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Cost-effectiveness analysis of antiviral therapy in patients with advanced hepatitis B virus-related hepatocellular carcinoma treated with sorafenib

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Key words
cost-effectiveness, antiviral therapy, hepatitis B virus, hepatocellular carcinoma, sorafenib.

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Abstract

Background and Aim: Antiviral therapy has been demonstrated to significantly improve the survival in patients with advanced hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). The aim of the study was to investigate the cost-effectiveness of antiviral therapy in patients with advanced HBV-related HCC treated with sorafenib.
Methods: To conduct the analysis, a Markov model comprising three health states (progression-free survival, progressive disease, and death) was created. The efficacy data were derived from medical records. Cost data were collected based on the Chinese national drug prices. Utility data came from the previously published studies. One-way sensitivity analyses as well as probabilistic sensitivity analyses were performed to explore model uncertainties.
Results: In the base-case analysis, addition of antiviral therapy to sorafenib generated an effectiveness of 0.68 quality-adjusted life years (QALYs) at a cost of $25 026.04, while sorafenib monotherapy gained an effectiveness of 0.42 QALYs at a cost of $20 249.64. The incremental cost-effectiveness ratio (ICER) was $18 370.77/QALY for antiviral therapy group *versus* non-antiviral therapy group. On the other hand, the ICER between the two groups in patients with high or low HBV-DNA load, with or without cirrhosis, normal or elevated alanine aminotransferase/aspartate aminotransferase were $16 613.97/QALY, $19 774.16/QALY, $14 587.66/QALY, $19 873.84/QALY, $17 947.07/QALY, and $18 785.58/QALY, respectively.
Conclusions: Based on the cost-effectiveness threshold ($20 301.00/QALY in China), addition of antiviral therapy to sorafenib is considered to be a cost-effective option compared with sorafenib monotherapy in patients with advanced HBV-related HCC in China from the patient's perspective.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly diagnosed malignancy and the second leading cause of cancer death worldwide.[1] Hepatectomy, liver transplantation, and radiofrequency ablation are potentially curative treatments for patients with early stage HCC.[2] Unfortunately, most of the HCC patients are found incurable at the time of diagnosis because of tumor progression and underlying liver dysfunction.[3] Sorafenib has been approved for the treatment of HCC with vascular invasion and/or distant metastasis.[4,5] Regardless of the multiple treatment alternatives mentioned above, the clinical outcome of advanced HCC is poor.

The incidence of HCC in China accounts for more than 50% of cases worldwide, and chronic HBV infection has been established as the dominant cause.[6] In China, 85% of the HCC cases are HBV-related.[7] Some previous studies have revealed a high HBV virus load as the key prognostic factor for the progression and recurrence of HCC.[8–11] Recently, a series of studies have investigated the function of antiviral therapy in the management of HBV-related HCC, which demonstrated that antiviral therapy improved the survival of advanced HBV-related HCC patients when combined with sorafenib, especially in patients with high HBV-DNA level.[12,13]

However, these studies did not take long-term therapy costs into consideration, which might result in a substantial economic burden for advanced HBV-related HCC patients because of the antiviral therapy and the prolongation of survival. On the other hand, there have been a large number of studies focusing on the cost-effectiveness of antiviral treatments in chronic hepatitis B patients, which suggested that antiviral therapy is a cost-effective option for patients with HBV infection.[14–16] Nevertheless, there has been no economic evaluation studying antiviral therapy for advanced HBV-related HCC patients treated with sorafenib. Is it a cost-effective strategy to give antiviral therapy combined with sorafenib for advanced HBV-related HCC patients? Therefore, the aim

of the study was to conduct an economic model to evaluate the long-term clinical benefit and cost-effectiveness of antiviral therapy for advanced HBV-related HCC patients treated with sorafenib.

Methods

Patients. In order to conduct the analysis, the information of a cohort of patients was collected from the medical records of the Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University (China): (i) confirmed advanced HCC (histologically or clinically confirmed); (ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0–2; (iii) Child–Pugh liver function class A/B; (iv) treatment with sorafenib as first-line regimen from 2010 to 2013; (v) detectable hepatitis B surface antigen positive; and (6) without co-infection with other viruses (hepatitis A, C, D virus or human immunodeficiency virus. This retrospective study was approved by the Ethics Committee of West China Hospital, Sichuan University. Informed consent was obtained from the patients or her/his family members.

