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ORIGINAL RESEARCH

Additional Hepatic Arterial Infusion Chemotherapy to Sorafenib Was Cost-Effective for Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis

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Purpose: The combination of sorafenib and hepatic arterial infusion chemotherapy (SoHAIC) has shown to enhance overall survival rates in patients with advanced hepatocellular carcinoma and major portal vein tumor thrombosis (HCC-Vp3-4) compared to sorafenib alone. Our objective was to evaluate the cost-effectiveness of SoHAIC versus sorafenib for the treatment of HCC-Vp3-4, taking into account the viewpoint of Chinese healthcare payers.

Methods: This pharmacoeconomic study employed a Markov model to assess the cost-effectiveness of treating HCC-Vp3-4 with SoHAIC in comparison to sorafenib. The patient characteristics were drawn from individuals from the trial conducted between June 2017 and November 2019, with cost and health value data sourced from published literature. The primary outcome measure in this research was the incremental cost-effectiveness ratio (ICER), which indicates the additional cost per quality-adjusted life year (QALY). The willingness-to-pay (WTP) threshold per QALY was set at $30,492.00. Furthermore, 1-way sensitivity and probabilistic sensitivity analyses were carried out to validate the consistency of the results.

Results: In the baseline scenario, sorafenib resulted in 0.42 QALY at a cost of $10,507.89, while SoHAIC generated 1.66 QALY at a cost of $32,971.56. When comparing SoHAIC to sorafenib, the ICER was $18,237.20 per QALY, which was below the WTP threshold per QALY. Furthermore, the 1-way sensitivity analysis demonstrated that the ICER remained within the WTP threshold despite fluctuations in variables. In the probabilistic sensitivity analysis, SoHAIC had a 98.8% probability of being cost-effective at the WTP threshold, considering a wide range of parameters.

Conclusion: In this cost-effectiveness evaluation, SoHAIC demonstrated cost-effectiveness over sorafenib for HCC with major portal vein tumor thrombosis, as observed from the perspective of a Chinese payer.

Keywords: HCC, portal vein tumor thrombosis, sorafenib, HAIC, Cost-effectiveness

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide, with China accounting for half of the confirmed cases globally.[1] Portal vein tumor thrombosis (PVTT) is detected in approximately 16%–30% of HCC patients at the time of diagnosis, leading to a poor prognosis.[2] While oral sorafenib is the established first-line treatment for patients with advanced HCC and PVTT, individuals with HCC and major PVTT (invading first branch [Vp3] or main trunk [Vp4] of portal vein, HCC-Vp3-4) typically have a median survival of less than six months post sorafenib treatment.[3]

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Transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) have shown limited benefits in patients with HCC and PVTT.[4–6] Hepatic arterial infusion chemotherapy (HAIC) enables the delivery of a concentrated dose of medication directly to liver tumors, resulting in a significant local antitumor effect. As per Japanese and Chinese guidelines, HAIC is recommended as the preferred treatment for HCC with PVTT, particularly in cases of major PVTT.[7,8] Additionally, the combination of sorafenib with HAIC (SoHAIC) has demonstrated enhanced survival outcomes over sorafenib in patients with HCC-Vp3-4.[9,10]

According to the "Chinese Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2024 Edition)", based on the findings from the IMbrave150, ORIENT-32, and CARES-310 studies, the combination therapies of atezolizumab with bevacizumab, sintilimab with a bevacizumab biosimilar, and camrelizumab with rivoceranib have demonstrated superior efficacy compared to monotherapy with sorafenib.[11] These combination therapies are recommended as first-line treatment options. However, several studies have raised concerns regarding the cost-effectiveness of atezolizumab with bevacizumab and sintilimab with a bevacizumab biosimilar when compared to sorafenib.[12,13] Meanwhile, the economic evaluation of camrelizumab with rivoceranib relative to sorafenib remains a subject of debate.[14,15] In China, the vast population of patients with HCC, coupled with limited medical resources, underscores the necessity for cost-effectiveness analyses of HCC treatment strategies to optimize societal benefits.[16,17] Consequently, our study aimed to compare the cost-effectiveness of SoHAIC compared to sorafenib in patients with HCC-Vp3-4 within the Chinese healthcare system.

