treatment. A significant difference was observed in the overall survival rates of the operation and nonoperation groups ($P = 0.03$)

Table 2. Responses to imatinib therapy[a]

	Operation group ($n = 19$)	Nonoperation group ($n = 20$)
Complete response	0	2
Partial response	13	6
Stable disease	6	9
Progressive disease	0	3

[a]The operation group response was evaluated before surgery and the nonoperation group response was evaluated at the end of follow-up

Table 1. Patient and tumor characteristics

	Operation group ($n = 19$)	Nonoperation group ($n = 20$)
Age (years)	53 (31–68)	55 (29–73)
No. of males	10 (52.6%)	11 (55%)
No. of liver metastases		
Single	7 (36.8%)	8 (40%)
Multiple (2–4)	12 (61.2%)	12 (60%)
Site of original tumors		
Stomach	11 (57.9%)	10 (50%)
Small bowel	5 (26.3%)	6 (30%)
Large bowel	1 (5.3%)	2 (10%)
Peritoneal and pelvic cavity	2 (10.5%)	2 (10%)
Size of metastatic tumor (cm)	8.9 (3.2–12.1)	9.3 (4.5–13.0)
Interval between the first surgery and hepatic metastasis		
<12 months	3 (15.8%)	4 (20%)
12–24 months	9 (47.4%)	10 (50%)
>24 months	7 (36.8%)	6 (30%)

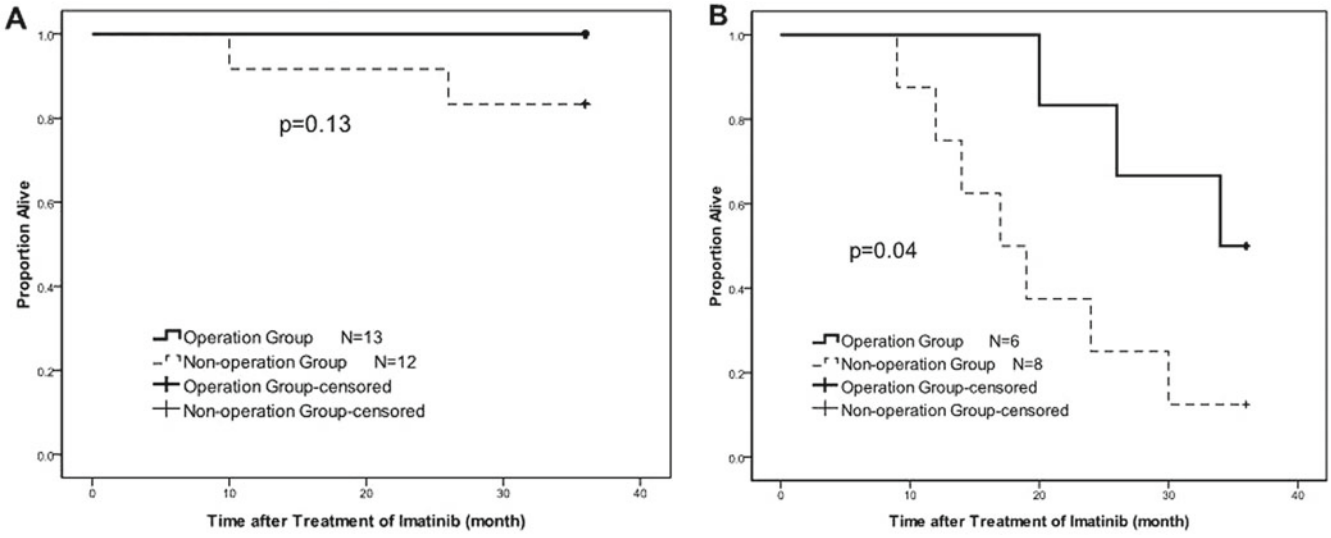

Fig. 2A,B. Impact of surgical resection on GIST liver metastases with differential responses to imatinib. **A** No difference was observed in overall survival rates between the operation and nonoperation groups of good responders ($P = 0.13$). **B** A significant difference was observed in overall survival rates between the operation and nonoperation groups of poor responders ($P = 0.04$)