Model structure. A decision analytic Markov model was constructed to simulate clinical and economic outcomes of patients with HBV-related HCC treated with sorafenib. The model consisted of three mutually exclusive health states: progression free survival (PFS), progressive disease (PD), and death. The cycle length was 1 month, and during each cycle, the patients either remained in their assigned health state or progressed to another health state as represented in Figure 1. Transition probabilities between health states were estimated according to the method described by previous studies.[17]

Cost data. Potentially differential direct medical costs included the costs of sorafenib, antiviral drugs, transcatheter arterial chemoembolization (TACE), and tests (laboratory and radiological tests). The prices of sorafenib, antiviral drugs, and TACE were obtained according to the Chinese national drug prices. The unit costs of laboratory and radiological tests were retrieved from West China Hospital, Sichuan University, China. Furthermore, the costs of grade 3/4 adverse events (AEs) were also included in our analysis. In addition, we also considered the assistance programs in our study. In the assistance program for sorafenib, the patients paid for the costs of the first 3 months, and then they obtained sorafenib for free until the occurrence of endpoints (PD, death, intolerance of AEs). All costs were converted to US dollars.

Effectiveness data. The effectiveness data of sorafenib group and sorafenib plus antiviral therapy group were extracted from the survival analysis of the patients collected from the medical records. Health outcomes were denoted in quality-adjusted life years (QALYs) gained, and utility scores of Markov states were obtained from previously published studies.[18]

Cost-effectiveness analysis. The cost-effectiveness analysis was conducted from the Chinese patient's perspective. The outcome of the cost-effectiveness analysis was measured as incremental cost-effectiveness ratio (ICER) of sorafenib plus antiviral therapy group compared with sorafenib monotherapy group, which was calculated as incremental costs divided by

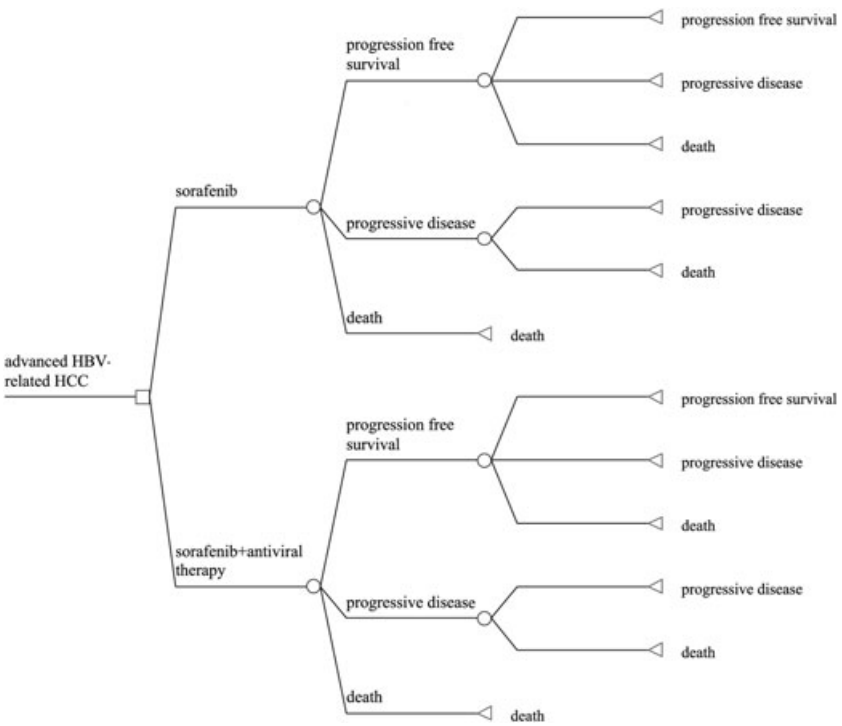

Figure 1 Markov model diagram for advanced hepatitis B virus (HBV)—related hepatocellular carcinoma (HCC).

incremental effectiveness. Willingness to pay (WTP) threshold in the model was set at 3 × the per capita GDP of China ($20 301.00/QALY) based on the WHO guidelines for cost-effectiveness analysis.[19] As the survivals in both groups were short, discount rates were not considered in the study.