Methods

The Trial Design

This Phase II randomized trial, conducted at a medical institution in China, compared the efficacy of SoHAIC with sorafenib in patients diagnosed with HCC-Vp3-4.[10] The primary inclusion criterion for the trial was the presence of HCC-Vp3-4 without prior intra-arterial or systemic therapy, with additional criteria specified on clinicaltrials.gov under registration NCT03009461. Between June 2017 and November 2020, a total of 64 eligible patients were randomly assigned to two groups, with 32 receiving SoHAIC treatment and 32 receiving sorafenib treatment in a 1:1 ratio. Among the participants, the mean age was 56 years, with 61 (95%) men. Of the individuals, 89.1% (57/64) had hepatitis B virus (HBV) infection, 44% (28/64) had HCCs with Vp3, and 56% (36/64) had HCCs with Vp4. Further treatment details can be found in the previous study.[10] Patients in the SoHAIC group underwent a maximum of six cycles of HAIC followed by sorafenib treatment. Within the SoHAIC group, subsequent treatments (n=16, 50%) included regorafenib for 10 patients (31%), transarterial chemoembolization (TACE) for 6 patients (19%), PD-1 inhibitors for 5 patients (16%), additional HAIC for 3 patients (9%), lenvatinib for 2 patients (6%), resection for another 2 patients (6%), and microwave ablation for 1 patient (3%). In contrast, among patients treated solely with sorafenib, the subsequent treatments (n=6, 19%) included regorafenib for 4 patients (13%), and TACE, PD-1 inhibitors, and lenvatinib each for 1 patient (3%).

Markov Model Construction

We utilized TreeAge software version 2011 and followed the CHEERS reporting guidelines to develop a Markov model for conducting a cost-effectiveness analysis.[18] The model classified health states into three groups: stable disease, progressive disease, and death. Patients were expected to undergo either SoHAIC or sorafenib treatment during the stable disease phase and receive second-line therapy upon disease progression until death. Our analysis determined the economic viability of SoHAIC based on whether the incremental cost-effectiveness ratio (ICER) fell below the specified willingness-to-pay (WTP) threshold. The WTP threshold represent the WTP per quality-adjusted life-years (QALYs), with the thresholds for China set at $30,492.00/QALY based on previous research.[19,] Table S1 outlines the model parameters and their sources. Additionally, if a patient underwent the SoHAIC procedure, an additional procedure fee was incurred. In this study, we assigned values to QALYs as follows: 0.76 for no disease progression, 0.68 for disease progression, and 0 for death. Specifically, this research took into account adverse events (AEs) such as hypertension, elevated total bilirubin, neutropenia, fatigue, elevated aspartate aminotransferase [AST]/alanine transaminase [ALT], and thrombocytopenia, as these AEs were commonly observed in HAIC in clinical settings.[20]

Table 1 Basic Cost-Effectiveness Results

	Sorafenib	SoraHAIC
Total cost ($)	10,507.89	32,971.56
QALYs	0.42	1.66
ICER ($/QALY)	/	18,237.20
Monte Carlo analysis showing cost-effectiveness	1.20%	98.80%

Abbreviations: HAIC, hepatic artery infusion chemotherapy; SoraHAIC, sorafenib and HAIC; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.

Statistical methods

In the cost-effectiveness analysis, sensitivity testing was conducted to evaluate the impact of uncertainties in treatment effectiveness, utility, and cost on the final ICER outcome. Model parameters were obtained from relevant literature and were adjusted within 20% of the baseline to define the parameter range. Additionally, the discount rate was varied between 0% and 5%. In Monte Carlo simulations, 1000 experiments were iterated, with each key parameter being assigned based on an appropriate distribution, such as costs following a Gamma distribution and utilities following a Beta distribution.

Results

Basic Findings

SoHAIC showed better survival outcomes compared to the sorafenib alone ($P < 0.01$, Figure S1). In our base case analysis, the SoHAIC arm accumulated a total cost of $32,971.56 and resulted in a corresponding QALY of 1.66. In contrast, the sorafenib arm incurred a total cost of $10,507.89 and yielded a corresponding QALY of 0.42. The discounted costs and QALYs are detailed in Table 1. Upon comparing SoHAIC with sorafenib, the ICER was computed to be $18,237.20/QALY, which was found to be below the Chinese reference WTP threshold of $30,492.00/QALY.

