

ORIGINAL ARTICLE

Metronomic S-1 chemotherapy plus transcatheter arterial chemoembolization (TACE): a promising treatment of hepatocellular carcinoma refractory to TACE

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Summary

Purpose: To assess the efficacy and safety of metronomic S-1 chemotherapy combination with transcatheter arterial chemoembolization (TACE) for the treatment of Barcelona Clinic Liver Cancer (BCLC) Stage B hepatocellular carcinoma (HCC) refractory to TACE.

Methods: Twenty six patients met the eligibility criteria and were enrolled. TACE was performed on day 1, and metronomic S-1 chemotherapy on days 2-15. Tumor assessment was performed one month later. The primary endpoints were time to progression (TTP) and adverse events (AE).

Results: Twenty six patients in total received 176 TACE interventions. There were 101 TACE interventions in 15 patients of metronomic S-1 chemotherapy plus TACE (TS) and 75 in 11 patients of TACE monotherapy (TM). Fifteen TS patients received a total of 55 cycles of treatment with S-1, with a median of 4 cycles (range 2-6). The total dose of S-1 was 6165 mg per day in 15 patients (average 120 mg,

range 100-125). Median TTP and overall survival (OS) of TS group were 6 months (95% CI, 4.7-7.3) and 17 months (95% CI, 15.6-18.4), respectively, while for the TM group were 4 months (95% CI, 2.4-5.6) and 15 months (95% CI, 9.2-20.8), respectively. Though there were higher tumor response rate (RR) and disease control rates (DCRs) in patients with TS, no significant differences were detected. Both treatment approaches were tolerable with low grade AE.

Conclusions: In the present study, metronomic S-1 chemotherapy plus TACE in the present study was tolerable and associated with a better but not statistically significant TTP, RR and OS. It showed that metronomic S-1 chemotherapy plus TACE may be a promising treatment of BCLC Stage B HCC refractory to TACE.

Key words: hepatocellular carcinoma, metronomic chemotherapy, S-1, transcatheter arterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent cancers worldwide. HCC ranks sixth in prevalence and third in mortality among malignant tumors [1]. The international recommendations on the management of HCC, presented in 2001 [2], adopted by the American Association for the Study of Liver Diseases (AASLD) in 2005 [3],

and recently updated by the European Association for the Study of Liver (EASL) [4,5], suggest TACE as the standard of care for patients with BCLC stage B HCC. Several randomized controlled trials (RCT) [6,7] have demonstrated that TACE improves OS when compared with best supportive care. In clinical practice TACE alone or combined with ra-

diotherapy [8] or ablation [9] was widely used). After refractoriness to TACE, however, there are no standard guidelines recommended for BCLC Stage B HCC.

Conventional chemotherapy often implicates pulsatile administration schedule for the treatment of patient using maximum tolerated dose of cytotoxic drug. The prolonged break between two therapy cycles not only allows recovery from toxicity, but also provides an opportunity for the tumor to recover [10]. On the contrary, metronomic chemotherapy is administered at frequent intervals using nontoxic or low-toxic doses with no prolonged break.

Based on its potent inhibition of dihydropyrimidine dehydrogenase (DPD), S-1 is expected to be more active than other flouropyrimidines against HCC with DPD activity when administered metronomically. China is a developing country, and S-1 is covered by Chinese medical insurance system. Recently, some studies have confirmed the efficacy of S-1 in HCC. In the study of Furuse et al., S-1 was shown to have an acceptable toxicity profile and promising antitumor activity in HCC [11]. In addition, in the study of Kim et al., S-1 and platinum combination chemotherapy had favorable efficacy and tolerability in advanced HCC [12].

The main aim of our study was to assess the efficacy and safety of TS therapy for the treatment of BCLC Stage B HCC refractory to TACE.

Methods

Patients

All patients referred to our tertiary hospital with the diagnosis of BCLC Stage B HCC between August 2012 and April 2015 and with refractoriness to TACE were included in this retrospective study. Patients were divided into two groups: the metronomic S-1 chemotherapy plus TACE (TS) group and TACE monotherapy (TM) group. The flow diagram of the patient selection procedure is described in Figure 1. Eligible patients had received only TACE therapy. Further inclusion criteria were as follows: age ≥ 18 years, life expectancy ≥ 3 months, Child-Pugh (CP) score ≤ 8 , at least one measurable lesion, an Eastern Cooperative Oncology Group

(ECOG) performance status (PS) score of 0, absolute neutrophil count $>1,500/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$, hemoglobin >9 g/dL, partial thromboplastin time (PTT) within normal limits and international normalized ratio (INR) <1.5 the upper limit of normal (ULN), serum creatinine $<1.5 \times \text{ULN}$, total bilirubin (TBil) levels ≤ 4.5 mg/dL, alanine transaminase (ALT) or aspartate transaminase (AST) $<5 \times \text{ULN}$, and alkaline phosphatase (ALP) $<4 \times \text{ULN}$.

