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Original Article

The comparative safety and efficacy of S-1 versus the best supportive care in advanced hepatocellular carcinoma

Yian Du[1,2*], Pengfei Yu[2*], Ling Huang[2], Gaiguo Dai[2], Xiujun Cai[1]

[1]Department of General Surgery, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou 310016, China; [2]Department of Abdominal Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China. [*]Equal contributors.

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Abstract: The safety and efficacy of S-1 relative to the best supportive care (BSC) for the treatment of advanced hepatocellular carcinoma (HCC) have not yet been elucidated. We retrospectively recruited 46 cases of advanced HCC from December 2009 to December 2014. Twenty-five patients received S-1 treatment, and twenty-one patients received BSC. The primary outcomes were progression-free survival (PFS), overall survival (OS), and the safety profiles of the two therapies. The median duration of follow-up was 12.3 months (range, 4-25 months). The median number of cycles administered in the S-1 group was 3.5 (range, 2-7 cycles). S-1 therapy was well tolerated. The most common grade 3-4 toxicities experienced in the S-1 group were leucopenia/neutropenia (16.0%), thrombocytopenia (12.0%), and an elevated serum aspartate aminotransferase level (12.0%). In the S-1 group, 2 patients (8.0%) had a partial response, 13 (52.0%) maintained stable disease, and 10 (40.0%) experienced disease progression. In the BSC group, 4 patients (19.0%) had stable disease, and 17 patients (81.0%) had progressive disease. The median PFS times of the S-1 and BSC group were 6.84 months (95% confidence interval [CI], 5.56-8.12 months) and 3.67 months (95% CI, 2.91-4.43 months), respectively (P=0.001). The median OS in the S-1 group was 14.56 months (95% CI, 12.70-16.42 months), which was significantly longer than that of 7.71 months (95% CI, 6.34-9.09 months) in the BSC group. S-1 was well tolerated in patients with advanced HCC. Patients who received S-1 therapy achieved better PFS and OS than those who received BSC. S-1 may be a promising therapeutic option for patients with advanced HCC.

Keywords: Chemotherapy, advanced hepatocellular carcinoma, S-1, best supportive care

Introduction

The prevalence of hepatocellular carcinoma (HCC) is listed as the sixth highest worldwide, and with its poor prognosis, HCC is among the top three contributors to cancer mortality [1]. For patients diagnosed with curable HCC, surgical resection, radiofrequency ablation (RFA), and liver transplantation are considered as the mainstay treatments [2]. Most patients are diagnosed with noncurative HCC, and transcatheter arterial chemoembolization (TACE) is their optimal treatment option [3]. However, although HCC patients who are diagnosed at advanced stages can receive locoregional therapies, the survival rate among these patients is still dismal due to rapid tumor growth and the lack of effective treatment options.

Sorafenib has been regarded as the first-line treatment for patients with advanced HCC globally. Previously, sorafenib was proven to be effective for advanced HCC patients in two large-scale randomized control trials [4, 5]. In the Asia-Pacific study, the median OS of patients treated with sorafenib was 6.5 months, and the time to progression (TTP) was 2.8 months. Notably, its survival benefit is modest and still unsatisfactory. On the other hand, the frequency of sorafenib-related adverse events in the Asia-Pacific population is higher than in Western patients. Therefore, further clinical research is urgently needed to investigate more effective therapeutic strategies for advanced HCC.

S-1, a novel orally pyrimidine fluoride-derived anticancer agent, possesses antitumor effici-

ency in various tumors and has been shown to be well-tolerated. S-1 consists of two enzyme inhibitors (CDHP, potassium Oxo) and tegafur (FT), at a molar ratio of 0.4:1:1 (CDHP:Oxo:FT) [6]. CDHP can reduce the degradation of 5-FU by inhibiting DPD, thereby maintaining an efficacious concentration of 5-FU in plasma and tumor tissues. Oxo acts as a competitive inhibitor of phosphorylation of 5-FU, resulting in a decline in 5-FU toxicity in the gastrointestinal tract. Briefly, S-1 is a well-designed anticancer agent with enhanced antitumor activities and reduced adverse effects. S-1 has been demonstrated to have activities against different types of solid tumors [7-9]. Notably, S-1 was also well-tolerated in an Asian population [10]. In several phase II studies, S-1 has shown encouraging antitumor efficacy in advanced HCC patients with acceptable tolerability [11, 12].