Table 3. Pathological characteristics of resected specimens

	Good responders ($n = 13$)	Poor responders ($n = 6$)
Size of metastatic tumor		
<5 cm	4 (30.7%)	1 (16.7%)
5–10 cm	7 (53.8%)	4 (66.7%)
>10 cm	2 (15.4%)	1 (16.7%)
Mitotic count		
<5 per 50 HPFs	3 (23.1%)	1 (16.7%)
6–10 per 50 HPFs	5 (38.5%)	2 (33.3%)
>10 per 50 HPFs	5 (38.5%)	3 (50%)
Necrosis	2 (15.4%)	1 (16.7%)
CD117 (+)	13 (100%)	5 (83.3%)
C-KIT mutation		
Exon 11	5 (38.5%)	2 (33.3%)
Exon 9	1 (7.7%)	2 (33.3%)
Not detected	7 (53.8%)	1 (16.7%)

HPFs, high-power fields

GISTs. The rate of CD117 positivity was 94.7%, and gene exon mutation was detected in 10 specimens. The pathological characteristics of the resected specimens are shown in Table 3. Only one specimen from a good responder had a positive incisal margin with GIST cells; the others had negative incisal margins.

Table 4 lists the complications associated with surgery. Four patients (15.8%) suffered complications after the resection of liver metastases, but none needed reoperation to rectify those complications. All of the complications were rectified within 3 months. Table 5 shows the side effects of imatinib in the two groups. Side effects developed in 78.9% of the patients in the operation group and in 85% of those in the nonoperation group.

Table 4. Postoperative complications

Postoperative complications	Operation group ($n = 19$)
Hepatic insufficiency	1
Bleeding	1
Biliary fistula	1
Intra-abdominal infection	2
Ascites	3

All of the side effects were grade 1 or 2. For most patients, only mild edema and depigmentation were observed. We recorded no drug discontinuance or decrement due to severe side effects.

Table 5. Side effects of imatinib

Side effects of imatinib	Operation group (n = 19)	Nonoperation group (n = 20)
Total side effects	15	17
Anemia	2	2
Leucopenia	5	2
Thrombocytopenia	2	3
Edema	11	10
Pruritus	2	1
Diarrhea	4	6
Nausea and vomiting	5	6
Hand–foot skin syndrome	2	1
Depigmentation	13	15
Hepatic dysfunction	4	4
Myalgia	1	1

Discussion

The findings of our study provide evidence that NSA is more effective than imatinib alone against GIST liver metastases. NSA improved overall survival, especially of patients who exhibited poor responses to imatinib after 6 months of treatment. Moreover, surgical complications developed in 15.8% of patients who underwent resection. There were no differences in the number or severity of adverse events between the operation and nonoperation groups. This indicates that resection had little effect on the patients' tolerance to imatinib.

Prior to studies on neoadjuvant therapy, the effect of adjuvant treatment with imatinib after surgery had been demonstrated by several clinical research studies. In the American College of Surgeons Oncology Group (ACOSOG) Z9000 trial, 107 patients with GISTs received adjuvant therapy with imatinib (400 mg/day) for 1 year after their operation. During a median follow-up of 4 years, the 1-, 2-, and 3-year overall survival rates were 99%, 97%, and 97%, respectively, and the 1-, 2-, and 3-year recurrence-free survival rates were 94%, 73%, and 61%, respectively.[10] Similar results were observed in the study by Zhan.[11] In the randomized, double-blind phase III ACOSOG Z9001 trial, 644 patients received imatinib (400 mg/day) or a placebo for 1 year after complete resection of a primary GIST. The 1-year recurrence-free survival rates of the patients who received imatinib and those who received the placebo were 98% and 83%, respectively. These studies demonstrated that adjuvant therapy with imatinib decreased recurrence rates and improved prognoses.[12]

Adjuvant therapy entails R_0 or R_1 resection of GISTs, especially primary GISTs; however, for patients with metastatic or large GISTs, neoadjuvant therapy with imatinib may be more appropriate. Because multiple GIST liver metastases are common, complete resection of all metastatic lesions is difficult and often involves high risks associated with the operation and the sacrifice of adjacent normal liver tissue. Neoadjuvant therapy may shrink the tumor, rendering previously unresectable tumors resectable. A phase II trial by the Radiation Therapy Oncology Group (RTOG S-0132) on 30 patients with primary GISTs and 22 with recurrent metastatic GISTs revealed 2-year progression-free survival rates of 83% and 77%, and estimated overall survival rates of 93% and 91%, respectively, for the two diagnostic groups.[13] Other studies have also suggested that neoadjuvant therapy with imatinib may decrease tumor volume, to increase rates of complete surgical resection or preserve organ functions.[14,15] Ebihara et al.[6] reported a case of successful neoadjuvant therapy for a rectal GIST, which allowed preservation of anal function.