1-Way Sensitivity Analysis

We performed 1-way sensitivity analyses to detect the critical model parameters in the comparison between SoHAIC and sorafenib. In Figure 1, a tornado diagram was utilized to visually illustrate how the cost-effectiveness of SoHAIC, in relation to sorafenib, fluctuates based on the modeled variables. According to the tornado diagram, the ICER of SoHAIC consistently remained below the reference WTP threshold of $30,492.00 per QALY across the entire range of modeled parameters when compared to sorafenib. Specifically, the parameters associated with AEs had minimal impact on the final variation in ICER; therefore, these AE parameters were not depicted in Figure 1.

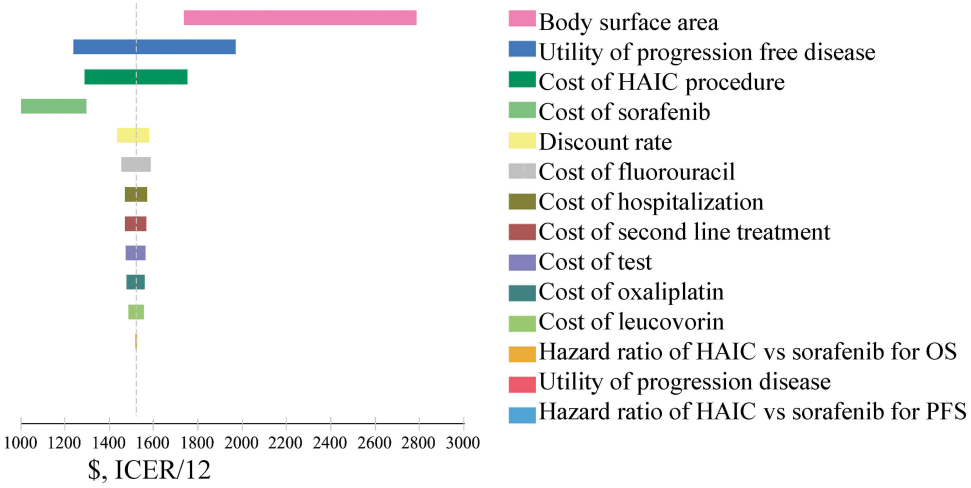

Figure 1 A tornado diagram used to conduct a 1-way sensitivity analysis of the ICER for SoHAIC and sorafenib, with the parameters arranged in order of magnitude.
Abbreviations: ICER, incremental cost-effectiveness ratio; SoHAIC, sorafenib plus hepatic artery infusion chemotherapy.

Probabilistic Sensitivity Analysis

In a probabilistic sensitivity analysis (Figure 2), SoHAIC emerged as the favored strategy in 98.8% of samples at a WTP threshold of $30,492.00. The cost-effectiveness acceptability curves demonstrated that as the WTP per incremental QALY increased, the percentage of modeled samples where SoHAIC was the most cost-effective option also increased, while sorafenib declined. At a WTP of $18,237.20 per incremental QALY, SoHAIC was equally cost-effective compared to sorafenib (Figure 3).