Patients with advanced cancer often received best supportive care (BSC). BSC includes, in particular, adequate pain management, infection therapy, biliary-stent intervention if needed, social support and on demand psycho-oncological intervention, and nutrition intervention [13]. Best supportive care was also a treatment option for advanced HCC [14].

The aim of this study was to compare the safety and efficacy of S-1 versus BSC in advanced HCC patients, with the expectation of providing more clinical evidence for better management of patients with advanced HCC.

Materials and methods

Study participants

The inclusion criteria were: HCC diagnosed by a clinical condition such as risk factors for chronic hepatitis and/or cirrhosis, elevated alpha-fetoprotein level (> 400 ng/ml), typical radiological imaging features of HCC, or a diagnosis of HCC by histologic or cytologic examination. Advanced HCC was considered if the patients were not eligible for an operation or locoregional therapies with/without extra-hepatic metastases, and/or vascular invasion and/or lymph node involvement [15]. Measurable disease was in accordance with the RECIST criteria (version 1.1); age 18~75 years old; the general condition was good, life expectancy > 3 months; at least one untreated dimensionally measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status 0~2; Prothrombin Time-International Normalized Ratio/Partial Thromboplastin Time (PT-INR/PTT) < 1.5 times the normal upper limit (NUL); albumin > 3 g/dL; serum creatinine ≤ NUL; alanine transaminase (ALT) and aspartate transaminase (AST) level < twice NUL; total bilirubin < 1.5 times NUL; hemoglobin > 9.0 g/dl; absolute neutrophil count > 1,500/μL; and platelet count > 75,000/μL.

Patients were excluded if they had a history of chemoembolization or radiotherapy such as 5-FU, UFT, and ordoxifluridine within 4 weeks prior to study enrollment, symptoms of meningeal tumors or brain metastasis, active serious infection or uncontrolled intercurrent illness, concomitant decompensated cirrhosis, or previous use of any other investigational agents or anticancer drugs.

S-1 group

Twenty-five advanced HCC patients who refused therapy with sorafenib received S-1 treatment at the Division of Abdominal Surgery, Zhejiang Cancer Hospital, from December 2009 to December 2014. S-1 contains 20 mg ftorafur in a capsule provided by Taiho Pharmaceutical Co. Ltd. (Japan). The S-1 dosage calculation was based on body surface area (BSA) (BSA > 1.5 m^2, 60 mg; 1.25 m^2 ≤ BSA ≤ 1.5 m^2, 50 mg; BSA < 1.25 m^2, 40 mg). The daily dose was obtained by rounding the calculated dose. The drug was dispensed to each patient. Each treatment cycle lasted 21 days. For the first 2 weeks, S-1 was orally administered two times every day after breakfast and dinner, followed by a 1-week recovery period. If the serum concentration of creatinine increased to grade 2 or higher, the AST or ALT level was elevated to grade 3 or higher, or hematological toxicity reached to grade 3 or higher, the dose of S-1 was reduced to the minimum dose (40 mg/day) or suspended. Treatment continued until evidence of disease progression was observed or the recovery period exceeded 2 weeks. If the patient requested to quit the treatment or if the patient experienced unacceptable toxicity, treatment was stopped according to the discretion of the investigators. We carefully monitored drug compliance and the adherence of each patient. Participants were required to

Table 1. Patient characteristics (n=46)

Characteristics	S-1 group (n=25)	BSC group (n=21)	*P*-value
Median age, years (range)	51.4 (33-71)	52.7 (29-70)	0.533
Sex (male/female)	(18/7)	(16/5)	0.747
Underlying liver disease			
HBV (+)	24	21	0.354
HBV (-)	1	0	
Cirrhosis (yes/no)	(19/6)	(15/6)	0.725
AFP, ng/ml (range)	791 (0-12000)	703 (0-12000)	0.232
Child-Pugh class			
A	23	18	0.495
B	2	3	
ECOG score			
0-1	23	19	0.855
2	2	2	
Previous therapy			
No previous therapy	5	4	0.953
Liver resection	11	10	
TACE	9	10	
RFA	3	2	
PVTT (yes/no)	11/14	6/15	0.280
Distant metastases			
Lymph node	6	4	0.505
Lung	5	3	
Adrenal glands	1	3	
Abdominal cavity	2	0	
Abdominal wall	1	1	

HBV, hepatitis B virus; AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PVTT, portal vein tumor thrombus.

record their intake of S-1 and other drugs in a diary.