The optimal duration of neoadjuvant therapy with imatinib, despite its importance, remains unclear. The ideal timeframe should allow for a noticeable positive response to imatinib and should be associated with the lowest possible risk of secondary mutation or resistance. Because most of the positive response to the drug occurs within 6 months of administration and because secondary mutations may be acquired after 10 months of treatment, Gold and DeMatteo[16] suggested 6 months as a suitable time frame before surgery, and described the combination of neoadjuvant therapy and surgery as "a race against resistance." The results of the current study provide new evidence to support that 6 months of preoperative therapy with imatinib may be adequate to improve prognosis. In addition, the optimal dose of imatinib neoadjuvant treatment seems to be 400 mg/day, because several large clinical studies have failed to find differences in outcome between the initial 400 mg/day and higher doses.[17–19] Whether higher doses of imatinib and surgery would be more effective is unknown and warrants further research.

Although NSA is a desirable model of combining surgery and molecular targeted therapy, the core of the treatment is surgery. However, the optimal timing of surgery and the best operative methods are still issues of much debate. Some researchers believe it unneces-

sary to resect metastatic tumors hastily because they say that patients can coexist with metastatic GISTs for a period provided that effective imatinib therapy is maintained, stressing the importance of continuous imatinib treatment to achieve the best tumor response. However, "waiting for the largest response" usually means waiting for secondary mutations of GISTs and resistance to imatinib. Thus, combining the resection of GIST liver metastases and imatinib is becoming increasingly accepted by surgeons. There are two aspects to the surgery: First, complete resection of liver metastases is important, although the surgery itself is without radical significance because the R status may affect prognosis. As GIST liver metastases are usually associated with intratumoral necrosis or cystic lesions, incomplete resection may result in the rupture of tumors and intra-abdominal dissemination. Second, an appropriate excision range is necessary. We think that regular hepatectomy is the safest and most effective way of obtaining at least a 1-cm incisional margin that is negative for GIST cells because these patients rarely have complications with liver cirrhosis, and advanced techniques make it safe to resect up to 50%–70% of the functional liver. Surgical complications developed in 15.8% of our patients, which parallels the findings of Nunobe et al.[8] and Eisenberg et al.,[13] who also considered surgical resection of GIST liver metastases to be safe after neoadjuvant therapy with imatinib.

Our study shows the necessity of resecting GIST liver metastases after neoadjuvant therapy with imatinib, especially for poor responders. The pathological characteristics of the resected specimens indicate that tumor size, mitotic count, and necrosis were independent of tumor response, but that gene mutation sites and KIT mutation locations (exons) may affect it. Mutations in KIT were negative in one of the six poor responders, and exon 9 mutations were detected in two. The poor responses to normal doses of imatinib indicated some less common locations of mutation than exon 11. In this situation, tumors may be less sensitive to imatinib and surgery appears to be required.

The current study also shows that evaluating the response of GIST liver metastases to preoperative therapy with imatinib plays a key role in surgical planning. Not only should the location and size of tumors to be resected be taken into account, but also should the prognosis and effects of NSA. Historically, the classic criteria in tumor response evaluation are derived from the Response Evaluation Criteria in Solid Tumors (RECIST),[20] which claims that CT is the best available and most reproducible method for measuring tumor response. These criteria mainly emphasize the change in tumor size. Choi et al.[21] suggest that the RECIST criteria underestimate the tumor's response to imatinib. They propose that the modified criteria should note changes in tumor nodules, density, and tumor vascularization, in addition to changes in tumor size. Another impressive advance in evaluating GIST response is ^{18}FDG-positron emission tomography (FDG-PET). Because glucose transport proteins would increase with overactive KIT in GIST cells, several studies have indicated that FDG-PET may provide additional information about early tumor response.[22,23] However, this may be of little value in residual tumor assessment after surgery.[13]

In conclusion, we found that NSA with imatinib is more effective than imatinib alone against GIST liver metastases. Therefore, we recommend that surgical resection and molecular targeted therapy be combined, specifically to perform hepatic resection within 6 months of preoperative therapy with imatinib, and that imatinib should be continued after tumor resection, to optimize the prognosis of patients with GIST liver metastases.

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