

ORIGINAL ARTICLE

S-1 plus sorafenib for the treatment of advanced hepatocellular carcinoma

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Summary

Purpose: To assess the efficacy and safety of S-1 plus sorafenib for the treatment of advanced hepatocellular carcinoma (HCC).

Methods: PubMed, the Cochrane Library, EMBASE, and ClinicalTrials.gov were searched using the terms "Hepatocellular Carcinoma" or "HCC" or "Hepatoma" or "Liver cancer" and "S-1" and "Sorafenib" or "Nexavar". Outcomes of main interest included overall survival (OS) and toxicities.

Results: We identified 2 studies of S-1 plus sorafenib from 77 references that included a total of 65 patients. The percentage of male patients ranged from 70.0 to 89.5%. Median age was 59.2 years and ranged from 48.0 to 65.5 years. The percentage of hepatitis B virus ranged from 23.1 to 90.0%. The recommended dose of S-1 and sorafenib was 80 or 64 mg/m²/day and 800 mg/day, re-

spectively and treatment was administered orally on days 1-14 and days 1-21, respectively. Median OS were 10.4 and 10.5 months, respectively. The incidence of all-grade toxicities of more than 30% were hand-foot syndrome (HFS) and rash. The incidence of grade 3/4 toxicities more than 5% were thrombocytopenia, elevated AST/ALT and hyperbilirubinemia.

Conclusion: This systematic review suggests that S-1 plus sorafenib showed modest clinical efficacy and tolerable toxicity profile in patients with advanced HCC. The recommended dose of S-1 and sorafenib was 80 or 64 mg/m²/day and 800 mg/day, respectively.

Key words: hepatocellular carcinoma, S-1, sorafenib, systematic review

Introduction

Worldwide, HCC is one of the most frequent malignancies. HCC ranks sixth regarding prevalence and third regarding mortality among malignant tumors [1] and accounts for 85–90% of all primary hepatic malignancies [2]. Cirrhosis is a major risk factor for HCC, and 60–80% of these tumors arise in patients with cirrhosis. The major chronic liver diseases underlying the development of cirrhosis and HCC include chronic viral

hepatitis (B and C), non-alcoholic steatohepatitis, and alcoholic liver disease. In the United States, the incidence of HCC has increased from 1.4 cases/100,000 in 1976–1980 to approximately 5 cases/100,000 in 2003–2006 [3,4]. Most patients diagnosed with HCC are not amenable to curative treatments because of advanced stage according to Barcelona Clinic Liver Cancer (BCLC) criteria [4].

As an oral multikinase inhibitor, sorafenib (Nexavar, Bayer Healthcare) blocks tumor cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase. Sorafenib also exerts an antiangiogenic role by targeting tyrosine kinase receptors, for example, vascular endothelial growth factor (VEGF) receptor and platelet derived growth factor (PDGF) receptor [5]. This agent has been recommended as standard medical therapy in advanced HCC. However, the survival benefit of sorafenib in advanced HCC is modest and unsatisfactory. Therefore, combining sorafenib with cytotoxic drugs may be a promising strategy to improve the overall efficacy. A review repeated that several studies on combined treatment have shown a tolerable toxicity profile and promising results [6].

S-1 (i.e. tegafur/gimeracil/oteracil potassium, known as Tijiào capsule in China) 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 transarterial chemoembolization (TACE) [7]. 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. Suppression of the activation of 5-FU in the gastrointestinal tract reduces the incidence of gastrointestinal toxicities [8]. S-1 is effective against some solid tumors [9], and also has an acceptable toxicity profile and promising antitumor activity against advanced HCC [10]. Moreover, S-1 plus sorafenib results in greater inhibition of tumor growth and remarkable thymidylate synthetase suppression when compared with S-1 or sorafenib alone in nonobese diabetic/severe combined immunodeficiency mice with subcutaneously inoculated HCC [11].

Literature doesn't show a systematic review of S-1 plus sorafenib for the treatment of HCC and therefore we conducted such a review to assess the efficacy and safety of S-1 for the treatment of advanced HCC.