BSC group

A total of 21 advanced HCC patients received BSC and formed the control group in this study. Like those in the S-1 group, these patients also declined sorafenib. They received pain management, infection therapy, biliary-stent intervention, or nutrition intervention. The characteristics of the patients and tumors are displayed in **Table 1**.

Ethics approval

The project was approved by the Ethics Committee of Zhejiang Cancer Hospital, which waived the requirement for individual patient consent because only routine patient data were used for this retrospective analysis.

Follow-up and assessment

Outpatient records combined with telephone interviews were used for follow-up. The assessment of efficacy and toxicity was done for all patients who received BSC or at least one dose of S1. Complete blood count and blood chemistry studies were performed before the initiation of each cycle. The tumor response was evaluated after each treatment cycle via the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) by performing a computed tomography (CT) or magnetic resonance imaging (MRI). The primary endpoint was overall response rate calculated by the changes in tumor dimensions. The progression-free survival (PFS), overall survival (OS), and safety profiles were assessed as the secondary endpoints. Adverse events were evaluated via the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE, Ver. 3.0). The attending physicians were responsible for determining the duration and causes of adverse events. All data were then reviewed by an independent review committee on the objective response and adverse effects.

Statistical analysis

Continuous and categorical data were analyzed using Student's *t*-test and a Chi-square test, as appropriate. A Kaplan-Meier analysis was used to calculate survival, and a log-rank test was performed to compare OS between groups. Data are presented as mean ± standard deviation or the median and range. Statistical analyses were conducted using SPSS 19.0 software (Chicago, IL, USA). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

In total, we recruited 46 patients, of whom 25 received S-1 treatment and 21 received BSC. **Table 1** summarizes the basic characteristics of the patients. There were no significant differ-

Table 2. Toxicities in the S-1 group

Toxicity	Grade 1/2 n (%)	Grade 3/4 n (%)
Hematological		
Leukopenia/Neutropenia	8 (32.0%)	4 (16.0%)
Thrombocytopenia	7 (28.0%)	3 (12.0%)
Non-hematological		
Transaminase elevation	9 (36.0%)	3 (12.0%)
Rash	4 (16.0%)	1 (4.0%)
Diarrhea	3 (12.0%)	0
Fatigue	3 (12.0%)	0

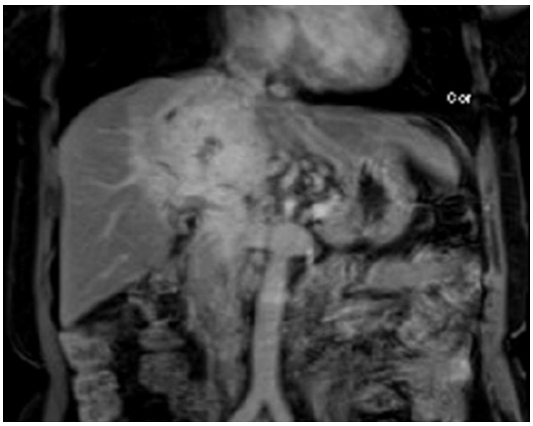

Figure 1. An MRI showing a large tumor located in the right liver that was close to the inferior vena cava (IVC).

ences between the two groups in terms of patient characteristics and liver function. At study entry, 24 of 46 (52.2%) patients had distant metastasis, 18 of 46 (39.1%) had developed single extrahepatic metastasis (8 cases of lymph node metastasis, 6 cases of lung metastases, 2 cases of adrenal gland metastasis, and 2 cases of abdominal cavity metastasis). Multiple sites of metastases were also observed in four patients, including the lymph nodes, adrenal glands, lungs and abdominal wall. Seventeen patients (37.0%) had portal vein tumor thrombus (PVTT).