Subgroup analyses. We also conducted subgroup analyses based on several essential clinical variables. The efficacy data of patients were also derived from the Kaplan–Meier survival curves of patients in these subgroups. The cost-effectiveness data of the addition of antiviral therapy to sorafenib compared with sorafenib monotherapy in these subgroups were measured as the methods mentioned previously.

Sensitivity analyses. To examine the impact of parameters uncertainty in our model, one-way sensitivity analyses were conducted. The results of the one-way sensitivity analyses were expressed as a tornado diagram. Furthermore, a probabilistic sensitivity analysis based on a Monte Carlo simulation of 1000 patients was also conducted, the results of which were presented using cost-effectiveness acceptability curves and scatter plots diagrams.

Model creation and data analysis were conducted by TreeAge 2011 (TreeAge, Williamstown, Massachusetts, USA) and SPSS Statistics (IBM, Armonk, New York, USA).

Results

Patients' clinical characteristics. Of the total 92 patients who fulfilled the inclusion criteria, 41 patients were from the antiviral group and 51 were from the non-antiviral group. The data of the patients in both groups, including gender, age, hepatitis e antigen, ECOG PS, Child-Pugh classification, Barcelona Clinic Liver Cancer (BCLC) stage, alpha fetoprotein (AFP), alanine aminotransferase (ALT)/aspartate aminotransferase (AST), total bilirubin (TBIL), liver cirrhosis, and HBV-DNA were analyzed, and the results were shown in Table 1. The baseline characteristics were balanced between the two groups, and there were no significant differences.

Treatment. The initial dose of sorafenib for advanced HCC was 400 mg twice per day. In general, patients in the antiviral group received 94.2% of the full dosage of sorafenib, and patients in the non-antiviral group received 90.2% of the full dosage of sorafenib. In the antiviral group, 20 patients were treated with lamivudine (100 mg per day), 8 patients were treated with adefovir dipivoxil (ADV, 10 mg per day), 7 patients were treated with entecavir (ETV, 0.5 mg per day), and 5 patients were treated with telbivudine (600 mg per day). Besides, there was one patient treated with ADV (10 mg per day) plus ETV (0.5 mg per day). The median course of antiviral treatment was 10.3 months (range: 1.7–28 months). During the treatment, there were only two patients who developed viral resistance, one in entecavir group and the other in adefovir dipivoxil group. ADV (10 mg per day) and ETV (0.5 mg per day) were added to the patients with entecavir resistance and adefovir dipivoxil resistance, respectively. Antiviral therapy did not increase adverse events to patients treated with sorafenib (Table 2).

Health outcomes. The survival data in both groups were presented as Kaplan–Meier survival curves in Figure 2. The median overall survival was 12.2 months in the antiviral group and 8.0 months in the non-antiviral group. In terms of median progression free survival, the data were 6.0 months in the antiviral group and 4.5 months in the non-antiviral group. The monthly transition probability between the Markov states and utility scores were presented in Table 2. Overall, the effectiveness was 0.68 QALYs in the antiviral group and 0.42 QALYs in the non-antiviral group. The incremental effectiveness between the two groups was 0.26 QALYs.

Cost. Of the patients, 82.9% (34 of 41) in the antiviral group and 76.5% (39 of 51) in the non-antiviral group received assistance from the assistance programs. The monthly costs of sorafenib, antiviral therapy, TACE, tests, and grade 3/4 AEs were shown in Table 2. During a life span time, patients in the antiviral group and non-antiviral group cost $25 026.04 and $20 249.64, respectively. The incremental costs were $4776.40 between the two groups.

Cost-effectiveness analysis. According to the cost analysis and effectiveness analysis described previously, the ICER between the antiviral group and non-antiviral group was $18 370.77/QALY (Table 2). Based on the cost-effectiveness threshold that was set in the study, the addition of antiviral therapy to HBV-related patients treated with sorafenib was of great cost-effectiveness value.