Written informed consent for metronomic S-1 and TACE administration was obtained from all patients prior to each treatment. The study protocol complied with all the provisions of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Affiliated Tumor Hospital of Xinjiang Medical University, China, and the need for written informed consent of clinical trial was waived since the data were analyzed anonymously and retrospectively.

BCLC stage B HCC

The diagnosis of HCC was based on the AASLD criteria. A patient was considered to have a confirmed HCC diagnosis when the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases) was observed in multidetector spiral computed tomography (CT) scan or dynamic contrast-enhanced magnetic resonance imaging (MRI) on nodules larger than 1 cm in diameter. Biopsies were reserved for uncertain diagnosis for high-grade dysplastic nodules or discordant results. The BCLC stage B of HCC included Child-Pugh class A or B, a single nodule >5 cm or multinodular disease (>3 nodules, with at least one lesion >3 cm), good PS (PS 0), and no extrahepatic disease or vascular invasion.

TACE and metronomic S-1 chemotherapy

TACE was administered on monthly cycles by selective transarterial chemoembolization of the vessels supplying the tumor using an emulsion of lipiodol (5-20 ml) and pirarubicin (20-60 mg) (with or without infusion chemotherapy with oxaliplatin 50-80 mg), followed by embolization with absorbable particles of gelatin sponge. One cycle of metronomic S-1 chemotherapy was 14 days. Patients on TS received S-1 30-40 mg/m² bid on day 2 after TACE (day 1) (Figure 1). Patients on TM received TACE only (day 1). One month after the previous TACE, a multidetector spiral CT of the upper abdomen and determination of a-fetoprotein (AFP) were performed to assess the need of a consecutive TACE. After the first time, TACE was performed on demand. If a follow-up CT scan showed viable tumor, another course of TACE was scheduled. When no change to viable tumor was seen on the CT, TACE was discontinued irrespective of group. If the CT scan revealed new lesions, the patient was evaluated for the feasibility of a new TACE intervention. If new lesions were present in the liver, the patient would be treated as disease progression and receive

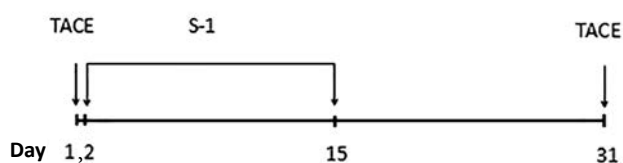


Figure 1. Treatment cycle schedule.

the next course of TACE. If new lesions were seen in extrahepatic sites or invasion of branches of portal vein the patient might receive TACE. Patients on TS might choose treatment with S-1 when there was disease progression. The last day of follow-up time was October 2015.

Refractoriness to TACE

There is no unified definition of “refractoriness to TACE”. In the present study, the definition “refractoriness to TACE” was regarded as disease progression or shrinkage of <25% in hypervascular-tumor lesions according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) after 1-2 cycles of TACE. When disease progression was considered by mRECIST, the JSH-LCSGJ updated criteria of 2014 were used to confirm refractoriness to TACE [13].

Assessment

The mRECIST criteria were used to assess lesion size and tumor response. A maximum of 2 lesions per organ and 5 lesions in total for one patient, as well as the presence or absence of distant metastases, were evaluated using CT or MRI images at the time of therapeutic assessment.

Study objectives

The primary endpoints were TTP and tumor response (TR). TTP was defined as the time from the start of treatment until appearance of progressive disease (PD). TR consisted of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). DCR was defined as the percentage of subjects achieving a confirmed CR, PR or SD. TTP and TR were evaluated using the mRECIST criteria. The secondary endpoints were OS and AEs. OS was measured from the start of treatment until the date of death or the end of follow-up. Patients who were alive or lost to follow-up were censored at the last date known to be alive. AEs were graded and evaluated according to the American Common Terminology Criteria for Adverse Events (CTCAE, version 3.0).