Treatment delivery and toxicity

The median number of cycles administered in the S-1 group was 3.5 (range, 2-7 cycles). The dose of S-1 had to be reduced in five patients (20.0%) due to chemotherapy toxicity. **Table 2** lists all S-1-related adverse events. In general, S-1 therapy had acceptable tolerability in patients with advanced HCC. Specifically, 9 of the 25 patients (36.0%) experienced grade 3-4 toxicity. The first most common hematological toxicities of grade 3-4 were leucopenia or neutropenia (16.0%), followed by thrombocytopenia (12.0%); the most frequently observed nonhematological toxic events of grade 3-4 included rashes (4.0%) and an elevated aspartate aminotransferase level (12.0%).

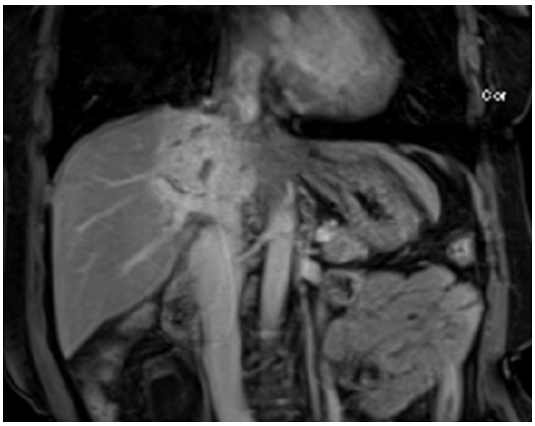

Figure 2. Significant decrease in the tumor size after treatment with four cycles of S-1.

Efficacy and survival outcomes

The median duration of follow-up was 12.3 months (range, 4-25 months). In the S-1 group, 2 patients (8.0%) had a partial response (**Figures 1**, **2**), 13 (52.0%) maintained stable disease, and 10 (40.0%) had no response to treatment and experienced disease progression. Among the patients who received BSC, none had a partial response, 4 (19.0%) had stable disease, and 17 (81.0%) experienced disease progression (**Table 3**). There was a statistically significant difference between these two groups (P=0.016). The median PFS times for the S-1 and BSC group were 6.84 months (95% confidence interval [CI], 5.56-8.12 months) and 3.67 months (95% CI, 2.91-4.43 months), respectively, and the difference between the two groups was significant (P=0.001; **Figure 3**). The median OS in the S-1 group was 14.56 months (95% CI, 12.70-16.42 months), which was significantly longer than that of 7.71 months (95% CI, 6.34-9.09 months) in the BSC group (P < 0.001; **Figure 4**).

Discussion

An established standard therapy is still lacking for patients with advanced HCC, which is a highly prevalent and fatal disease. Although there are many options for HCC patients such

Table 3. Tumor responses in the S-1 and BSC groups

Type of response	S-1 group (n=25)	BSC group (n=21)	*P*-value
Complete response	0	0	0.016
Partial response	2	0	
Stable disease	13	4	
Progressive disease	10	17	

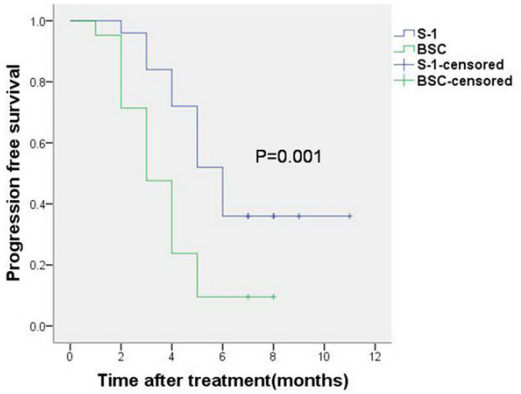

Figure 3. The S-1 group exhibited significantly better progression-free survival compared to the BSC group (P=0.001).

as surgical resection, liver transplantation, local ablation and TACE [16, 17], these treatments are not suitable for advanced HCC patients. To improve the prognosis of advanced HCC patients, researchers have made various efforts and found that a small population of advanced HCC patients benefit from systemic treatments [18]. Sorafenib is the first drug used for systemic treatment that has been proven to have the ability to prolong survival; however, severe adverse effects have been observed frequently, especially in Asia-Pacific patients [4, 5]. Chemotherapy is another choice of systemic treatment [19]. The commonly used chemotherapy regimens for HCC are doxorubicin, fluoropyrimidine, and platinum alone or in combination [20, 21]. Although promising response rates have been achieved by some combined regimens, the survival benefits are minimal, especially for clinically unacceptable adverse effects [22]. As a novel antitumor drug, S-1 is able to sustain a high level of blood 5-FU consistent with intravenously administrated 5-FU as well as to alleviate gastrointestinal toxicity [23]. It exerts anticancer effects in various solid tumors [7-9]; however, whether S-1 has promising efficacy in patients with advanced HCC remains unclear.

