Transcatheter arterial chemoembolization for gastrointestinal stromal tumors with liver metastases

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Abstract

AIM: To evaluate the efficacy and safety of transcatheter arterial chemoembolization (TACE) for gastrointestinal stromal tumor (GIST) with liver metastases after the failure of tyrosine kinase inhibitors (TKIs).

METHODS: Patients with histologically confirmed CD117-positive GIST with liver metastases who were resistant and/or intolerant to prior imatinib and/or sunitinib and who received TACE for at least one treatment cycle or only best supportive care and TKI reintroduction were eligible for the study. The patients were divided into two groups: those in TACE group received TACE treatment containing 5-20 mL iodized oil and 40-80 mg doxorubicin hydrochloride and TKI reintroduction or best supportive care, those in control group only received TKI reintroduction or best supportive care. The primary end-point was overall survival and the secondary end-points were, progression-free survival (PFS), response rates, and safety.

RESULTS: Sixty patients admitted between June 2008 and October 2011 were eligible for this study, including 22 in TACE group and 38 in control group. In the TACE group, 12 (54.5%) achieved liver partial response, 5 (22.7%) had stable disease, and 5 (22.7%) had liver progressive disease. Disease control rate of liver metastases was 77.3% in the TACE group and 39.5% in the control group. The median liver PFS in TACE group was 47.1 wk (95% CI: 23.9-70.3). The median PFS in TACE group was longer than in control group (30.0 wk, 95% CI: 20.1-39.9 vs 12.9 wk, 95% CI: 11.9-13.9) (P = 0.0001). The median overall survival in TACE group was also longer than in control group (68.5 wk, 95% CI: 57.4-79.6 vs 25.7 wk, 95% CI: 23.2-28.2) (P = 0.0001). TACE treatment significantly reduced the risk of death (hazard ratio: 0.109). Patients without extrahepatic metastases treated with TACE had significantly better prognosis. Most of the adverse events were of grade 1 or 2 and tolerable.

CONCLUSION: TACE is effective and well tolerated in GIST patients with liver metastases after TKI failure, and it may be an optional treatment for this disease.

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Key words: Gastrointestinal stromal tumor; Liver metastases; Transcatheter arterial chemoembolization; Tyrosine kinase inhibitor failure; Overall survival

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and account for about 2% of gastrointestinal tract tumors.[1,2] Tyrosine kinase inhibitors (TKIs) imatinib and sunitinib have demonstrated efficacy against GISTs, and are referred to as the first- and second-line therapeutic drugs.[3,4] However, resistance to such kind of TKIs remains a substantial problem. Around 4%-5% patients showed evidence of primary resistance and nearly half of the patients will experience secondary resistance within two years.[5,6] At present, there is still no standard treatment for metastatic GIST after imatinib and sunitinib failure. The National Comprehensive Cancer Network (NCCN) guideline (2010)[7] recommended considering reintroduction of a TKI for palliation of symptoms in patients with GIST progression despite prior imatinib and sunitinib.

Liver is the most common site of metastasis from GISTs, with a reported incidence of 55%-72% in patients with recurrence, and metastatic liver disease is a major determinant of patient survival.[8,9] Some studies[10,11] have shown favorable results of transcatheter arterial chemoembolization (TACE) for GIST with liver metastases. However, there are few studies about the role of TACE in the treatment of GIST patients after TKIs failure, moreover, there is no control study comparing TACE with best supportive care (BSC) and/or TKI reintroduction. Herein we retrospectively analyzed the survival benefit of TACE, BSC and/or TKI reintroduction in the patients with liver metastatic GISTs treated in the Peking University Cancer Hospital when resistance and/or intolerance occurred to imatinib and/or sunitinib.

MATERIALS AND METHODS

Study design

It is an open, retrospective, controlled study to evaluate the efficacy and safety of TACE in Chinese GIST patients with liver metastases after TKI treatment failure. Patients with histologically confirmed CD117-positive GIST with liver metastases who were resistant and/or intolerant to prior imatinib and/or sunitinib and who received TACE for at least one treatment cycle or only BSC and TKI reintroduction were eligible for the study. Following a retrospective review of the medical records of the patients seen at our hospital between June 2008 and October 2011, a total of 60 patients were found to meet the study criteria. There were 22 in TACE treatment group and 38 in BSC/TKI reintroduction group, which served as control group.

Patient characteristics: The following demographic and clinicopathological information was retrospectively obtained from the patient records: gender, age, extent of liver disease, and extrahepatic metastases.

Treatment: Data of TKI reintroduction and TACE treatment, including dose of TKI, interval between TKI and TACE, TACE procedure, and cycles of TACE, were collected.

