Original Article

Economic Evaluation of Sorafenib Treatment of Patients with Advanced Hepatocellular Carcinoma at Chulabhorn Hospital

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Background: Sorafenib is not included to the National List of Essential Medicines [NLEMs] and the program for the high-cost cancer (Onco Prior Authorization Program, OCPA) medicine. There have been no studies on the cost-effectiveness of Sorafenib treatment for these reimbursement policies in Thailand.

Objective: To evaluate the lifetime cost-effectiveness of Sorafenib treatment versus the palliative care in the advanced hepatocellular carcinoma patients based on the retrospective real practice data at Chulabhorn Hospital.

Materials and Methods: An analysis of cost-effectiveness was conducted according to a third-party payer perspective. Heath-state transition probabilities and resources use were retrieved from the Chulabhorn Hospital's computerized database, which was queried from 1 January 2009 through 31 January 2014 to assign patients to Sorafenib group or palliative group. The transition probabilities and costs were determined until 28 February 2017. A Markov model was developed to estimate lifetime costs and quality-adjusted life years. The incremental cost-effectiveness ratio, including the sensitivity analysis, was determined.

Results: Using base-case and probabilistic analysis, Sorafenib treatment was more costly and less effective compared with palliative care.

Conclusion: Palliative therapies were more beneficial and economically for managing for patients with advanced hepatocellular carcinoma compared with Sorafenib treatment.

Keywords: Economic evaluation, Cancer, Cost-effectiveness, Sorafenib, Hepatocellular Carcinoma

J Med Assoc Thai 2018; 101 [Suppl. 6]: S171-S183
Website: http://www.jmatonline.com

Hepatocellular carcinoma [HCC] is the fifth most common cancer worldwide, with more than half a million new cases each year[1]. The incidence rate is increasing in the United States and Europe, and HCC is currently the leading cause of death among patients with cirrhosis[1]. In the West, the hepatitis C virus[2] infection is the main risk factor for HCC, along with other causes of cirrhosis such as chronic alcohol consumption, steatosis, diabetes, and hepatitis B virus [HBV] infection. The incidence is particularly high in Asian and Sub-Sahara regions[3] and chronic HBV

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How to cite this article: Sangmala P, Lamlertthon W, Siri P, Jaroenpatarapesaj S. Economic Evaluation of Sorafenib Treatment of Patients with Advanced Hepatocellular Carcinoma at Chulabhorn Hospital. J Med Assoc Thai 2018;101;Suppl.6: S171-S183.

infection appears to be an important risk factor for development of HCC[2]. For example, the prevalence of hepatitis B viral infection was 65% in patients with HCC in Thailand[4].

The 5-year survival of patients with early HCC is 50 to 80% after the administration of curative therapies such as liver transplantation, resection and percutaneous ablation[5-8]. However, most patients are diagnosed at intermediate to advanced stages and there is no definitive management consensus for these patients who are not eligible for curative surgery. Thus, the prognosis of these patients is invariably poor. Suggested options include ablation, chemoemboliza tion, or radioembolization, external beam radiation therapy [EBRT], stereotactic body radiation therapy [SBRT], Sorafenib, or systemic chemotherapy and palliative therapies[9-11]. Further, the 5- and 6-year survival rates of patients with HCC who are unsuitable for curative therapy are 17 to 20% and 9%, respectively[12,13].

Palliation is treatment aimed to alleviate the symptomatic effects of a disease rather than to provide a cure[11]. The palliative options for HCC include surgery, chemotherapy [CT], and as regional therapies such as transarterial chemoembolization [TACE], palliative radiotherapy [RT], and pain management therapies. The 5-year survival rate achieved using RT is 50%, followed by that palliative CT (40%)[14]. For the patients with terminal-stage HCC, the best supportive care presents the only treatment option. Nevertheless, patients would require multiple paracentesis or abdominal drainage for ascites and pain control using opiates. Treatment of complications such as infection or ruptures of the tumor is important to rescue these critically ill patients[15].

Sorafenib significantly prolongs overall survival[1] and is considered the first-line treatment for patients with advanced HCC who can no longer be treated with potentially more effective therapies[16]. The safety and efficacy of Sorafenib was tested in the Sorafenib HCC Assessment Randomized Protocol [SHARP][17] and the Asia-Pacific clinical trials[18]. The SHARP study found that Sorafenib significantly prolonged overall survival [OS] compared with that of patients treated with placebo (median OS 10.7 months vs. 7.9 months) and prolonged time-to-progression [TTP] by 73% (5.5 months vs. 2.8 months). The etiology of HCC in patients included in the Asia-Pacific trial was different from that of those in the SHARP trial. More than 70% of the patients in the former trial were infected with HBV, and the OS rates of those treated with Sorafenib vs placebo controls were 6.5 months and 4.2 months, respectively, and the median TTP were 2.8 months and 1.4 months, respectively.