Subgroup analyses. Furthermore, we conducted a series of subgroup analyses to investigate the cost-effectiveness of patients with different essential baseline characteristics (Table 3). Addition of antiviral therapy to sorafenib was suggested as a cost-effective regimen both in patients with low (ICER $19 774.16/QALY) or high HBV-DNA load (ICER $16 613.97/QALY). Likewise, whether for patients with liver cirrhosis or without liver cirrhosis, addition of antiviral therapy to sorafenib was also likely to be a potentially cost-effective treatment. We also found similar results in patients with elevated (ICER $18 785.58/QALY) or normal ALT/AST (ICER $17 947.07/QALY). Thus, the subgroup analyses demonstrated that addition of antiviral therapy to sorafenib could improve the cost-effectiveness of sorafenib monotherapy regardless of above baseline characteristics.

Sensitivity analyses. To investigate the impact of the most influential variables on our results, one-way sensitivity analyses were conducted by varying the model parameters over their range of value (±30%). The most influential parameters in both the antiviral group and the non-antiviral group were shown in the tornado diagram (Fig. 3). In the analyses, the key drivers on the results were duration of PFS state for antiviral group, duration of PFS state for non-antiviral group, and duration of PD state for non-antiviral group. Parameters such as utility of PD state, price of sorafenib, costs of tests for antiviral group, utility of PFS state, costs of tests for non-antiviral group, costs of TACE for non-antiviral group, costs of TACE for antiviral group,

Table 1 Baseline characteristics of HBV-related HCC patients treated with sorafenib

Variables	Total ($n = 92$)	Antiviral group ($n = 41$)	Non-antiviral group ($n = 51$)	*P*-value
Age (years)				
Median (range)	49 (28-77)	48 (36-77)	50 (28-71)	0.611
Male [*n* (%)]	80 (87.0)	36 (87.8)	44 (86.3)	0.828
HBeAg				
Positive [*n* (%)]	18 (19.6)	9 (22.0)	9 (17.6)	0.605
Negative [*n* (%)]	74 (80.4)	32 (78.0)	42 (82.4)	
ECOG PS				
0 [*n* (%)]	20 (21.7)	8 (19.5)	12 (23.5)	0.894
1 [*n* (%)]	63 (68.5)	29 (70.7)	34 (66.7)	
2 [*n* (%)]	9 (9.8)	4 (9.8)	5 (9.8)	
Child–Pugh class				
A [*n* (%)]	70 (76.1)	32 (78.0)	38 (74.5)	0.692
B [*n* (%)]	22 (23.9)	9 (22.0)	13 (25.5)	
BCLC stage				
B [*n* (%)]	27 (29.3)	13 (31.7)	14 (27.5)	0.656
C [*n* (%)]	65 (70.7)	28 (68.3)	37 (72.5)	
AFP (ng/ml)				
≤400 [*n* (%)]	45 (48.9)	19 (46.3)	26 (51.0)	0.658
>400 [*n* (%)]	47 (51.1)	22 (53.7)	25 (49.0)	
ALT/AST				
Normal [*n* (%)]	28 (30.4)	12 (29.3)	16 (31.4)	0.827
Elevated [*n* (%)]	64 (69.6)	29 (70.7)	35 (68.6)	
TBIL				
Normal [*n* (%)]	75 (81.5)	31 (75.6)	44 (86.3)	0.190
Elevated [*n* (%)]	17 (18.5)	10 (24.4)	7 (13.7)	
Liver cirrhosis				
Yes [*n* (%)]	43 (46.7)	23 (56.1)	20 (39.2)	0.107
No [*n* (%)]	49 (53.3)	18 (43.9)	31 (60.8)	
Pre-sorafenib HBV-DNA				
$\leq 10^4$ copies/mL [*n* (%)]	55 (59.8)	23 (56.1)	32 (62.7)	0.518
$>10^4$ copies/mL [*n* (%)]	37 (40.2)	18 (43.9)	19 (37.3)	
MVI				
Yes [*n* (%)]	49 (53.3)	20 (48.8)	29 (56.9)	0.440
No [*n* (%)]	43 (46.7)	21 (51.2)	22 (43.1)	
Extrahepatic metastasis				
Yes [*n* (%)]	23 (25.0)	11 (26.8)	12 (23.5)	0.716
No [*n* (%)]	69 (75.0)	30 (73.2)	39 (76.5)	
TACE				
Yes [*n* (%)]	32 (34.8)	15 (36.6)	17 (33.3)	0.746
No [*n* (%)]	60 (65.2)	26 (63.4)	34 (66.7)	