Methods

Search strategy

We followed the PRISMA recommendations for systematic literature analysis [12]. PubMed, the Cochrane Library, EMBASE and ClinicalTrials.gov were searched using the terms "Hepatocellular Carcinoma" or "HCC" or "Hepatoma" or "Liver cancer" and "S-1"

and "sorafenib" or "Nexavar" in the title or abstract fields. The date of the last search was December 20, 2015. We screened each abstract resulting from these searches for eligibility. We also examined reference lists of each selected original article or conference abstract and the protocol registration system of clinical trials to identify additional articles that might meet our eligibility requirements. Any discrepancies among reviewers were resolved by consensus discussion.

Inclusion criteria

Studies were included in our review if they evaluated the efficacy and safety of S-1 plus sorafenib for treatment of advanced HCC; reported data on at least one of the outcomes of median survival, overall survival (OS), disease-free survival (DFS); and were published on or before December 20, 2015.

Exclusion criteria

1. Duplicated record; 2. Irrelevant topic; 3. Review article; 4. Nonhuman study; 5. Same study from different databases; 6. Meeting abstract; 7. Case report; 8. Letters to the editor; 9. Editorials; 10. Research protocols.

Data collection and registration

The data extracted from each report were: phase, country, study type (prospective or retrospective), number of patients, percentage of men/female; median age of study participants, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, percentage of patients with Child-Pugh score A/B, percentage of patients with hepatitis B/C; related treatment indicators of S-1 and sorafenib (level, dose of S-1, S-1 administration, dose of sorafenib, sorafenib administration, days of one cycle, and total no. of cycles); median overall survival (OS), median progression-free survival (PFS), median time to progression (TTP), tumor response (CR, PR SD PD), disease control rate (DCR), and common toxicities of \geq grade 3 (anemia, thrombocytopenia, neutropenia, elevated AST/ALT, hyperbilirubinemia, diarrhea, rash, HFS and bleeding).

Results

Systematic review flow

The flow diagram of the systematic review is shown in Figure 1. Our initial search yielded 77 references including 10 from PubMed, 62 from Embase, 4 from ClinicalTrials.gov and 1 from Cochrane Library. In the step of "Titles and abstracts screened", there were 57 excluded studies (54 irrelevant topics, 2 reviews and 1 nonhuman study) [11]. In the step of "Full-text articles screened", 5 studies were excluded by reading the full text from 7 studies. In the 5 studies, a same study was