Sorafenib is considered the standard of care for patients with advanced HCC because of its safety profile determined in clinical trials and was therefore included in the National Comprehensive Cancer Network, NCCN guideline[19]; however the effective ness of Sorafenib therapy was validated in field-practice (Sorafenib Italian Assessment, [SOFIA])[20]. The safety profile and tolerability of Sorafenib in the SOFIA trial are worse compared with those reported by the SHARP trial. Moreover, a global phase IV, international, prospective, open-label, multicenter, non-interventional post-marketing study of patients with advanced HCC who received Sorafenib in the field-practice, under real world conditions [GIDION][21], found that the safety profile of Sorafenib similar to the pivotal registration studies.

Sorafenib[22] was approved for the treatment of HCC in 2007 by the United States Food and Drug Administration [FDA][23] and by the Thai FDA in April 2007. The cost of one tablet of Sorafenib for patients treated at Chulabhorn Hospital in 2017 is 1,593 Thai Baht [THB]. Sorafenib is not included in the National List of Essential Medicines [NLEMs] and in the Onco Prior Authorization [OCPA] program, which require submitting the treatment protocol for patients to receive initially approved or re-approval at 3-month interval for six high cost and non-essential drugs reimbursement as required by the Civil Servants' Medical Benefit Scheme [CSMBS]. Patients under the universal coverage scheme [UC] are unable to access Sorafenib because it is not in the NLEMs. In contrast, for patients covered by the CSMBS, access to Sorafenib may be easier compare with those for other targeted new agent because Sorafenib is not on the OCPA program.

The evaluation of cost-effectiveness is one type of outcome research[24] which is widely used in many countries and has become an integral component of health technology assessment in Thailand[25]. The leading evaluation of cost-effectiveness of Sorafenib were conducted in the United States and Canada[26,27] using similar methodologies. The results indicate that Sorafenib is cost-effective compared to best supportive care [BSC], with a cost-effectiveness ratio within the established threshold that citizens of these countries are willing to pay. However, the National Institute for Clinical Excellence [NICE] do not recommend the use of Sorafenib, under the economic evaluation from the United States and Canada and indicate that justified

outcome measures should include the survival benefit as well as the outcomes, particularly health-related quality of life [HRQoL][28].

Although Sorafenib was found to significantly prolong survival and have cost-effective results within the threshold of some high income countries, Thai citizens have mainly low or middle-incomes and the government of Thailand bears a significant financial burden for providing Sorafenib. The cost-effectiveness study, using real-world data from clinical practice from one hospital in Thailand can be further considered by policy decision-makers to delineate the benefits package or improving the accessibility to drug.

This study aimed to determine the lifetime cost-effectiveness of Sorafenib treatment versus the palliative care for patients with advanced HCC using real-world data available in the database of Chulabhorn Hospital.

Materials and Methods

Study population and design

The protocol of this research was reviewed and approved by the Ethics Committee for Human Research, Chulabhorn Research Institute (EC No. 010/2557). All patients with HCC at Chulabhorn Hospital with advanced disease defined by the diagnosis-related group [DRG] coding of c22.0 from their medical records were focused. Patients who received Sorafenib or palliative care from 1 January 2009 through 31 January 2014 were divided into two groups, respectively. Survival function or cumulative survival was calculated and defined as the time from the start of Sorafenib/palliative care to progression or, discontinuation of Sorafenib, whichever occurred first, or death in term of the duration of time caused those event occurred and were identified as the health outcomes. The patient data included those health outcomes and associated costs were retrospectively collected until February 28, 2017. A quality check was performed to clean the out-of-range value and inconsistency of data. Cost-effectiveness analysis model was constructed in Microsoft Office Excel® 97-2003 (Microsoft Corp., Redmond, WA) and undertaken based on Thai government [CSMBS] perspective.

Model structure

The model considered patients diagnosed with advanced HCC. Due to the chronic, progressive and evolutionary nature of the disease, a Markov modeling approach was employed following patients as they passed through a series of clearly defined and mutually exclusive health states throughout the disease. The model was designed to track the health states of patients with HCC in both treatment groups. The four main health states included (1) Sorafenib/or palliative treatment-no progression (2) Sorafenib treatment continued-post progression (3) palliative care-post progression and (4) death (Figure 1). The model structure was same as in Sorafenib economic evaluation in the US and Canada[26] and the model was also consistent with clinical practice and other economic models developed in oncology[29-31]. The monthly cycles (30 days) was used to match treatment pattern that was patients had the possibility to move from one health state to another every month. The model was run until all patients died (lifetime horizon extrapolation).