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MVI, macroscopic vascular invasion; xTACE, transcatheter arterial chemoembolization; MVI, macroscopic vascular invasion.

costs of antiviral therapy before progression, duration of PD state for antiviral group, costs of antiviral therapy after progression, and extra costs after progression were also important factors influencing our results. However, parameters including costs of AEs for antiviral group and costs of AEs for non-antiviral group had little impact on the robustness of the analysis.

The uncertainty of the cost-effectiveness analysis was also investigated by a probabilistic sensitivity analysis. The results of the analysis were presented in Figure 4 using cost-effectiveness acceptability curves. The acceptability curves showed that the addition of antiviral therapy to sorafenib was a more cost-effective treatment in 82.2% of the simulations at the WTP threshold of $20 301.00/QALY. According to WTP threshold beyond $20 301.00/QALY, combination of antiviral therapy with sorafenib was also the better option compared with sorafenib monotherapy.

Moreover, scatter plots diagrams for our analysis also indicated that addition of antiviral therapy to sorafenib was a cost-effective option compared with sorafenib monotherapy when the WTP threshold was set at $20 301.00/QALY (Fig. 4B).

We also tested the stability of our model from the societal perspective. Overall, patients in the antiviral group gained 0.68 QALYs at a cost of $57 468.22, while patients in the non-antiviral group cost $36 233.30 and obtained 0.42 QALYs. The

Table 2 Base-case cost and effectiveness estimated

AEs [*n* (%)]	Antiviral group		Non-antiviral group	
	Total	Grade 3/4	Total	Grade 3/4
HFS	21 (51.2)	2 (4.9)	32 (62.7)	4 (7.8)
Diarrhea	17 (41.5)	3 (7.3)	23 (45.1)	5 (9.8)
Fatigue	10 (24.4)	0 (0.0)	9 (17.6)	0 (0.0)
Hypertension	4 (9.8)	0 (0.0)	6 (11.8)	1 (2.0)
Anorexia	10 (24.4)	2 (4.9)	12 (23.5)	2 (3.9)
Nausea	9 (22.0)	1 (2.4)	10 (19.6)	2 (3.9)
Cost per month ($)				
Cost of sorafenib	3643.93		4511.33	
Antiviral cost before PD	123.16		0.00	
Cost of TACE	133.42		195.02	
Cost of tests	182.10		187.06	
AE-related costs	4.51		6.68	
Extra cost after PD	102.50		102.50	
Antiviral cost after PD	58.00		0.00	
Cost for the PFS state	3953.70		4705.07	
Costs for the PD state	342.60		289.56	
Utility				
PFS	0.76		0.76	
PD	0.68		0.68	
Death	0		0	
Transition probability				
$P_{\text{PFS-PFS}}$	0.836		0.774	
$P_{\text{PFS-PD}}$	0.109		0.143	
$P_{\text{PFS-death}}$	0.055		0.083	
$P_{\text{PD-PD}}$	0.894		0.820	
$P_{\text{PD-death}}$	0.106		0.180	
Cost ($)				
Cost for the PFS state	22 131.08		18 466.36	
Cost for the PD state	2148.14		1017.87	
Total cost	25 026.04		20 249.64	
Incremental cost		4776.40		
Effectiveness (QALYs)				
Effectiveness for the PFS state	0.32		0.22	
Effectiveness for the PD state	0.36		0.20	
Total effectiveness	0.68		0.42	
Incremental effectiveness		0.26		

AEs, adverse events; HFS, hand-foot syndrome; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TACE, transcatheter arterial chemoembolization.