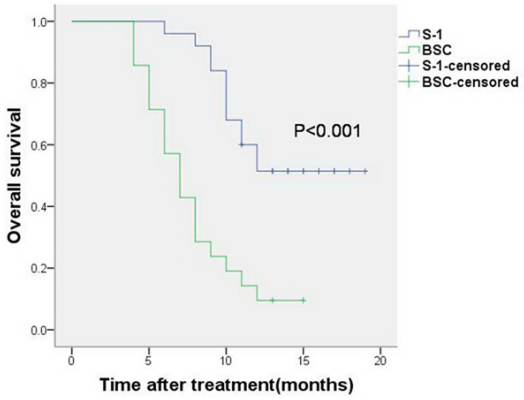

Figure 4. The S-1 group exhibited significantly better overall survival compared to the BSC group (P < 0.001).

The safety and efficacy of S-1 in advanced HCC patients was investigated in the present study. S-1 was conveniently delivered via oral administration to each patient, and the patients tolerated the treatment well. The most common hematological toxic effects were thrombocytopenia and leucopenia/neutropenia. Only seven patients developed severe toxic effects. The hematological toxicities in patients with advanced HCC were comparable to those in other cancers, and elevated aspartate aminotransferase levels occurred more frequently in the S-1 therapy group than reported in previous studies [24]. However, the nonhematological toxicities that occurred in the S-1 therapy group were comparable with those observed in the phase II S-1 clinical trial for HCC patients [11]. The differences may be due to the unique features of various solid tumors and individual variance.

In the S-1 treatment group, among 25 evaluable patients, 2 patients experienced a partial response and 13 patients maintained stable disease, which was a promising result. Additionally, with S-1 treatment, the median PFS increased to 6.84 months (95% CI, 5.56-8.12 months), and the median OS was prolonged to 14.56 months (95% CI, 12.70-16.42 months). Compared with a previous sorafenib phase III study in an Asia-Pacific population [5], the PFS and OS with S-1 therapy were even better. For patients who had progressive disease after S-1 or BSC treatment, other treatments including radiotherapy, other systemic regimes, or hepatic arterial infusion chemotherapy were applied to prevent a worsening of the disease, which could contribute to the better OS observed in our study.

The combination of S-1 with molecular-targeted therapies as the new systemic chemotherapy regimens has been reported in some centers [10, 25], with S-1 used together with sorafenib. However, the survival benefits were not improved largely compared with those of S-1 monotherapy. Another study in Japan found that the combination of S-1 and TSU-68 (a multiple-receptor tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 [VEGFR-2] and platelet-derived growth factor receptor beta [PDGFR-β]) was also well tolerated, and the median PFS and OS reached 8.0 months and 16.3 months, respectively [26]. Thus, whether S-1 combined with molecular-targeted therapies will be a promising therapy for patients with advanced HCC warrants further research.

Several limitations existed in our study. First, this was a retrospective study, so selection bias could not be avoided. Second, the sample size was small. Therefore, our findings may be affected by several confounding factors. However, this was the first study evaluating the safety and efficacy of S-1 for patients with advanced HCC in China, so the results provide evidence for clinicians to formulate treatment strategies for these patients.

Conclusions

S-1 was well tolerated in patients with advanced HCC. Patients who received S-1 therapy achieved a better PFS and OS compared with those who received BSC. S-1 may be a promising therapeutic option for patients with advanced HCC. However, larger randomized controlled studies are needed to further confirm the efficacy and safety of S-1.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

BSC, best supportive care; HCC, advanced hepatocellular carcinoma; PFS, progression-free survival; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TTP, time to progression; FT, tegafur; AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; BSA, body surface area; PVTT, portal vein tumor thrombus.

Address correspondence to: Xiujun Cai, Department of General Surgery, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou 310016, China. Tel: 86-571-88128041; E-mail: xiujuncai@126.com

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