Patients in stable condition started to receive Sorafenib until radiological documentation of disease progression or until a Sorafenib-limiting reasons event (on and off in real practice, intention to treat), such as

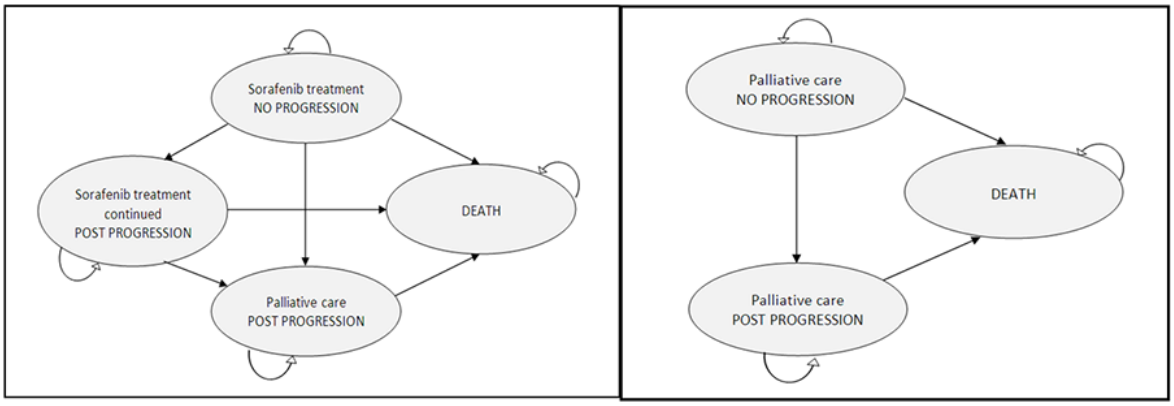

Figure 1. Markov model schema for Sorafenib and palliative care group.

adverse events, financial problem or loss to follow-up (Sorafenib-no progression). When progression was detected, patients could continue Sorefanib treatment (Sorafenib continued-post progression) or switch to palliative care (palliative care-post progression). For patients who started receiving palliative care (palliative care- no progression), only disease progression was recorded (palliative care-post progression). At any point in the model, patient might die because of all cause (general) mortality.

Multimodal palliative care was selected to be the comparator because in the practice, late stage patients have a poor prognosis, and the treatments of choice were provided to enhance their benefits. Sorafenib was compared with palliative care, in which both groups incorporated outpatient visits, hospitalization, radiological investigations, operating procedures, laboratory tests, medication to treated adverse events, and the multimodalities such as systemic chemotherapy, TACE or radiation therapy.

Model parameters: valuing health effects

Markov model transitional probabilities were derived primarily from patients' survival and TTP. Probabilities of shorter survival from time zero were processed and analyzed from each monthly-cycle event using Stata/SE version 12 software, (Stata Corp LP, College Station, TX, USA). Probabilities during the cycle were calculated for survival and treatment failures. The transitional probabilities of failure values were calculated as follows:

Transitional probability per cycle = 1-exp (ln (P)/t]

P is the probability of survival during the cycle. These estimated transition probabilities were applied to generate the model's results. The details of transition probabilities of each health state in the treatment groups are shown in Table 1.

HRQoL, which has become an important outcome measure in patients with chronic liver disease [CLD], emerges as a tool for measuring patient's outcomes by incorporating social, psychological, physiological and physical functioning[32]. The assessment of HRQoL was performed for patients with CLD in different countries[33-35]. The CLD questionnaire was translated from the original version to Thai language with permission, using the validation process described by Sobhonslidsuk A. et al[36]. The average CLD quality [Q] score was significantly correlates with the general health domain of the short-form 36 [SF-36] ($p = 0.01$). Further, the validated Thai versions of SF-36 and CLDQ were performed in Thai patients to investigate factors influencing HRQoL[37]. Although HRQoL has been studied, extensive data on the health utilities of patients are not available in Thailand unlike other countries[38-40]. Therefore, the Chinese SE-6D preference values of stages of chronic hepatitis B of HCC patients used to estimate quality-adjusted life years in this study was 0.72, likely because of the population's characteristics[41].