Statistics

The Statistical Package for Social Science (SPSS, version 15.0) was used for all statistical analyses. For all tests a p value <0.05 was considered statistically significant. Demographic and clinicopathological data were collected from the electronic patient records in a computer database. Continuous data were expressed as mean±standard deviation (SD). Continuous variables were analyzed using t-test. Categorical variables were analyzed using the Pearson's χ^2 and for small sample data Fisher's exact test was used. Survival analysis of TTP and OS was performed by the Kaplan–Meier method and the log-rank test.

Results

Baseline characteristics

A total of 26 patients were included in the study. Baseline characteristics are summarized in Table 1. Viral hepatitis accounted for 73% (19/26) of the patients (mainly hepatitis B). Cirrhosis, mainly caused by viral hepatitis, accounted for 65% (17/26) of the patients. The median previous TACE of two groups were 3 (range 1-5). Compared to the TM, no significant differences in the patient characteristics were observed between the two groups (Table 1). Because of low incidence of hepatitis C, statistical comparison was not performed.

Table 1. Baseline characteristics

Variables	ST group (N = 15)	TM group (N = 11)	p value
Gender, male/female (N)	10/5	7/4	1.000
Age, years (mean±SD)	61.7±11.0	62.1±11.6	0.925
Size of tumor lesions, cm (mean±SD)	7.9±3.8	7.2±4.4	0.658
Number of tumor lesions, median (range)	3 (1-10)	4 (1-8)	0.854
Cirrhosis, N	10	7	1.000
Hepatitis B, N	10	8	1.000
Hepatitis C, N	1	0	NA
a-fetoprotein, >400 ng/m, N	8	6	1.000
Total bilirubin, μ mol/L (mean±SD)	21.1±5.4	20.5±7.2	0.786
Albumin, g/dl (mean±SD)	34.9±4.6	35.5±4.1	0.742
Alanine aminotransferase, U/L (mean±SD)	46.8±21.9	44.6±17.9	0.781
Platelets, 10^3 /ul (mean±SD)	97.5±27.4	96.6±37.6	0.949
Prothrombin time, seconds (mean±SD)	12.4±1.9	12.7±2.1	0.650
Previous TACE, median (range)	3(1-5)	3(1-5)	0.808

NA: not available

Treatment of TACE and S-1

Twenty six patients received 176 TACE interventions in total. There were 101 cycles in 15 patients of TS and 75 cycles in 11 patients of TM. TS patients received a median of 8 (range 3-13) TACE interventions, resulting in a mean dose of oxaliplatin of 44.9±36.7 mg, pirarubicin of 33.8±13.0 mg and lipiodol of 10.4±4.1 ml. Meanwhile, TM

Table 2. TACE and drugs

	N	TACE	Oxaliplatin	Pirarubicin	Lipiodol
		Median (range)	mean±SD (mg)	mean±SD (mg)	mean±SD (ml)
TS group	101	8 (3-13)	44.9±36.7	33.8±13.0	10.4±4.1
TM group	75	7 (4-12)	49.5±37.3	37.9±12.4	11.8±3.4
p value		0.280	0.413	0.035	0.012

patients received a mean of 7±2.4 (range 4-12) TACE interventions, resulting in a mean dose of oxaliplatin of 49.5±37.3 mg, pirarubicin of 37.9±12.4 mg and lipiodol of 11.8±3.4 ml (Table 2). For S-1, one cycle was 14 days. Fifteen TS patients received a total of 55 cycles of treatment with S-1, with a median of 4 cycles (range 2-6). The total dose of S-1 was 6165 mg per day during treatment, while the mean was 120 mg for 15 TS patients.

TTP and tumor response

Median TTP of TS group was 6 months (95% CI, 4.7-7.3) while for the TM group was 4 months (95% CI, 2.4-5.6) with significant difference (Table 3 and Figure 2). Calculations of tumor response

Table 3. Time to progression and overall survival, months, median (range)

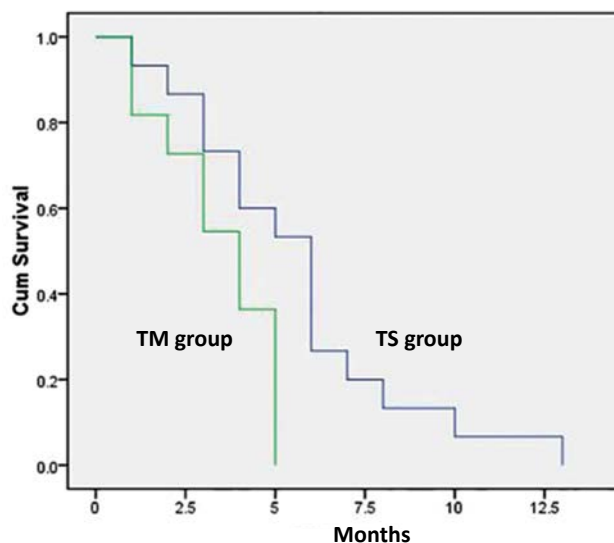
Variable	TS group	TM group	p value
TTP	6 (1-13)	4 (1-5)	0.015
OS	17 (8-25)	15 (7-21)	0.535