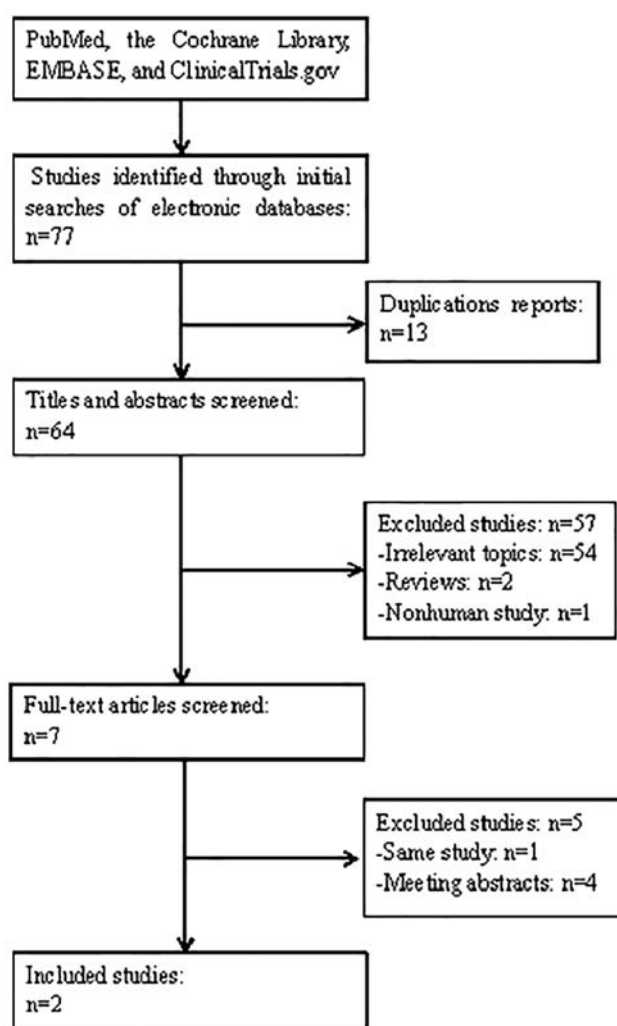


Figure 1. Flow diagram of studies identified, included, and excluded.

registered in ClinicalTrials.gov and then published in the Journal of Investigational New Drugs [13]. The other 4 studies were meeting abstracts.

Baseline patient demographic and disease characteristics

Baseline patient demographic and disease characteristics, which included a total of 65 patients of 2 studies, are summarized in Table 1. One phase I study came from Korea [13] and the other

(phase I/II) came from Japan [14]. The 2 studies were prospective and didn't describe control group. The percentage of male patients ranged from 70.0 to 89.5%. Median age was 59.2 years (range 48.0-65.5). The percentage of hepatitis B virus ranged from 23.1 to 90.0%.

Treatment of S-1 and sorafenib

The relevant treatment data of S-1 and sorafenib are displayed in Table 2. All studies described dose of S-1/sorafenib, days of S-1/sorafenib administration and one cycle. The recommended dose of S-1 and sorafenib was 80 mg/m²/day and 800 mg/day in the Lee et al. phase I study [14], respectively. However, in Ooka et al. phase I study [14], the recommended dose of S-1 and sorafenib was 64 mg/m²/day and 800 mg/day, respectively. It was certain that the recommended dose of sorafenib was 800 mg/day (i.e. 400 mg bid). S-1 and sorafenib in all studies and levels were administered orally on days 1-14 and days 1-21 of a 21-day cycle, respectively.

Efficacy evaluation

Efficacy evaluation of S-1 plus sorafenib for the treatment of advanced HCC are summarized in Table 3. Two studies provided precise OS. Median OS was 10.4 months in the Lee et al. phase I study [13] and 10.5 months in the Ooka et al. phase II study [14], respectively. Unfortunately, there was no OS or PFS in the Ooka et al [15]. No CR was seen in both studies. The DCRs were 52.9 [13] and 61.5 % [14], respectively.

Toxicity

Toxicities of S-1 plus sorafenib are shown in Table 4, which mainly summarizes grade 3 and 4. S-1 plus sorafenib showed tolerable toxicity profile. The incidence of all grades toxicities of more than 30% were HFS and rash in the two studies. The incidence of grade 3/4 toxicities more than 5% were thrombocytopenia, elevated AST/ALT

Table 1. Baseline patient demographic and disease characteristics

Study	Phase	Country	Study type	Patients N	Male/Female (%)	Median age (years)	ECOG PS 0/1/2 (%)	Child-Pugh A/B (%)	Etiology (HBV/HCV%)
Lee, 2012 [14]	I	Korea	Prospective	20	70.0/30.0	48.0	40.0/55.0/5.0	95.0/5.0	90.0/NA
Ooka, 2014 [15]	I	Japan	Prospective	19	89.5/10.5	62.4	78.9/21.1/0	100.0/0	42.1/47.4
	II	Japan	Prospective	26	88.5/11.5	65.5	73.1/26.9/0	100.0/0	23.1/57.7

NA: not available, ECOG PS: Eastern Cooperative Oncology Group performance status, HBV: hepatitis B virus, HCV: hepatitis C virus