Model parameter: valuing costs

The analysis was conducted from the perspective of a third-party payer as the CSMBS of Thailand. Therefore, the total costs (in THB) estimated using the model were the direct medical costs evaluated, which were retrieved from the hospital's computerized information system that is required for the management of each patient. The frequencies of resources use and

Table 1. Markov Model Probabilities in Each 30-day Cycle

Model parameters	Sorafenib mean (SE)	Palliative care mean (SE)
Sorafenib or palliative care treatment- no progression		
Probability of Sorafenib continued post progression	0.2088 (0.0203)	-
Probability of no progression*	0.4227 (0.0309)	0.7330
Probability of palliative care post progression	0.1955 (0.0198)	0.1520 (0.0026)
Probability of death	0.1731	0.1150 (0.0045)
Sorafenib treatment continued-post progression		
Probability of Sorafenib post progression*	0.4451	-
Probability of palliative care post progression	0.4152 (0.0616)	-
Probability of death palliative care post progression	0.1397 (0.0096)	-
Probability of palliative care post progression*	0.4152 (0.0616)	0.7808
Probability of death	0.5848	0.2192 (0.0030)

* Staying in the same health state (progression free)

unit costs were used to calculate the total costs of managing patients with HCC in each health state of the model and in accordance with the mean monthly costs. The unit costs for medical services were acquired from publicly available sources including standard items for medical billing of the comptroller general's department. Drug and other unit costs were extracted from Chulabhorn Hospital's records as an average charge submitted to the CSMBS for reimbursement. Table 2 presents the unit costs of patient management classified according to resource type. The cost in 2017 of one 200 mg Sorafenib tablet was 1,593 THB, which was

Table 2. Unit costs associated with the management of HCC

Resources	CGD code	Unit costs (THB) Mean (SE)	Source
Outpatient service (per time)	55020	50 (50)	CGD price list
Hospital item (per day)			
Intensive care unit + nursing care (55012)	21101	1,600 (1,600)	CGD price list
General ward + nursing care (55010)	21201	1,300 (1,300)	CGD price list
Radiological tests (per test)			
CT upper abdomen + nonionic CM 100 ml (44901)	44501	6,500 (6,500)	CGD price list
CT chest + nonionic CM 100 ml (44901)	44301	6,500 (6,500)	CGD price list
MRI upper abdomen +Gd CM 15 ml (45901)	45501	10,500 (10,500)	CGD price list
US upper abdomen	43501	650 (650)	CGD price list
Chest PA upright	41003	220 (220)	CGD price list
Procedures (per procedure)			
Chest pleural drain + tube (3101)	71341	700 (700)	CGD price list
Thoracocentesis	71340	200 (200)	CGD price list
Abdominal parecentesis	71510	200 (200)	CGD price list
Liver biopsy	71512	250 (250)	CGD price list
Leukocyte poor PRC	23253	550 (550)	CGD price list
Leukocyte poor pooled platelet conc.	23302	4,800 (4,800)	CGD price list
Fresh frozen plasma (FFP-red cross)	23401	400 (400)	CGD price list
Laboratory tests (per test)			
Surgical pathology: Liver needle biopsy	38121	500 (500)	CGD price list
AFP test: ELISA	37302	270 (270)	CGD price list
Liver function test (LFT)		350 (350)	CGD price list
Coagulation test		130 (130)	CGD price list
Complete blood count (CBC)	30101	90 (90)	CGD price list
Stool direct smear	31201	40 (40)	CGD price list
Total calcium	32106	50 (50)	CGD price list
Glucose	32203	80 (80)	CGD price list
Complete metabolic panel		300 (300)	CGD price list
Diagnosis related group (per admission)			
DRG c22.0		10,628 (10,628)	Chulabhorn Hospital DRG reimbursement
DRG c22.0 with TACE		26,205 (26,205)	Chulabhorn Hospital DRG reimbursement
DRG c22.0 with RFA		71,935 (71,935)	Chulabhorn Hospital DRG reimbursement
DRG c22.0 with thoracocentesis		10,628 (10,628)	Chulabhorn Hospital DRG reimbursement
DRG c22.0 with parecentesis		13,546 (13,546)	Chulabhorn Hospital DRG reimbursement
DRG c22.0 with chemo		8,574 (8,574)	Chulabhorn Hospital DRG reimbursement
Systemic chemotherapy (per a cycle of regimen)			
FOLFOX		47,558 (47,558)	Chulabhorn Hospital drug price
Doxorubicin		1,656 (1,656)	Chulabhorn Hospital drug price
Medicine treated adverse events (OPD) (per tablet/piece)		See detail	Chulabhorn Hospital price
Radiation therapy (per time)		7,500 (17,500)	Chulabhorn Hospital drug price
Sorafenib 200 mg (per tablet)		1,593 (1,593)	Estimate Chulabhorn Hospital drug price