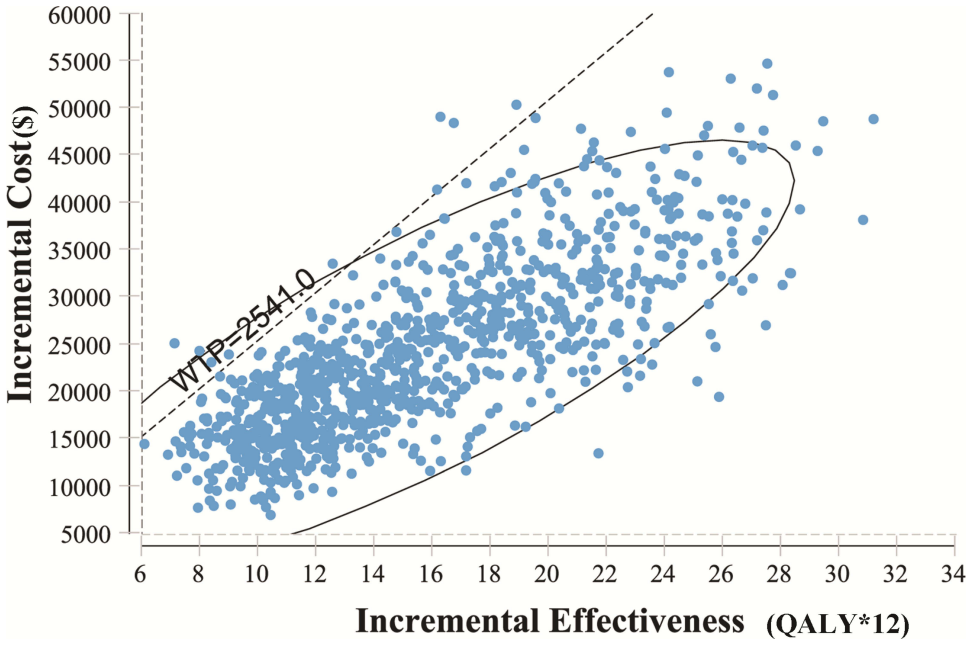

Figure 2 The probabilistic sensitivity analysis revealed that SoHAIC emerged as a cost-effective treatment choice. To assess the impact of parameter uncertainty on the outcomes of the cost-effectiveness analysis, 1000 Monte Carlo simulations were conducted utilizing the input parameters and their corresponding distributions outlined in Table S1. The dots positioned below the lines indicate simulations where the cost per QALY gained fell below the WTP threshold.
Abbreviations: SoHAIC, sorafenib plus hepatic artery infusion chemotherapy; QALY, quality-adjusted life year; WTP: willingness-to-pay.

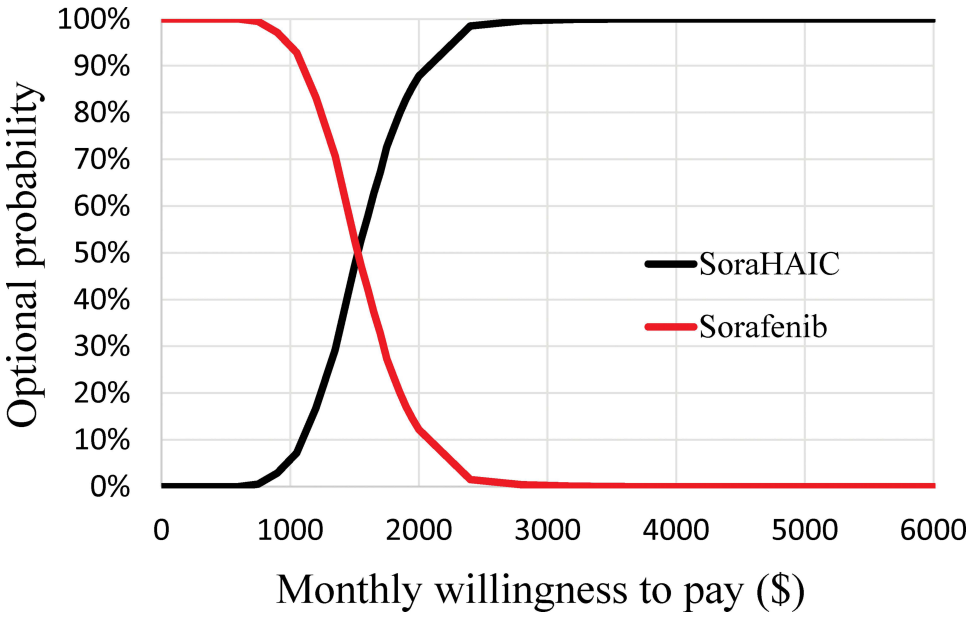

Figure 3 The curves illustrate the probabilities of cost-effectiveness for SoHAIC and sorafenib.
Abbreviation: SoHAIC, sorafenib plus hepatic artery infusion chemotherapy.

Discussion

The cost of HCC treatment represents a significant portion of cancer healthcare spending in China,[21] underscoring the importance of health economics evaluation in assessing the practical value of SoHAIC in comparison to sorafenib. Through the utilization of a Markov model, this study aimed to analyze the cost-effectiveness of SoHAIC and sorafenib for patients with advanced HCC (HCC-Vp3-4). The study findings revealed that, from the perspective of Chinese payers, SoHAIC emerged as a cost-effective treatment option. This research is expected to offer valuable insights for healthcare providers, policymakers, and patients, enabling them to assess the economic implications of using SoHAIC in the management of HCC.