Follow-up: Overall survival (OS) and progression-free survival (PFS) were acquired.

Study end-points

The primary end-point was OS and the secondary end-points were PFS, disease control rate (DCR) of liver metastases defined as a combination of complete response + partial response (PR) + stable disease (SD), and safety. Response rate was evaluated every 6 wk. OS was defined as the time from the first TACE or BSC/TKI reintroduction to the occurrence of death from any cause. The PFS was defined as the time from the first time of TACE or BSC/TKI reintroduction to the occurrence of disease progression or death from any cause. Disease control rate was assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical analysis

All the statistical analyses were performed using the SPSS 15.0 (SPSS Inc., Chicago, IL, United States). PFS and OS curves were constructed by the Kaplan-Meier method and compared with log-rank test. In order to adjust for confounding variables, we used Cox proportional hazards models to estimate the simultaneous effects of prognostic factors on survival. Frequency and percentage descriptions were used for categorical variables and the $\chi^2$ test was used to compare the incidence of different events. If the theoretical frequency was lower than 1, $F$ test was conducted. Continuous variables were expressed as mean ± SD and mean differences between two groups were compared using Student’s $t$ test.

RESULTS

Patient characteristics

There were 45 males and 15 females with a median age of 55.0 years (95% CI: 51.8-58.2). All the patients at registration were assessed to have the Eastern Cooperative Oncology Group (ECOG) performance status grade 0-2 and had received imatinib treatment. Among them, 35 took sunitinib after imatinib failure prior to TACE or BSC/TKI introduction treatment. Thirty-four (56.7%) had liver metastases and the others had extrahepatic metastases. Clinical features of the patients in the two groups are shown in Table 1.

In TACE group, 15 (68.2%) had an extent of liver involvement within 50%, 6 (27.3%) within 50%-70%,

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Table 1 Clinicopathologic features of the patients

| Clinicopathologic features | TACE n = 22 (%) | Control n = 38 (%) | Statistical test | P value |
|---------------------------|----------------|-----------------|-----------------|--------|
| Sex                       |                |                 |                 |        |
| Male                      | 16 (72.7)      | 29 (76.3)       | $\chi^2 = 0.310$ | 0.578  |
| Female                    | 6 (27.3)       | 9 (23.7)        |                 |        |
| Age (yr)                  | 53.0 (49.5-59.6) | 55.0 (48.0-62.0) | $U = 5.000$     | 0.279  |
| ECOG PS                   |                |                 |                 |        |
| 0-1                       | 16 (72.7)      | 20 (52.6)       | $\chi^2 = 2.344$ | 0.126  |
| 2                         | 6 (27.3)       | 18 (47.4)       |                 |        |
| Primary location          |                |                 |                 |        |
| Stomach                   | 9 (40.9)       | 15 (39.5)       | $\chi^2 = 0.012$ | 0.994  |
| Small intestinal          | 9 (40.9)       | 16 (42.1)       |                 |        |
| Other                     | 4 (18.2)       | 7 (18.4)        |                 |        |
| Number of liver lesions   |                |                 | $\chi^2 = 1.805$ | 0.406  |
| 1                         | 8 (36.4)       | 8 (21.1)        |                 |        |
| 2-5                       | 9 (40.9)       | 20 (52.6)       |                 |        |
| > 5                       | 5 (22.7)       | 10 (26.3)       |                 |        |
| Extrahepatic metastases   |                |                 | $\chi^2 = 0.083$ | 0.773  |
| Yes                       | 9 (40.9)       | 17 (44.7)       |                 |        |
| No                        | 13 (59.1)      | 21 (55.3)       |                 |        |
| Sunitinib second-line therapy before TACE |                |                 | $\chi^2 = 0.992$ | 0.319  |
| Yes                       | 11 (50.0)      | 24 (63.2)       |                 |        |
| No                        | 11 (50.0)      | 14 (36.8)       |                 |        |
| TKI reintroduction         |                |                 | $\chi^2 = 1.778$ | 0.182  |
| Yes                       | 10 (45.5)      | 24 (63.2)       |                 |        |
| No                        | 12 (54.5)      | 14 (36.8)       |                 |        |

TACE: Transcatheter arterial chemoembolization; ECOG PS: The Eastern Cooperative Oncology Group performance status; TKI: Tyrosine kinase inhibitors.

and 1 more than 70%. Eight patients (36.4%) had only 1 liver metastasis, 9 (40.9%) had 2-5 liver metastases, and the others had more than 5. The mean TACE treatment cycles received by all the patients in TACE group was 2.64, with 6 (27.3%) receiving only one TACE, and 16 (72.7%) received more than one TACE. Fifteen patients (68.2%) showed a good blood supply of liver metastases.