CGD = the comptroller general's department;
Liver function test (LFT) included total bilirubin (32208), direct bilirubin (32207), ALP (32309), SGOT (32310), SGPT (32311), albumin (32403), total protein (32402) were 50 THB per item
Coagulation test included PT (30201) 60 THB and PTT (30202) 70 THB
Complete metabolic panel included BUN (32201) 50 THB, Creatinine (32202) 50 THB, Sodium (32102) 40 THB, Potassium (32103) 40 THB, Chloride (32104) 40 THB, CO2 (32105) 40 THB
Medicine treated adverse drug events included triamcinolone 15 gm 16 THB, urea 20% 30 gm 49 THB, CPM inj 2.5 THB, Prednisolone 5 mg tab 1 THB, Hydoxyzine 10 mg tab 0.5 THB, Morphine 50 ml 61 THB, Kapanol 20 mg cap 33 THB, MST 10 mg tab 16.5 THB, tramadol 50 mg cap 2.5 THB, amitriptyline 10 mg tab 0.5 THB, loperamide 2 mg cap 1 THB, domperidone 10 mg tab 0.5 THB, metoclopramide 10 mg tab 0.5 THB, ondanzetron 8 mg tab 7.5 THB, omeprazole 20 mg cap 1.5 THB, ORS 1.75 THB

reimbursed by the CSMBS and included in the Sorafenib group. Further, Table 3 shows the mean of monthly costs of individual patients in each health state divided by the type of medical services according to the resources use in practice.

Model assumption

For the analysis, the assumptions were made as follows:

No-progression health state means that disease was stable. The patients were included in the model according to the physicians' diagnosis of advance or unresectable HCC as well as the requirement for treatment with Sorafenib, palliative care, or best supportive care.

The progression health state would be detected and indicated according to the radiological findings,

Dose reduction or interruption included in the model could occur, because data were collected for all the patients with the intention to treat. The patients who continued to receive Sorafenib or those for whom treatment was temporarily discontinued, were included in the health state of Sorafenib-no progression. The last time the patients received Sorafenib would be defined as the day when the drug treatment would finished, and it would be defined as the day that care was changed to the health state of palliative care-no progression,

This model included the patients who lose to follow-up. All death date from the civil registry could be acquired. However, the resources other than those provided by Chulabhorn Hospital might be occurred and not included in the model.

Resource use was based on the treatment patterns of Chulabhorn Hospital, and administered differently in all health states.

The possibility of Sorafenib-associated adverse events such as rash/desquamation, fatigue or pain, diarrhea or nausea/vomiting and hand-foot skin reaction were assumed to have cost consequences by determining drug use to treat these symptoms. These data were included in the analysis.

Costs of FOLFOX and doxorubicin chemotherapy were estimated according to patients' body surface area (1.5 m^2) and Chulabhorn Hospital's drug price submitted for reimbursement and equal to those for one regimen cycle.

Costs of one-visit radiation therapy were assumed as the price of the simulation, 3-D CT planning, 3D-CRT radiation, customized block, and 3D Image: CBCT kV (setup verification).

QOL utilities for different health states and between intervention group were estimated as equal, and the QOL utilities from the study of Southern Chinese were generalized to this study[41].

Table 3. The estimated mean of monthly cost data from the real practice

Medical services	Sorafenib group (mean, THB)			Palliative care group (mean, THB)	
	Sorafenib no progression	Sorafenib post progression	Palliative post progression	Palliative no progression	Palliative post progression
1) Outpatient medical contact charge	163.59	76.41	166.36	112.79	117.34
2) Radiological tests	1,324.90	2,825.44	600.94	4,762.63	1,489.67
3) Outpatient procedures	48.13	5.27	17.70	10.45	42.69
4) Outpatient laboratory tests	1,214.59	592.79	534.84	820.49	846.59
5) Outpatient medicines to treat ADEs*	164.09	221.09	94.86	93.91	174.35
6) Hospitalization	3,270.73	178.12	2,741.99	807.80	6,176.75
7) Inpatient DRG charge	4,310.01	608.68	9,007.28	3,586.05	11,593.76
8) Other treatment eg. radiation therapy or chemotherapy	1,127.63	0.00	15,450.30	2,535.55	1,617.11
9) Sorafenib	140,557.57	6,293.86	00.00	00.00	00.00

*ADEs = adverse drug events

Outcome and discounting

Health effects are expressed as life-years [LYs], and quality-adjusted life-years [QALYs]. A QOL utility was adapted from the study of Southern Chinese[41] because of the lack of the data for Thailand. This study calculated an SF-6D value = 0.720 for patients with HCC, which was used to estimate QALYs. Costs represent the 2017 THB. The results are presented as incremental life-year, incremental QALYs, incremental costs and the incremental cost-effectiveness ratio [ICER] as functions of cost per life-year gained and cost per QALYs gained. An annual discount rate of 3%[42] was applied to both health benefits as well as to costs incurred after the first year.