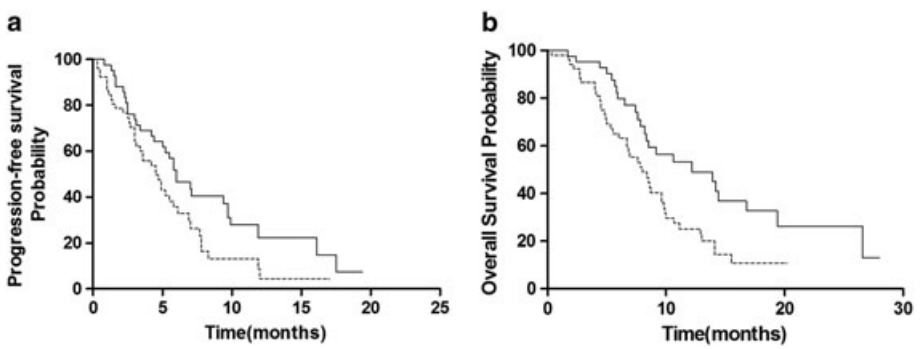

Figure 2 Kaplan–Meier curves of PFS and OS. (A) Kaplan–Meier estimates of the progression-free survival of patients in the antiviral therapy group and non-antiviral therapy group. (B) Kaplan–Meier estimates of the overall survival of patients in the antiviral therapy group and non-antiviral therapy group. —, Antiviral group; - - -, Non-antiviral group.

Table 3 Cost-effectiveness analysis of subgroups classified according to essential parameters

Variables		Cost ($)	Incremental cost ($)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ($/QALYs)
Baseline HBV-DNA $\leq 10^4$ copies/mL	Antiviral	27 781.86	4943.54	0.79	0.25	19 774.16
	Non-antiviral	22 838.32		0.54		
Baseline HBV-DNA $> 10^4$ copies/mL	Antiviral	26 397.00	6147.17	0.71	0.37	16 613.97
	Non-antiviral	20 249.83		0.34		
With liver cirrhosis	Antiviral	24 584.46	4668.05	0.70	0.32	14 587.66
	Non-antiviral	19 916.41		0.38		
Without liver cirrhosis	Antiviral	25 872.19	4968.46	0.78	0.25	19 873.84
	Non-antiviral	20 903.73		0.53		
Elevated ALT/AST	Antiviral	26 200.60	4508.54	0.68	0.24	18 785.58
	Non-antiviral	21 692.06		0.44		
Normal ALT/AST	Antiviral	25 538.12	4845.71	0.76	0.27	17 947.07
	Non-antiviral	20 692.41		0.49		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.

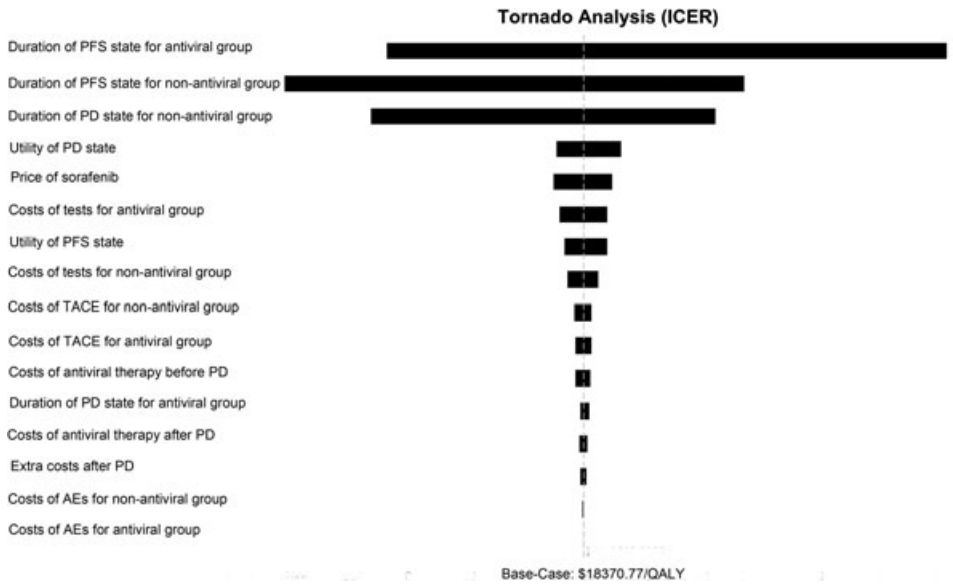

Figure 3 Tornado diagram of the one-way sensitivity analysis for ICER. AEs, adverse events; ICER, incremental cost-effectiveness ratio; PD, progressive disease; PFS, progression-free survival; QALY, quality-adjusted life year; TACE, transcatheter arterial chemoembolization.