Treatment in TACE group

TACE protocol: Eligibility criteria for TACE included well-preserved hepatic and renal function, the Child-Pugh classification within A and B, adequate hematologic function, and ECOG performance status of 0-2. Patients with high-risk factors, such as portal vein occlusion, no hepatopetal flow, massive ascites, encephalopathy, or active cardiac failure, were excluded.

Local anesthesia was obtained with 1% lidocaine. After the introduction of a selectave catheter through the femoral artery using the Seldinger technique, the localization of the hepatic arteries was checked with celiac and mesenteric arteriography. This was performed to define vascular anatomy. Next, indirect portography was performed to outline the portal circulation in the venous phase. A 5 French catheter was placed in the celiac trunk to identify the hepatic artery. Depending on the size, localization, and arterial supply to the tumor, a micro-catheter was advanced further into the segmental feeding arteries to perform embolization. An emulsion containing 5-20 mL iodized oil and 40-80 mg doxorubicin hydrochloride was used according to the tumor size. Additional embolization was performed using 1-2 mm diameter gelated sponge particles according to the status of blood supply. The ideal embolization end-point is the stasis of flow in tumor-feeding branches. Follow-up abdominal imaging (computed tomography) was generally performed two months after the first embolization. The follow-up images were assessed by two radiologists (Cao K and Cui Y) and compared with the baseline images to assess response.

TKI reintroduction: Ten patients received TKI reintroduction during the intermittent period of TACE. Among them, 6 patients took imatinib 400 mg/d and 4 patients took sunitinib 37.5 mg/d. The interval between TKI therapy and TACE was 2 wk.

Treatment in control group

All the patients in control group had GIST resistant to imatinib and 35 had tumor resistant to sunitinib. Among them, 9 patients received imatinib 400 mg/d and 15 received sunitinib 37.5 mg/d reintroduction, and the others only received best supportive care. Efficacy was evaluated every 6-8 wk according to the RECIST criteria.

Response rate: All the patients had measurable metastatic disease according to the RECIST criteria and tumor assessment was performed at least once. In TACE group, 12 (54.5%) achieved liver PR, 5 (22.7%) had SD, and 5 (22.7%) showed liver disease progression (PD) after TACE treatment. The DCR of liver metastases was 77.3%. In addition, 8 patients had PD when all the lesions were evaluated, and the DCR of all the lesions was 63.6%. In the control group, 12 patients receiving TKI reintroduction and 3 patients receiving BSC had SD, and the others had PD. The DCR in the control group was 39.5%.

PFS: As of May 2012, 19 (86.0%) patients in TACE group had liver metastasis progression. The median liver PFS of all 22 patients was 47.1 wk (95% CI: 23.9-70.3). In control group, all the patients had tumor progression. The median PFS in TACE group was longer than in control group (30.0 wk, 95% CI: 20.1-39.9 vs 12.9 wk, 95% CI: 11.9-13.9) ($P = 0.0001$, Figure 1A).

OS: As of May 2012, 4 patients in TACE group and 2 patients in control group were alive, and deaths occurred because of tumor progression. The median OS in TACE group was longer than in control group (68.5 wk 95% CI: 57.4-79.6 vs 25.7 wk 95% CI: 23.2-28.2) ($P = 0.0001$, Figure 1B). TACE significantly reduced the risk of death in GIST patients with liver metastases according to the Cox proportional hazards regression model [hazard ratio (HR): 0.109; 95% CI: 0.044-0.271].
Univariate and multivariate analysis

Results of the univariate and multivariate analysis are summarized in Table 2. The results showed the P value of number of liver metastases is 0.086. The patients without extrahepatic metastases and the patients treated with TACE were the two factors significantly associated with good survival. The two factors led to a reduction of death risk by 53.7% (HR: 0.463, \( P = 0.007 \)) and 58.5% (HR: 0.415, \( P = 0.005 \)), respectively.

In TACE group, univariate and multivariate analysis showed that absence of extrahepatic metastases, more than one session of TACE, and DCR of more than 3 mo after TACE were significantly associated with a good survival (\( P = 0.006, P = 0.02, P = 0.012 \)).

Adverse events

Most patients in TACE group developed post-embolization complications, which included abnormal liver function, abdominal pain, fever and nausea. The incidence of fever, alanine aminotransferase increase and nausea in TACE group was higher than in control group (\( P < 0.05 \)). However, the majority of adverse events were of grade 1-2, and in most cases, these symptoms were effectively resolved with supportive measures. No patient died within 1 mo after TACE. Other adverse events included anemia, neutropenia, thrombocytopenia, ascites, pleural effusion and hemorrhage (Table 3). No one discontinued treatment because of adverse events.