With recent significant advancements in systemic therapy, which include multikinase inhibitors like sorafenib and lenvatinib, as well as immune checkpoint inhibitors such as atezolizumab plus bevacizumab, systemic therapy has now become the primary treatment option for advanced HCC with PVTT.[22] Despite these advancements, the overall tumor response and prognosis for patients with advanced HCC remain limited and unsatisfactory.[23] Therefore, the efficacy of HAIC in combination with standard systemic therapy has been studied and confirmed.[10] Given that SoHAIC has demonstrated more favorable clinical outcomes compared to sorafenib, it is imperative to conduct a health economic evaluation of SoHAIC.

Limited cost-effectiveness studies on HAIC or HAIC-based therapy have been published, contributing to uncertainty in healthcare decision-making.[19,24,25] First, in a study on HAIC monotherapy, Chen et al discovered that HAIC was a cost-effective alternative to sorafenib for advanced high-risk HCC cases with Vp4 portal vein invasion, bile duct invasion, and/or tumor occupancy of ≥50% of the liver.[19] The ICER for HAIC was $10,190.41 per QALY, falling below the WTP threshold. Probabilistic sensitivity analysis indicated a probability of ≥99.9% favoring HAIC. Similarly, the current study demonstrated a 98.8% probability favoring SoHAIC over sorafenib, underscoring the cost-effectiveness of SoHAIC in HCC-Vp3-4. Second, in an analysis on HAIC-based therapy, Li et al reported that SoHAIC did not exhibit cost-effectiveness compared to sorafenib monotherapy in treating patients with HCC involving portal vein invasion.[24] However, this conclusion should be interpreted cautiously due to their assumption that patients would continue HAIC treatment until tumor progression. The authors of the study set the HAIC treatment duration in the Markov model at 8 years, a duration significantly longer than the actual clinical practice. Therefore, it is reasonable to assume that the use of the Markov model by Li et al to simulate the cost-effectiveness of SoHAIC may deviate from the real-world HAIC treatment cycle. For patients who survive beyond 6 months post-HAIC treatment, the Markov model may substantially inflate the treatment costs associated with HAIC therapy. This highlights the importance of conducting health economic evaluations in collaboration between clinical and statistical experts,[26] rather than solely relying on statistical expertise.

SoHAIC was identified as a cost-effective approach compared to sorafenib when AEs were integrated into the Markov model. While the impact of AEs on cost-effectiveness may be limited, their clinical significance remains crucial as they not only influence patients' healthcare experiences but also directly affect treatment adherence. In the study by Zheng et al, AEs of grade 3 or higher were more prevalent in the SoHAIC group and included diarrhea, hand-foot syndrome, and thrombocytopenia.[10] Kudo et al noted that AEs of grade 3 or higher were more frequently observed in HAIC combined with sorafenib, but these were manageable by adjusting treatment or reducing dosage.[27] The combination therapy of HAIC and other systemic treatment has been a key focus of research, and further studies are essential not only to assess the safety and clinical efficacy of the treatment but also to explore its potential economic advantages in the future.[11]

The current study had several limitations. Firstly, the trial used as the basis for our model had a relatively small sample size, indicating the need for additional trials to validate the results further. Nonetheless, the clinical outcomes reported were consistent with those of other Phase III trials, such as the FOHAIC-1 trial.[20] Secondly, the majority of patients in the study had HBV infection. It is worth noting that sorafenib's efficacy is limited in HBV-infected patients but has shown significant survival improvements in patients with hepatitis C virus (HCV) infection.[28] As a result, the uncertainty remains in the health economic evaluation of SoHAIC versus sorafenib for patients in regions where HCC is caused by factors like alcohol consumption or HCV infection. Thirdly, even within China, there have been reports of variability in chemotherapeutic regimens.[29] Therefore, future studies should be designed to offer a more precise assessment of the safety and cost-effectiveness of different HAIC strategies across diverse populations. Lastly, it is important to acknowledge that Markov modeling has limitations based on assumptions and the quality of input data.

However, our findings remained robust across a wide range of model inputs, indicating that additional inputs would not significantly alter the results.

In conclusion, SoHAIC (sorafenib plus hepatic arterial infusion chemotherapy) demonstrated to be a cost-effective treatment option compared to sorafenib alone for patients with HCC-Vp3-4 (HCC invading first branch [Vp3] or main trunk [Vp4] of portal vein) in China.

Statement of Ethics

Written informed consent was obtained. This study complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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