Table 2. Treatment of S-1 and sorafenib

Study	Phase	Level	S-1	Dose of S-1 administration	Dose of sorafenib	Sorafenib administration	One cycle	Total No. of cycles
			(mg/m ² /day)	(days)	(mg/day)	(days)	(days)	
Lee 2012 [14]	I	1	50	1-14	800	1-21	21	6
		2	60	1-14	800	1-21	21	25
		3	70	1-14	800	1-21	21	17
		4	80	1-14	800	1-21	21	29
Ooka 2014 [15]	I	1	48	1-14	400	1-21	21	NA
		2a	48	1-14	800	1-21	21	NA
		2b	64	1-14	400	1-21	21	NA
		3	64	1-14	800	1-21	21	NA
		4	80	1-14	800	1-21	21	NA
	II	3	64	1-14	800	1-21	21	NA

NA: not available

Table 3. Efficacy evaluation

Study	Phase	Median OS	Median PFS	Median TTP	Tumor response (%)				DCR
		(months)	(months)	(months)	CR	PR	SD	PD	(%)
Lee, 2012 [14]	I	10.4	3.9	NA	0	5.8	47.1	47.1	52.9
Ooka, 2014 [15]	I	NA	NA	NA	NA	NA	NA	NA	NA
	II	10.5	NA	2.4	0	3.8	57.7	38.5	61.5

NA: not available, OS: overall survival, PFS: progression-free survival, TTP: time to tumor progression, DCR: disease control rate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

Table 4. Toxicity (%)

Study	Phase	Anemia		Thrombocytopenia		Neutropenia		Elevated AST/ALT		Hyperbilirubinemia		Diarrhea		Rash		HFSR		Bleeding	
		Grade		Grade		Grade		Grade		Grade		Grade		Grade		Grade		Grade	
		All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
Lee, 2012 [14]	I	0	0	25	10	20	5	30	25	15	10	35	5	35	0	65	5	5	0
Ooka, 2014 [15]	I	NA	NA	NA	NA	NA	NA	NA	5.3	NA	NA	NA	NA	NA	NA	NA	11	NA	5.3
	II	73.1	3.8	80.8	23.1	50	19.2	92.3	38.5	92.3	15.4	19.2	0	42	12	62	3.8	12	3.8

NA: not available, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HFSR: hand-foot syndrome

and hyperbilirubinemia in the both studies. The incidence of the top three grade 3/4 toxicities were elevated AST/ALT (25%), thrombocytopenia (10%) and hyperbilirubinemia (10%) in the Lee et al. study [13] and elevated AST/ALT (38.5%), thrombocytopenia (23.1%) and neutropenia (19.2%) in the Ooka et al. study [14]. Obviously, the most common grade 3/4 toxicities were elevated

AST/ALT and thrombocytopenia.

Discussion

There is currently little information on S-1 plus sorafenib for the treatment of HCC. However, studies of S-1 or sorafenib monotherapy in HCC have been largely reported with or without con-

trolled group. In a study examining S-1 treatment vs best supportive care (BSC), S-1 treatment prolonged significantly OS by 6.8 months (from 8.3 to 15.1 months) ($p=0.027$) [15]. In another study, S-1 treatment vs placebo failed to prolong OS (337.5 vs 340.0 days) [16]. In another two phase III, randomized, placebo-controlled clinical trials, sorafenib treatment prolonged OS by 2.3 to 2.8 months (one from 4.2 to 6.5 months [17], and the other from 7.9 to 10.7 months [18]). This systematic review reveals that the treatment of S-1 plus sorafenib showed modest clinical efficacy in advanced HCC. In the two studies, the median OS was 10.4 and 10.5 months, respectively. Owing to lack of control group in the two included studies, the contribution of S-1 plus sorafenib in advanced HCC is not clear.