**DISCUSSION**

There is still no standard treatment for the GIST patients after imatinib and sunitinib failure. TKI reintroduction, BSC or drugs in clinical trial are recommended for these patients. Some studies\[15-19\] reported that the novel TKIs had potential activity against metastatic GIST, but the efficacy remains to be validated in prospective randomized controlled trials. Liver is the most common metastatic site of GIST and some patients even have only liver metastases other than other diseases till death. Resection of liver metastases has improved the overall survival\[20-22\], again the efficacy of resection should be further confirmed by prospective clinical trials. Some retrospective studies\[11-14\] showed that TACE may be potentially effective for GIST resistant to TKI. In this study, the patients with liver metastatic GIST receiving TACE after imatinib and/or sunitinib failure gained better PFS and OS than the patients receiving TKI reintroduction or BSC. In the sunitinib phase III trial\[23\], the median time to progression of the patients receiving placebo was only 6.4 wk. The results demonstrated that TACE may benefit the patients with liver metastases.

In TACE group, 68.2% patients had good blood

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**Table 2 Univariate analysis by each variable**

| Variable                      | \( n \) | OS (wk) | \( P \) value |
|-------------------------------|--------|---------|---------------|
| Gender                        |        |         |               |
| Male                          | 45     | 34.3    | 0.133         |
| Female                        | 15     | 25.7    |               |
| Primary tumor location        |        |         |               |
| Stomach                       | 24     | 25.7    | 0.825         |
| Intestine                     | 25     | 34.3    |               |
| Others                        | 11     | 30.0    |               |
| ECOG PS                       |        |         |               |
| 0-1                           | 36     | 35.8    | 0.102         |
| 2                             | 24     | 24.5    |               |
| Number of liver metastases   |        |         |               |
| 1                             | 16     | 42.9    | 0.079         |
| 2-5                           | 29     | 25.7    |               |
| > 5                           | 15     | 38.6    |               |
| Extrahepatic metastases      |        |         |               |
| Yes                           | 26     | 25.7    | 0.005         |
| No                            | 34     | 42.9    |               |
| TKI reintroduction            |        |         |               |
| Yes                           | 34     | 30.0    | 0.657         |
| No                            | 26     | 30.0    |               |
| TACE treatment                |        |         |               |
| Yes                           | 32     | 68.5    | 0.0001        |
| No                            | 38     | 25.7    |               |

OS: Overall survival; ECOG PS: The Eastern Cooperative Oncology Group performance status; TKI: Tyrosine kinase inhibitors; TACE: Transcatheter arterial chemoembolization.
supply of liver metastases. Some suspensions such as iodized oil (lipiodol) can occlude small tumor vessels and cause obstruction in the vascular bed of liver metastases. Unresectable or metastatic GIST resists the conventional cytotoxic chemotherapy, so cytotoxic drugs are not recommended in TACE. Further to an earlier report which showed that doxorubicin had slight efficacy in metastatic GIST, it has been reported recently that the chemo-embolization with doxorubicin elusion with the iodized oil demonstrated a potential efficacy.

Lipiodol and microspheres concentrate and prolong the retention of the chemotherapeutic agent (doxorubicin) in the tumor.

The results of this study showed that TACE significantly reduced death risk by 89.1%. In the subgroup analysis, DCR of more than 3 mo after TACE was correlated to good survival, indicating the benefit of TACE with regard to the overall survival. In the univariate and multivariate analysis, absence of extrahepatic metastases and TACE treatment were the independent prognostic factors. The similar results were seen in subgroup analysis in TACE group. These results showed that the patients without extrahepatic metastases can enjoy a longer survival after TACE. At the same time, a single session of TACE may not be adequate enough to control liver metastases. The results were consistent with the earlier report. However, bias of patient selection may exist in this retrospective study. More prospective trials are expected to confirm the efficacy of TACE in this group of patients. In this study, all cases enrolled had advanced GIST with relatively larger liver lesions after the TKI failure. TACE still yielded a good control rate in this study. All cases enrolled had advanced GIST with relatively larger liver lesions after the TKI failure. TACE still yielded a good control rate in this study. More prospective trials are expected to confirm the efficacy of TACE in this group of patients.