TTP: time to progression, OS: overall survival

Table 4. Tumor response

Month	TR	TS group (N=15) N (%)	TM group (N=11) N (%)
1	CR	1 (6.7)	0 (0.0)
	PR	5 (33.3)	2 (18.2)
	SD	5 (33.3)	5 (45.5)
	PD	4 (26.7)	4 (36.4)
2	CR	1 (6.7)	0 (0.0)
	PR	6 (40.0)	2 (18.2)
	SD	5 (33.3)	4 (36.4)
6	CR	3 (20.0)	5 (45.5)
	PR	4 (26.7)	1 (9.1)
	SD	5 (33.3)	4 (36.4)
6	CR	0 (0.0)	0 (0.0)
	PR	4 (26.7)	1 (9.1)
6	SD	5 (33.3)	4 (36.4)
	PD	6 (40.0)	6 (54.5)

For abbreviations see text

Survival Functions**Figure 2.** Kaplan-Meier time to progression of metronomic S-1 chemotherapy plus TACE (TS group) and TACE monotherapy group (TM group) (hazard ratio 0.359, 95% CI 0.139-0.930, p 0.035).

(TR) were based on 26 patients at 1, 2, and 6 months. Detailed TRs and DCRs of two groups are displayed in Tables 4 and 5, respectively.

Overall survival

Median OS of TS group was 17 months (95% CI, 15.6-18.4) and 15 months (95% CI, 9.2-20.8) of the TM group. This result was considered positive

Table 5. Disease control rate (DCR)

DCR	TS group %	TM group %	χ^2	p value
Month 1	73.3 (11/15)	63.6 (7/11)	0.280	0.683 ^a
Month 2	80.0 (12/15)	54.5 (6/11)	1.930	0.218 ^a
Month 6	60.0 (9/15)	45.5 (5/11)	0.540	0.462 ^b

a: Fisher's exact test; b: Pearson's χ^2 test

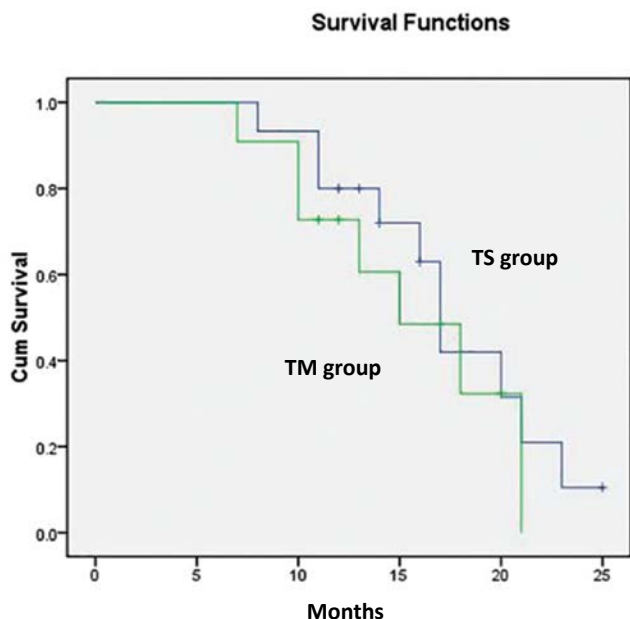


Figure 3. Overall survival curves of metronomic S-1 chemotherapy plus TACE (TS group) and TACE monotherapy group (TM group) (hazard ratio 0.738, 95% CI 0.273-1.995, p 0.549).

but no significant difference was detected (Table 3 and Figure 3). In the TS group one patient chose to be treated with sorafenib and another one received combination chemotherapy with cisplatin