incremental costs and effectiveness between the two groups were $21 234.92 and 0.26 QALYs, respectively. The ICER between the two groups was $81 672.77/QALY. Thus, from the societal perspective, addition of antiviral therapy to sorafenib was not demonstrated to be of cost-effectiveness value compared with sorafenib monotherapy.

Discussion

Hepatocellular carcinoma is rampant in many countries around the world. The incidence of HCC is much higher in China than in any other country.[20] Although a series of treatments have improved the overall survival of HCC, the prognosis of advanced HCC is unsatisfactory. HBV has been well known as the key risk factor for HCC, and a high serum HBV-DNA load is associated with the progression of HCC in patients with chronic hepatitis B.[8–11] Recently, a series of articles suggested that the survival of advanced HBV-related HCC was significantly improved by using antiviral therapy.[12,13] However, all these studies are lacking of financial implications.[21] Sorafenib is the only molecular agent to treat advanced HCC while it has not been demonstrated to be a cost-effective drug in China;[22] hence, it is of great importance to distinguish the population who may benefit from the agent most, or, in other words, to make the agent more cost-effective.

In our study, the addition of antiviral therapy to sorafenib improved the effectiveness of advanced HBV-related HCC by 0.26 QALYs when compared with sorafenib monotherapy (0.68 QALYs *vs* 0.42 QALYs) with an incremental cost of $4776.40 ($25 026.04 *vs* $20 249.64). The ICER in our analysis was

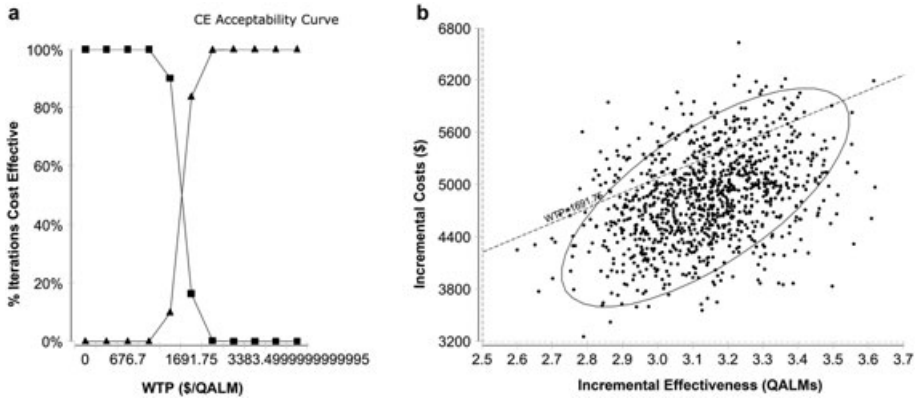

Figure 4 Cost-effectiveness acceptability curves and scatter plots diagrams of antiviral therapy group and non-antiviral therapy group. (A) Cost-effectiveness acceptability curves of antiviral therapy group and non-antiviral therapy group. (B) Scatter plots diagrams of antiviral therapy group and non-antiviral therapy group. CE, cost-effectiveness; QALM, quality-adjusted life month; WTP, willingness to pay.

$18 370.77/QALY of antiviral group compared with non-antiviral group, which was lower than the WTP threshold set in our study ($20 301.00/QALY). Thus, based on the results of our study, we have demonstrated that the addition of antiviral therapy to sorafenib is likely to be a cost-effective option for patients with advanced HBV-related HCC in China.

