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BRIEF ARTICLE

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.

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[3-5]. 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[4,6,7]. At present, there is still no standard treatment for metastatic GIST after imatinib and sunitinib failure. The National Comprehensive Cancer Network (NCCN) guideline (2010)[8] 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[9,10]. Some studies[11-14] 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 restrospective 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 χ^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%,

Table 1 Clinicopathologic features of the patients

Clinicopathologic features	TACE *n* = 22 (%)	Control *n* = 38 (%)	Statistical test	*P* value
Sex			$\chi^2 = 0.310$	0.578
Male	16 (72.7)	29 (76.3)		
Female	6 (27.3)	9 (23.7)		
Age (yr)	53.0 (49.3-59.6)	55.0 (48.0-62.0)	$U = 5.000$	0.279
ECOG PS			$\chi^2 = 2.344$	0.126
0-1	16 (72.7)	20 (52.6)		
2	6 (27.3)	18 (47.4)		
Primary location			$\chi^2 = 0.012$	0.994
Stomach	9 (40.9)	15 (39.5)		
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 selective 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, location, 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].

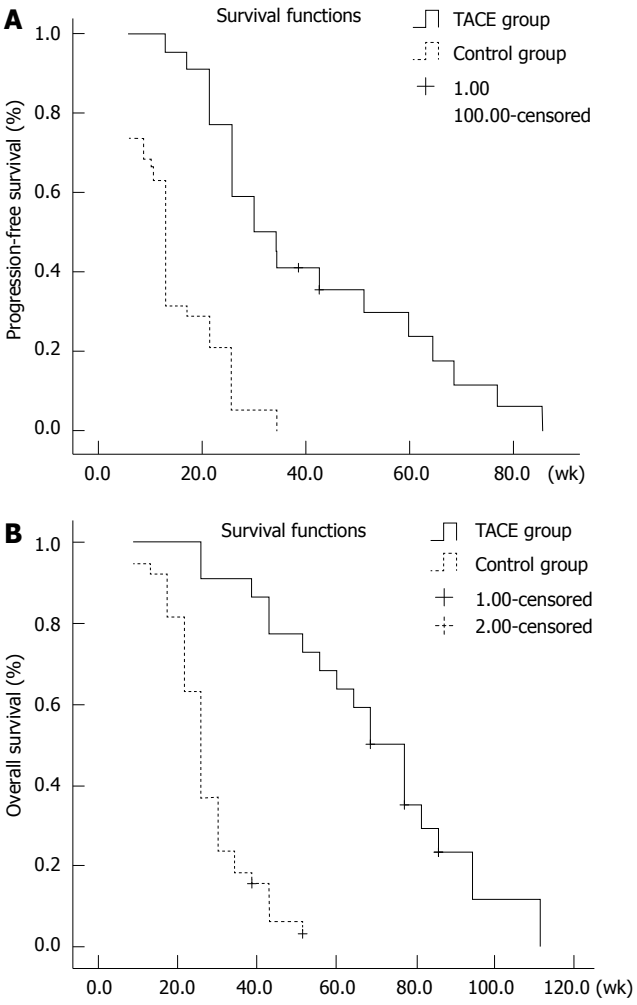

Figure 1 The median progression-free survival (A) and overall survival (B) were longer in transcatheter arterial chemoembolization group than in control group (*P* = 0.0001). TACE: Transcatheter arterial chemoembolization.

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.

Table 2 Univariate analysis by each variable

Variable	*n*	OS (wk)	*P* value
Gender			0.133
Male	45	34.3	
Female	15	25.7	
Primary tumor location			0.825
Stomach	24	25.7	
Intestine	25	34.3	
Others	11	30.0	
ECOG PS			0.102
0-1	36	35.8	
2	24	24.5	
Number of liver metastases			0.079
1	16	42.9	
2-5	29	25.7	
> 5	15	38.6	
Extrahepatic metastases			0.005
Yes	26	25.7	
No	34	42.9	
TKI reintroduction			0.657
Yes	34	30.0	
No	26	30.0	
TACE treatment			0.0001
Yes	22	68.5	
No	38	25.7	

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

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

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
Fatigure	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
Diarhoea	4 (18.2)	5 (13.2)	0.712	0 (0)	0 (0)	NA
Hemorrhage	3 (8.3)	4 (10.5)	0.700	1 (4.5)	2 (5.3)	1.000
Neutropenia	12 (54.5)	16 (42.1)	0.352	3 (12.6)	3 (7.9)	0.659
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.

supply of liver metastases. Some suspensions such as iodizedoil (lipiodol) can occlude small tumor vessels and cause obstruction in the vascular bed of liver metastases. Unresectable or metastatic GIST resists the conventional cyto-toxic chemotherapy[9,24,25], so cyto-toxic drugs are not recommended in TACE. Further to a earlier report[24] 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[11-14]. Lipiodol and microspheres concentrate and prolong the retention of the chemotherapeutic agent (doxorubicin) in the tumor[26].

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 to the earlier report[11]. However, bias of the 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 group of patients. Whether TACE procedure should be recommended earlier even before TKI failure warrants future studies.

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 reintroduction 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.

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.