This systematic review also shows that S-1 plus sorafenib had a tolerable toxicity profile in patients with advanced HCC. The most frequently described toxicities of S-1 and sorafenib are anemia, thrombocytopenia, neutropenia, elevated AST and ALT, hyperbilirubinemia, reduced serum albumin, fatigue, nausea, diarrhea, stomatitis, pigmentation, HFS, bleeding, and rash. Toxicities of S-1 plus sorafenib in this systematic review were mainly of grade 3 and 4. In both studies, the incidence of grade 3/4 toxicities more than 5% were thrombocytopenia, elevated AST/ALT and hyperbilirubinemia, which were observed in 10%, 25%, 10% [13] and 23.1%, 38.5%, 15.4% [14], respectively. The incidence of the top three grade 3/4 toxicities was elevated AST/ALT (25%), thrombocytopenia (10%) and hyperbilirubinemia (10%) in the Lee et al. study [13] and elevated AST/ALT (38.5%), thrombocytopenia (23.1%) and neutropenia (19.2%) in the Ooka et al. study [14]. Obviously, in the treatment of S-1 plus sorafenib, the most common grade 3/4 toxicities were elevated AST/ALT and thrombocytopenia. This was similar to the studies of Richly et al. [19] and Hsu et al. [20], where the incidence of elevated AST/ALT and thrombocytopenia were observed in 33% and 20% of the patients, respectively. Moreover, the incidence of all-grade toxicities of more than 30% were HFS and rash in the two studies, which were similar to the studies of Petrini et al. [21] and Abou-Alfa et al. [22]. HFS has been connected with some antineoplastic agents, such as molecular targeted drugs, 5-FU and its derivatives (S-1 and capecitabine [23]), and its pathogenesis is not clear [24].

In the included studies, the dose of sorafenib was the same, but the dose of S-1 was different in the combination therapy. Lee et al. designed to escalate S-1 at 4 different dose levels with a fixed dose

of sorafenib (400 mg bid). The 4 dose levels were as follows: level 1, D1-14 S-1 50 mg/m²/day; level 2, D1-14 S-1 60 mg/m²/day; level 3, D1-14 S-1 70 mg/m²/day; and level 4, D1-14 S-1 80 mg/m²/day. Finally, the recommended dose of S-1 was 80 mg/m²/day [13]. In a phase I trial of transarterial infusion chemotherapy with cisplatin plus S-1 for HCC treatment, cisplatin (65 mg/m²) was administered with S-1 at 50 mg/m²/day (level 1), 60 mg/m²/day (level 2), or 80 mg/m²/day (level 3), and the result supported the dose of 80 mg/m²/day [25]. In the phase I study of Ooka et al., the dose of S-1 and sorafenib was planned as follows: cohort 1, S-1 48 mg/m²/day and sorafenib 400 mg/day; cohort 2a, S-1 48 mg/m²/day and sorafenib 800 mg/day; cohort 2b, S-1 64 mg/m²/day and sorafenib 400 mg/day; cohort 3, S-1 64 mg/m²/day and sorafenib 800 mg/day; cohort 4, S-1 80 mg/m²/day and sorafenib 800 mg/day. Finally, the recommended dose of S-1 and sorafenib in patients with advanced HCC was 64 mg/m²/day and 800 mg/day, respectively [14]. Thus it can be seen that the recommended dose of S-1 and sorafenib was 80 or 64 mg/m²/day and 800 mg/day, respectively.

There are some limitations in this systematic review that should be acknowledged. Firstly, the two studies included were not case-control. Hence, the evidence is not high. Secondly, there may be phase bias in this review. Two phases I and one phase II were included in these two studies. The data were extracted from a phase I and a phase II results, because OS and adequate toxicities could not be extracted from the other phase I result [14]. Thirdly, there is clearly a lot of confounding factors (ECOG PS score, age and etiology) that make analysis and summary difficult. Fourthly, efficacy evaluation except OS was not consistent between the two studies with one study using PFS while the other was using TTP.

Conclusions

The current evidence from the available clinical studies suggests that S-1 plus sorafenib showed modest clinical efficacy and tolerable toxicity profile in patients with advanced HCC. The recommended dose of S-1 and sorafenib was 80 or 64 mg/m²/day and 800 mg/day, respectively. Randomized, multicentric, controlled trials are eagerly warranted to further investigate this treatment option for advanced HCC.

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Conflict of interests

The authors declare no conflict of interests

Authors' contributions

WH, LY and DL drafted the manuscript. XF, WH and LY participated in the design of the study. The remaining authors participated in the coordination and helped to write the manuscript.

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