Sensitivity analysis

To identify model drivers and examine key areas of uncertainty within the model, sensitivity analyses were conducted as follows: (1) one-way deterministic analysis (tornado diagram) and (2) probabilistic sensitivity analysis [PSAs].

One-way deterministic sensitivity analyses are illustrated for all major model variables. All parameters were varied according to the standard error for the efficacy parameters or transitional probabilities of each health states, and costs between the extremes of $\pm$100% from the mean were selected as reasonable upper and lower bounds. The effects of the values of certain parameters at a time, while holding the others constant, compared the level of influence on ICER values. The findings are presented using tornado diagrams. PSAs were performed using the probabilistic mean and standard error. Microsoft Office Excel® 97 to 2003 (Microsoft Corp., Redmond, WA) was used to perform PSAs. Monte Carlo simulations were run with key input values randomly selected from probabilistic density functions. Findings were shown on a cost-effectiveness plane, using 1,000 iterations. The gamma distribution was employed for cost estimate and the beta distribution for efficacy estimate. The ceiling willingness-to-pay threshold [WTP] for the present study was defined as approximately 160,000 THB/QALY.

Results

The number of patients in the Sorafenib and palliative group were 39 and 141, respectively. The characteristics and available baseline measures were shown in Table 4. The estimated lifetime costs and outcomes are presented in Table 5.

Analyses of the bases case revealed that mean life expectancies patients undergoing Sorafenib and palliative care were approximately 0.1962 years (2.35 months), and 0.4310 years (5.17 months), respectively. The lifetime costs per patient for patients undergoing Sorafenib and palliative care were approximately 143,940 THB and 89,286 THB, respectively.

Thus, treatment with Sorafenib costs, which cost 54,654 THB more than palliative care, was accompanied by decreased life expectancy as indicated above. Patients administered palliative care lived longer compared with those treated with Sorafenib. Thus, the outcomes of Sorafenib treatment were inferior compared with palliative care. Conversely, palliative care was associated with lower costs and better outcomes.

Table 4. Patient characteristics and baseline measures from the retrospective medical record

Characteristics	Sorafenib group (n = 39)	Palliative care group (n = 141)	*p*-value**
Age (years), mean (SD)	57.19 (13.96)	57.56 (12.16)	0.871
Male, n (%)	34 (87.18%)	113 (80.14%)	0.361
Hepatitis B, n (%)*	27 (69.23%)	83 (58.87%)	0.270
Child Pugh*			0.006
A, n (%)	26 (66.67%)	56 (39.72%)	
B, n (%)	6 (15.38%)	25 (17.73%)	
Missing	7 (17.95%)	60 (42.55%)	
Combined modalities			0.012
TACE, n (%)	7 (17.95%)	55 (39.01%)	
FOLFOX4, n (%)	3 (7.69%)	2 (1.42%)	
Doxorubicin, n (%)	6 (15.40%)	8 (5.67%)	
Radiation therapy, n (%)	5 (12.82%)	14 (9.93%)	
None, others, n (%)	18 (46.15%)	62 (43.97%)	

* Incomplete medical data recording was found; ** Two-sample t-test, exact probability test.

Table 5. Estimated lifetime costs and health outcomes between 2 groups

Group	Total costs (THB)	Life year (years)	Quality adjusted life years (QALYs)
Sorafenib	143,940	0.1962	0.1413
Palliative care	89,286	0.4310	0.3100
Incremental costs	54,654	-	-
Incremental effectiveness	-	(-) 0.2349	(-) 0.1691