REFERENCES

1 **Joensuu H**, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. *Lancet Oncol* 2002; **3**: 655-664

2 **Goettsch WG**, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. *Eur J Cancer* 2005; **41**: 2868-2872

3 **van Oosterom AT**, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, Martens M, Webb A, Sciot R, Van Glabbeke M, Silberman S, Nielsen OS. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; **358**: 1421-1423

4 **Demetri GD**, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347**: 472-480

5 **Demetri GD**, Huang X, Garrett CR, Schöffski P, Blackstein ME, Shah MH, Verweij J, Tassell V, Baum CM, Casali PG. Novel statistical analysis of long-term survival to account for crossover in a phase III trial of sunitinib (SU) vs placebo (PL) in advanced GIST after imatinib (IM) failure. *J Clin Oncol* 2008; **26** (Suppl): abstr 10524

6 **Verweij J**, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R, Judson I. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; **364**: 1127-1134

7 **Blanke CD**, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, Corless CL, Fletcher CD, Roberts PJ, Heinz D, Wehre E, Nikolova Z, Joensuu H. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008; **26**: 620-625

8 **National Comprehensive Cancer Network**. NCCN clinical practice guidelines in oncology: Soft tissue sarcoma v.2.2010

9 **DeMatteo RP**, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51-58

10 **Bayraktar UD**, Bayraktar S, Rocha-Lima CM. Molecular basis and management of gastrointestinal stromal tumors. *World J Gastroenterol* 2010; **16**: 2726-2734

11 **Kobayashi K**, Gupta S, Trent JC, Vauthey JN, Krishnamurthy S, Ensor J, Ahrar K, Wallace MJ, Madoff DC, Murthy R, McRae SE, Hicks ME. Hepatic artery chemoembolization for 110 gastrointestinal stromal tumors: response, survival, and prognostic factors. *Cancer* 2006; **107**: 2833-2841

12 **Maluccio MA**, Covey AM, Schubert J, Brody LA, Sofocleous CT, Getrajdman GI, DeMatteo R, Brown KT. Treatment of metastatic sarcoma to the liver with bland embolization. *Cancer* 2006; **107**: 1617-1623

13 **Kobayashi K**, Szklaruk J, Trent JC, Ensor J, Ahrar K, Wallace MJ, Madoff DC, Murthy R, Hicks ME, Gupta S. Hepatic arterial embolization and chemoembolization for imatinib-resistant gastrointestinal stromal tumors. *Am J Clin Oncol* 2009; **32**: 574-581

14 **Rajan DK**, Soulen MC, Clark TW, Baum RA, Haskal ZJ, Shlansky-Goldberg RD, Freiman DB. Sarcomas metastatic to the liver: response and survival after cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol chemoembolization. *J Vasc Interv Radiol* 2001; **12**: 187-193

15 **Gelderblom H J**, Montemurro M, Schütte J, Rutkowski P, Hartmann J T, Bui B, Pariente A, Leyvraz S, Blay J. Sorafenib fourth-line treatment in imatinib, sunitinib, and nilotinib resistant metastatic GIST: A retrospective analysis. *Gastrointestinal Cancers Symposium* 2009: abstr 51

16 **George S,** von Mehren M, Heinrich MC, Wang Q, Corless CL, Butrynski JE, Morgan JA, Wagner AJ, Choy E, Tap WD, Manola J, Yap JT, Van Den Abbeele AD, Solomon S, Fletcher JA, Demetri GD. A multicenter phase II study of regorafenib in patients (pts) with advanced gastrointestinal stromal tumor (GIST), after therapy with imatinib (IM) and sunitinib (SU). 2011 ASCO Annual Meeting. *J Clin Oncol* 2011; **29** (Suppl): abstr 10007

17 **Trent JC**, Wathen K, von Mehren M, Samuels BL, Staddon AP, Choy E, Butrynski JE, Chugh R, Chow WA, Rushing DA, Forscher CA, Baker LH, Schuetze S. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). 2011 ASCO Annual Meeting. *J Clin Oncol* 2011; **29** (Suppl): abstr 10006

18 **Demetri GD,** MC Heinrich, Chmielowski B, Morgan JA, George S, Bradley R, Blackman RK, Teofilovici F, Fletcher JA, Tap WD, von Mehren M. An open-label phase II study of the Hsp90 inhibitor ganetespib (STA-9090) in patients (pts) with metastatic and/or unresectable GIST. 2011 ASCO Annual Meeting, *J Clin Oncol* 2011; **29** (Suppl): abstr 10011

19 **Dumez H,** Reichard P, Blay JY, Schöffski P, Morgan JA, Ray-Coquard IL, Hollaender N, Jappe A, Demetri GD. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients (pts) with imatinib-resistant gastrointestinal stromal tumors (GIST). 2008 ASCO Annual Meeting. *J Clin Oncol* 2008; **26** (Suppl): abstr 10519

20 **Turley RS**, Peng PD, Reddy SK, Barbas AS, Geller DA, Marsh JW, Tsung A, Pawlik TM, Clary BM. Hepatic resection for metastatic gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Cancer* 2012; **118**: 3571-3578

21 **Raut CP**, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnolli MM. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006; **24**: 2325-2331

22 **Nowain A**, Bhakta H, Pais S, Kanel G, Verma S. Isolated hepatic metastasis from a gastrointestinal stromal tumor (GIST) 17 years after initial resection: need for long-term surveil-

lance. *J Clin Gastroenterol* 2005; **39**: 925

23 **Demetri GD**, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368**: 1329-1338

24 **Trent JC**, Beach J, Burgess MA, Papadopolous N, Chen LL, Benjamin RS, Patel SR. A two-arm phase II study of temozolomide in patients with advanced gastrointestinal stromal tumors and other soft tissue sarcomas. *Cancer* 2003; **98**: 2693-2699

25 **Edmonson JH**, Marks RS, Buckner JC, Mahoney MR. Contrast of response to dacarbazine, mitomycin, doxorubicin, and cisplatin (DMAP) plus GM-CSF between patients with advanced malignant gastrointestinal stromal tumors and patients with other advanced leiomyosarcomas. *Cancer Invest* 2002; **20**: 605-612

26 **Tellez C**, Benson AB, Lyster MT, Talamonti M, Shaw J, Braun MA, Nemcek AA, Vogelzang RL. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. *Cancer* 1998; **82**: 1250-1259

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