NCCN guideline recommended considering reintroduction of a TKI for palliation of symptoms in patients with GIST progression despite prior imatinib and sunitinib. Does TKI reintroduction combining with TACE improve PFS and OS of GIST with liver metastases, especially for the patients with extrahepatic metastases? In this study it seemed that the patients receiving combined TACE and TKI reintroduction had longer overall survival than those receiving TACE alone, but there was no statistical significance ($P = 0.638$). This may be attributed to the small case number in this study. However, TKI re-introduction did not increase the incidence of complication during TACE treatment. The interval time of 2 wk between TKI and TACE is appropriate. For the patients without extrahepatic metastases, the combined TACE and TKI reintroduction may be an optional method of treatment.

Many patients in TACE group suffered from post-embolization complications, such as abdominal pain, fever and nausea. Most of them were of grade 1 or 2, and 22.7% patients were of grade 3. But all the adverse events were ameliorated within 1-2 wk with supportive measures. No adverse events out of expectation happened and no one discontinued treatment because of severe adverse events. The combined TACE and TKI reintroduction was well tolerated in the majority of the patients.

In summary, TACE may be an optional treatment for GIST with liver metastases after TKI failure. TACE can better benefit the patients without extrahepatic metastases.

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**COMMENTS**

**Background**

There is still no standard treatment for metastatic gastrointestinal stromal tumor (GIST) after imatinib and sunitinib failure. Liver is the most common site of metastasis from GISTs and liver metastasis is one of the major causes of death in these patients. The authors evaluated the efficacy and safety of transcatheter arterial chemoembolization (TACE) in GIST with liver metastases after the failure of tyrosine kinase inhibitors.

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**Table 3  Adverse events in the two groups**

| Adverse events       | All grades (%) | Grade 3-4 (%) |
|----------------------|----------------|---------------|
|                      | TACE group ($n = 22$) | Control group ($n = 38$) | P value | TACE group ($n = 22$) | Control group ($n = 38$) | P value |
| Fever                | 20 (90.9) | 5 (13.2) | 0.0001 | 2 (9.1) | 0 (0) | 0.061 |
| Fatigue              | 16 (72.7) | 28 (73.7) | 0.936 | 5 (22.7) | 8 (21.1) | NA |
| Abnormal ALT         | 16 (72.7) | 6 (15.8) | 0.0001 | 5 (22.7) | 0 (0) | 0.005 |
| Nausea               | 14 (63.6) | 14 (36.8) | 0.045 | 1 (4.5) | 0 (0) | 0.367 |
| Ascites              | 5 (22.7) | 10 (26.3) | 0.757 | 0 (0) | 0 (0) | NA |
| Diarrhoea            | 4 (18.2) | 5 (13.2) | 0.712 | 0 (0) | 0 (0) | NA |
| Hemorrhage           | 3 (6.3) | 4 (10.5) | 0.780 | 1 (4.5) | 2 (5.3) | 1.000 |
| Neutropenia          | 12 (54.5) | 16 (42.1) | 0.352 | 3 (12.6) | 3 (7.9) | 0.699 |
| Anemia               | 7 (31.8) | 24 (63.2) | 0.019 | 3 (12.6) | 6 (15.8) | 1.000 |
| Thrombocytopenia     | 7 (31.8) | 10 (26.3) | 0.649 | 2 (10.5) | 1 (2.6) | 0.548 |

TACE: Transcatheter arterial chemoembolization; ALT: Alanine aminotransferase; NA: Not applicable.
Research frontiers
There are few studies about the role of TACE in the treatment of GIST patients after tyrosine kinase inhibitors (TKIs) failure, moreover, there is no control study comparing TACE with best supportive care (BSC) and/or TKI reintroduction.

Innovations and breakthroughs
This study is the first controlled report to evaluate the therapeutic effect of TACE combining with BSC and/or TKI reintroduction in GISTs with liver metastases after TKI failure. The results of the paper showed that TACE improved progression-free survival and overall survival of GIST patients with liver metastases after TKI failure as compared with those receiving only BSC and/or TKI reintroduction.

Applications
This study provided some evidences that TACE may be an optional treatment for GIST with liver metastases after TKI failure. TACE can better benefit the patients without extrahepatic metastases.

Terminology
GIST is the most common mesenchymal tumor of the gastrointestinal tract and TKI is the standard treatment for metastases GIST. TACE is the abbreviation of transcatheter arterial chemoembolization. TACE is the use of vascular embolizing material combined with cytotoxic drugs to induce tumor ischemic necrosis and prolonged drug transit time, and often used in treatment of hepatocellular carcinoma.

Peer review
This is a nice review of a unique series of patients with metastatic GIST. The authors should specify what the chemotherapy in the TACE procedure actually is. It appears only to be lipid.

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