Table 6. Adverse events

Adverse events	TS group (N=101) N (%)	TM group (N=75) N (%)	p value
Abdominal pain	71 (70.3)	52 (69.3)	0.890
Anorexia	25 (24.8)	9 (12.0)	0.034
Nausea	40 (39.6)	17 (22.7)	0.018
Diarrhea	0 (0.0)	1 (1.3)	NA
Hyperbilirubinemia	61 (60.4)	47 (62.7)	0.760
Transaminase elevation	65 (64.4)	46 (61.3)	0.681
Anemia	30 (29.7)	21 (28.0)	0.805
Neutropenia	35 (34.7)	22 (29.3)	0.456
Thrombocytopenia	42 (41.6)	27 (36.0)	0.453
Hand-foot syndrome	0 (0.0)	0 (0.0)	NA
Neuropathy	1 (1.3)	0 (0.0)	NA
Bleeding	0 (0.0)	0 (0.0)	NA

NA: not available

Table 7. CTCAE grading of adverse events

	TS group				TM group			
	1	2	3	4	1	2	3	4
Abdominal pain	34	31	5	1	28	20	3	1
Anorexia			1	1			0	0
Nausea	20	16	3	1	8	8	1	0
Diarrhea	0	0	0	0	1	0	0	0
Hyperbilirubinemia	30	29	1	0	25	21	1	0
Transaminase elevation	22	38	4	1	18	25	3	0
Anemia	18	11	1	0	10	10	1	0
Neutropenia	15	20	0	0	11	11	0	0
Thrombocytopenia	22	18	1	1	13	14	0	0
Hand-foot syndrome	0	0	0	0	0	0	0	0
Neuropathy	1	0	0	0	0	0	0	0
Bleeding	0	0	0	0	0	0	0	0

and capecitabine after failure of TS treatment. Three patients were lost to follow-up. All patients were followed-up for at least 6 months.

Adverse events

AEs were evaluable in 26 patients and 176 treatment cycles of TACE with or without S-1. A total of 612 AEs occurred during the treatments, 367 in the TS and 245 in the TM groups. The most frequent AEs are detailed in Tables 6 and 7. The most frequent AE was abdominal pain (70.3% in TS and 69.3% in TM group). Differences in AEs, except anorexia and nausea, were not significant and may be attributed to S-1. Anorexia and nausea were acceptable because they could reduce or disappear after supportive therapy. Only few grade 3-4 AEs were registered.

Discussion

Referring to the administration of low dose of a drug on a frequent schedule, metronomic chemotherapy without extended interruption, lacks the acute toxicity of intravenous chemotherapy, yet it is effective against tumor growth because it inhibits angiogenesis and reduces the nutrition supply of the tumor [14]. The reports on antiangiogenic effect of metronomic chemotherapy increase as it is administered in combination with

targeted antiangiogenic drugs [15]. Metronomic chemotherapy is administered as adjuvant [16] and was shown to be effective in palliative care with low toxicity [14].

HCC is one of the most common gastrointestinal malignancies. For a patient with BCLC stage B HCC who is not candidate for resection, TACE is safe [17] and the main therapeutic option [18]. Many Chinese patients with BCLC stage B HCC have been treated with TACE, and have obtained a certain effect. However, due to tumor resistance, there was probable refractoriness to TACE after several cycles. Patients refractory to TACE may have poor prognosis. Currently, for patients with BCLC stage B HCC refractory to TACE there are no consistent criteria on further treatment selection. Metronomic chemotherapy plus interventional treatment has been used to treat unresectable biliary tract cancer in a phase I trial [19].

Iwamoto et al. showed that a hepatocellular tumor cell line responded well to metronomic chemotherapy with low dose S-1, which was resistant to high concentration of fluorouracil in vitro [20]. Chen et al. in their study of HCC in an animal model showed that metronomic chemotherapy with S-1 destabilized tumor vasculature and inhibited neo-angiogenesis [21]. S-1 is a novel oral 5-fluoro-2, 4 (1h, 3h) pyrimidinedione (5-FU) analog, which contains tegafur and two biochemical modulators for 5-FU. Tegafur is a metabolically activated prodrug of 5-FU, and effective as adjuvant chemotherapy after TACE [22]. 5-Chloro-2,4-dihydropyridine can enhance the pharmacological actions of 5-FU by inhibiting its degradation by dihydropyrimidine dehydrogenase (DPD). Potassium oxonate is localized in the mucosal cells of the gastrointestinal tract after oral administration. By means of suppressing the activation of 5-FU in the gastrointestinal tract, it reduces the incidence of gastrointestinal toxicities [23]. S-1 showed a better antitumor activity and lower toxicity compared to 5-FU [24]. A phase I/II study suggested that S-1 was effective and had an acceptable toxicity profile in patients with advanced HCC [11]. With ongoing research on S-1, there are some articles published in 2015. In his study, Yu aimed to compare the efficacy of S-1 vs best supportive care in advanced HCC, and demonstrated that S-1 showed an acceptable safety profile and survival benefit in patients with advanced HCC [25]. Another study demonstrated that although S-1 did not statistically prolong OS compared to the placebo in patients with sorafenib-refractory advanced HCC, the sub-

group analysis showed S-1 had potential to improve OS [26].