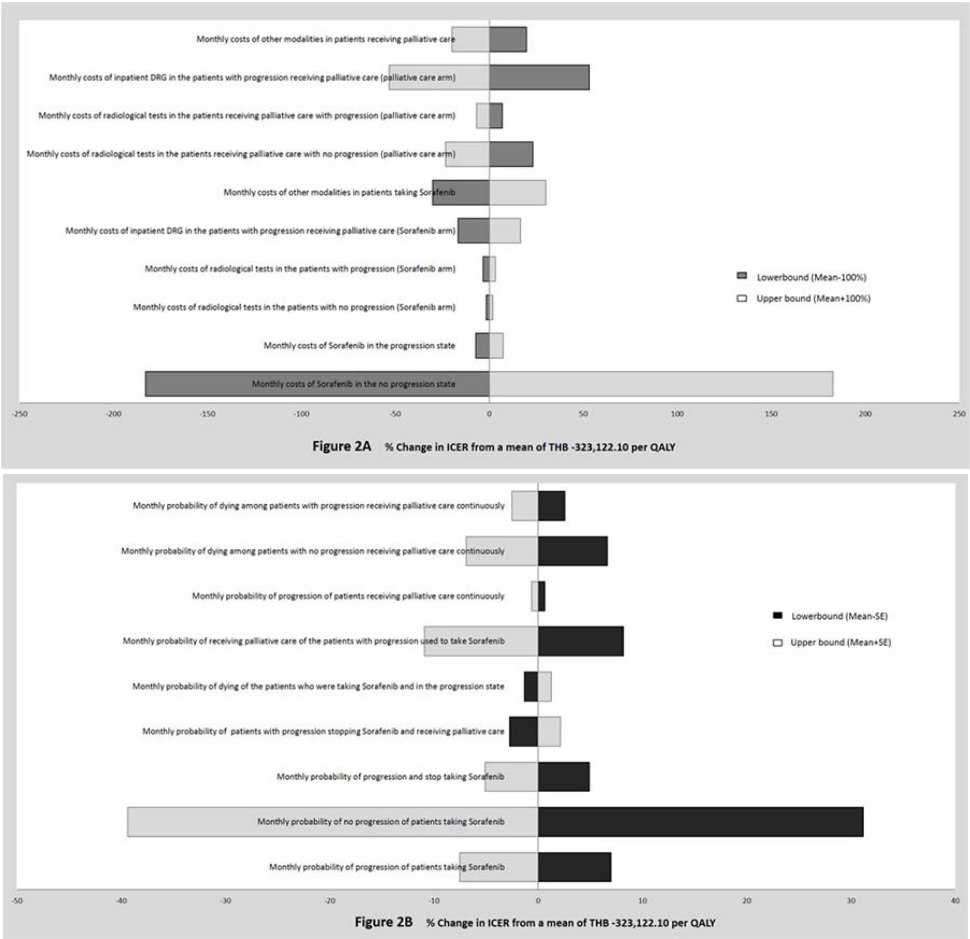

Figure 2. One-way sensitivity analysis of Sorafenib versus palliative care; A = cost parameter, B = effectiveness parameter.

Figure 2 presents the results of one-way sensitivity analyses of the model's parameters. The costs of Sorafenib used to treat patients with stable disease greatly influence the ICER (180%). Furthermore, the reduction of hospitalization treatment costs of patients undergoing palliative care without Sorafenib was associated with an increase in the ICER. The effects of radiological investigations and the costs of other active modalities on ICER were minor.

With regard to effectiveness parameter, a monthly probability of patient with stable disease while taking Sorafenib had the most influence the ICER, increasing this probability to >0.4535 (upper bound), and although the QALYs were improved, care was still

expensive. The palliative care achieved better outcomes with lower costs than Sorafenib treatment.

Derived from the cost-effectiveness analysis plane for probabilistic sensitivity analysis (Figure 3), the palliative care was always more effective than Sorafenib (100%) and was less costly 66.1% of the time.

Discussion

Sorafenib, although expensive, is approved as the most effective option for managing patients with advanced HCC. Increasing the cost-effectiveness of Sorafenib is therefore essential. The present study is, to our knowledge, the first economic evaluation of Sorafenib in Thailand. Our study has some limitations. For example, we collected clinical data and cost information only from Chulabhorn Hospital medical records, and the records for staging were incomplete upon enrollment. Further, the use of combinations of therapies for individualized management represents another limitation. We also included this scenario into the analysis because it could manifest the real situation in the real life management, which all patients were diagnosed as advanced HCC. Thus, the available data are presented as the costs and clinical management with the existing baseline characteristics of the study population. Therefore, our retrospective analysis of patients' data collection must be cautiously interpreted because of these limitations. We highly recommended the interpretation our results should focus on the population of Chulabhorn Hospital before extrapolation to different practice scenarios.

The cost and outcome of Sorafenib treatment was inferior compared with those of palliative care. However, the NICE recommendation and the study from the SEER-Medicare database show that Sorafenib administered to elderly patients with advanced HCC was not cost-effectiveness among those with hepatic decompensation[44]. In addition, the SOFIA study (Sorafenib Italian Assessment)[45] found that full-dose Sorafenib was not cost-effective compared with BSC for patients with the intermediate or advanced stages of HCC. An analysis of consistency and cost-effectiveness conducted in China demonstrates that Sorafenib is unlikely to represent a cost-effective regimen compare with BSC, according to China's commonly accepted willingness-to-pay threshold[46].