Hepatitis B virus replication is associated with severe liver cirrhosis and dysfunction, and the level of serum HBV-DNA is an important risk factor for HCC.[23] A high level of HBV-DNA in HCC patients independently predicted poor disease-free survival and OS after surgical resection.[8–11] For HCC patients treated with sorafenib, the impacts of the HBV load and antiviral therapy on survival have demonstrated by some retrospective studies.[12,13] Antiviral therapy could improve OS of HBV-related HCC patients treated with sorafenib, especially in patients with high baseline HBV-DNA load. In our study, the efficacy data were consistent with previous studies both in high baseline HBV-DNA load group and in low baseline HBV-DNA load group. Addition of antiviral therapy to sorafenib was demonstrated to be an economic regimen for patients with advanced HBV-related HCC no matter the baseline viral load. The financial implication was improved more significantly in the high viral load group as the survival was prolonged much longer by antiviral therapy in the high HBV-DNA load group than in the low HBV-DNA load group. It could be interpreted that antiviral therapy could decrease HBV-DNA replication, decrease the risk of liver failure, and increase the chances of receiving more treatment modalities for HBV-related HCC.

A large part of patients with hepatitis B will develop cirrhosis and complications of end-stage liver disease.[24] Previous studies have shown the marked decrease in survival among patients with decompensated cirrhosis.[25,26] In our study, we have demonstrated that antiviral therapy may decrease the progression of cirrhosis, hepatic decompensation, and prolong the survival of patients with advanced HBV-related HCC. This could be interpreted that antiviral therapy could suppress HBV replication, normalize liver function, and reduce hepatitis necroinflammation and fibrosis in patients with chronic hepatitis B. Thus, addition of antiviral therapy to sorafenib could also improve the cost-effectiveness both in liver cirrhosis group and no liver cirrhosis group.

Liver dysfunction has been also demonstrated as a prognostic factor for HCC; the prognosis of unresectable HCC patients with impaired liver function is much worse.[27,28] ALT/AST was the primary indicator of liver function. Antiviral therapy could significantly improve the survival regardless of the ALS/AST status of these patients. Moreover, addition of antiviral therapy to sorafenib could improve the economic implication of sorafenib both in elevated ALT/AST group and normal ALT/AST group. This may be explained that antiviral therapy could decrease the viral load and improve liver function in patients with advanced HBV-related HCC.[29] On the other hand, given the improved liver function, these patients could become available to more treatment option.

It should be pointed out that cost-effectiveness analysis could be conducted from different perspectives, with the argument that which perspective should be used to enhance the accuracy and extend the application of the results of the analysis.[30] Thus, we also conducted our analysis from the societal perspective in the sensitivity analysis. However, the results from the societal perspective were not consistent with the results from the patient's perspective. The ICER was $81 672.77/QALY from the societal perspective, which was much higher than the cost-effectiveness threshold set in the study. Given the high price of sorafenib and the modest incremental effectiveness between the two groups, it was no wonder that addition of antiviral therapy to sorafenib was not a more cost-effective option compared with sorafenib monotherapy from the societal perspective.

It is essential that several limitations of this current study need to be addressed. First, as the data in our study were retrospectively collected from medical records, prospective randomized control trials are required to further verify the role of antiviral therapy in improving the cost-effectiveness of sorafenib in patients with HBV-related HCC. Second, because of the lack of utility data for HCC patients in China, the data were obtained from literature previously published abroad, which may not reflect the Chinese situation exactly. In addition, the costs of the supportive care were not included in our analysis as the data were too complicated to calculate.

In conclusion, our analysis suggested that compared with sorafenib monotherapy, addition of antiviral therapy to sorafenib

is a more cost-effective option for advanced HBV-related HCC patients in China. Moreover, we demonstrated that antiviral therapy can also improve the cost-effectiveness of sorafenib regardless of the HBV-DNA load, with or without cirrhosis and liver function status. To the best of our knowledge, this is the first study to investigate the cost-effectiveness of antiviral therapy in patients with advanced HBV-related HCC treated with sorafenib. Unlike those clinical trials, this analysis provided evidences for addition of antiviral therapy to the treatment of HBV-related HCC from an economic aspect, and the results of the analysis can also help for the decision-making of the patients, the governments, and the healthcare financial structures.

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