Patients on TS received S-1 30-40 mg/m² bid on day 2 after TACE (day 1) in this study. One cycle of metronomic S-1 chemotherapy was 14 days. Under normal conditions, the dose of S-1 is 40, 50 or 60 mg/m² bid on days 1-28. Because this was a retrospective study, there was no unified or pre-set dose of S-1. Moreover, due to the combination with TACE, the dose of S-1 in clinical practice was lower than the conventional one. In a phase I trial of transarterial infusion combination chemotherapy plus S-1 for advanced HCC, the recommended dose for further evaluation was 65 mg/m² cisplatin and 80 mg/m² (i.e. 40 mg/m² bid) S-1 [27]. In this study, doses of S-1 were roughly the same to the phase I trial.

In the present study, we aimed to evaluate the efficacy and safety of metronomic S-1 chemotherapy plus TACE for the treatment of BCLC Stage B HCC refractory to TACE. Based on this consideration, we designed this retrospective study. There were no significant differences in the toxicities reported between the two groups except anorexia and nausea. So we consider that the differences of anorexia and nausea should be due to S-1, and both could be improved by subsequent supportive therapy. Importantly, combination therapy with TACE and S-1 did not appear to lead to worse AEs. Therefore, the combination therapy of TACE and S-1 was safe.

There was also satisfactory TTP in this study. Median TTP was 6 months (range, 1-13) in the TS group vs 4 months (range, 1-5) in the TM group ($p=0.015$). Chao et al. studied another combination of TACE with sorafenib in patients with HCC (START study) and reported median TTP of 13.8 months [28]. START was a phase 2, investigator-initiated, open-label, prospective single-arm multicenter trial, which investigated the efficacy and safety of sorafenib combined with TACE in Southeast Asian patients with HCC, and its population was BCLC stage B and A HCC patients. The difference was only in BCLC Stage B HCC patients selected in the present study. Furthermore, all of the patients in our study were refractory to previous TACE. In another study, the median TTP reported was 5.4 months (162 days) for the TACE plus sorafenib group compared to 3.7 months (111 days) in the placebo group [29]. Therefore, the median TTP of TACE and S-1 of 6 months was favorable.

In this study, TR was based on 26 patients assessed in 1, 2 and 6 months, because we planned

to observe the changing role of S-1 for disease control, in order to provide more data for further research. In a study of HCC patients refractory to TACE, the DCR (CD+PR+SD) was 60.4 % in the sorafenib group and 28.8 % in the group of hepatic arterial infusion chemotherapy (HAIC) using cisplatin ($p=0.001$) [30]. Compared to 60.4 %, the DCR of 80.0% in the present study appears to be higher considering, however, that there were different baseline data. However, the DCR of 80.0% was very encouraging in patients with BCLC Stage B HCC refractory to TACE and strengthened our confidence to proceed to further research.

The main limitations of the present study were its retrospective nature and the small sample size of patients included. Because of the small sample size of patients treated with TS, heterogeneous patients were included in different chemotherapy drugs used (with or without oxaliplatin) and dose and cycles of S-1 and this could possibly impact the outcomes. But, considering the limited data of S-1 in BCLC Stage B HCC refractory to TACE reported thus far, our study provides basic data for further research on the combination treatment of TACE and S-1 in HCC. We are already preparing a prospective study of metronomic S-1 chemotherapy plus TACE as first-line treatment in BCLC Stage B HCC to assess its efficacy and safety.

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Conclusions

Metronomic S-1 chemotherapy plus TACE in the present study showed good tolerance and was associated with promising TTP, TR and OS results. Randomized, controlled, prospective trials are needed to further investigate the efficacy and safety of this therapeutic approach.

Authors' contributions

WH, LY and SY contributed equally to this work, and drafted the manuscript. XF, WH and LY participated in the design of the study. Others participated in the coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank particularly Dr. Guohong Han (the seventh Department of Gastroenterology, the Affiliated Xijin Hospital of Fourth Military Medical University) for his mental stimulation.

Funding

This work was supported by the Grants from Science and Technology Supporting Xingjiang Province (no.201491186).

Conflict of interests

The authors declare no conflict of interests.

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