Sorafenib did not improve patients' survival nor was it incrementally costs compared with palliative care. These findings can be explained by the characteristics of the two groups.Thus, TACE was provided more frequently to the palliative group (39.01%) compared with Sorafenib group (17.95%), indicating that the disease was more localized in the former and that metastases were present in the latter. The life expectancies determined in our retrospective study are inconsistent with those reported by a published clinical trial. Therefore, macrovascular invasion or extrahepatic spread condition should be considered important criteria to select patients for Sorafenib treatment or other treatment modalities and palliative care.

Regarding the retrospective data analyzed here, the results represent the broad eligible criteria that reflect the diversity of actual clinical practice and

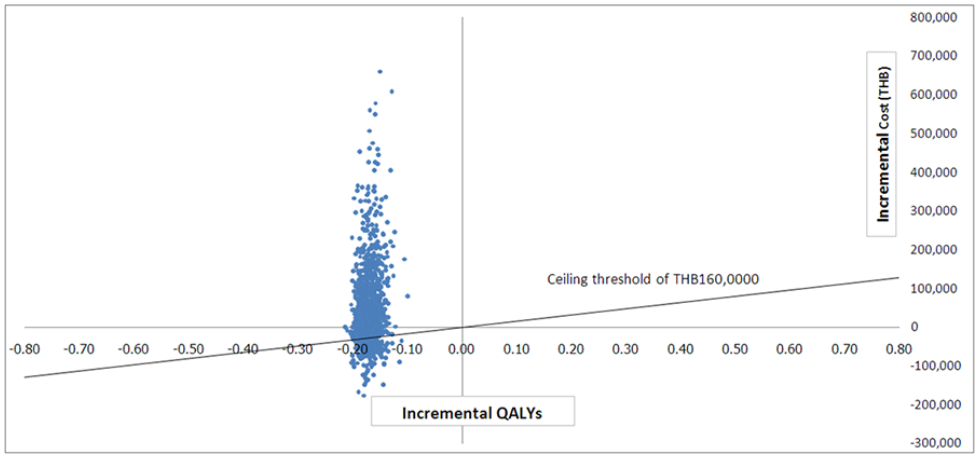

Figure 3. Incremental cost-effectiveness plane illustrating ICER of Sorafenib (ICER = Incremental cost-effectiveness ratio; QALY=quality adjusted life years; THB = 2017 Thai Baht).

management[47] as well as consistency with the treatment guidelines from Asian countries that have adopted several therapeutic modalities and their combinations according to clinical experience. These findings indicated that patients with advanced HCC must be referred to multidisciplinary teams and administered individualized treatment whenever possible[48,49]. For example, we found that both treatment groups were combined with other active therapeutic modalities.

Further investigation are therefore required to identify additional specific evidence-based data associated with the treatment of advanced HCC, as presented elsewhere for optimal management, as well as stratified analyses of cost-effectiveness[50-54]. For example, one study found that stereotactic body radiotherapy [SBRT] administered to patients with advanced HCC in Taiwan was cost-effective at a willingness to pay threshold defined by WHO guidelines[55]. Another study found that transarterial radioembolization [TARE] was a cost-effective strategy compared with Sorafenib treatment for patients with intermediate or advanced HCC[56].

We show here that the keys variables that had great impact on the ICER value were the associated with progression free survival, minimization in hospitalization, the cost of Sorafenib reimbursed by CSMBS, the number of doses taken, or the time that Sorafenib was administered. The present study included all the patients taken Sorafenib (Table 3), and we found that the mean monthly costs of Sorafenib administered to patients with stable disease was 140,557.57 THB, or approximately 88 tablets per month (full course = 120 tablets per month). Data from the practice differed from those of the trial, demonstrating the consequences of dose-adjustment as well as discontinued or interrupted therapy. We suggest that the roles of these factors should be considered during the design of future comparative trials.

Nevertheless, our study of cost-effectiveness considered the characteristics of all possible patient subgroups that may be encountered in routine practice. We noted that the use of data from clinical practice included a heterogeneous population compared with those of retrospective clinical trials, potentially altering the clinician's conclusion.

Conclusion

The costs and outcome of Sorafenib treatment were inferior to those of palliative care conducted according to CSMBS perspective at Chulabhorn Hospital. We conclude therefore that Sorafenib should not be included in the NLEMs and the OCPA programs.

What is already known on this topic?

Previous economic evaluation of Sorafenib treatment of patients with advanced HCC, which were conducted in the United States and Canada and supported by the pharmaceutical industry, used similar methodologies according to the outcomes of the SHARP trial. The results show that Sorafenib cost-effective within their societal willing-to-pay thresholds[26,27]. A study of cost-effectiveness analysis of real world data acquired from the SEER-Medicare database[44] and medical records studied in China[46] found that Sorafenib was not cost-effective option. These findings are similar to those of the filed-practices SOFIA trial conducted in Italy[45]. The NICE, which produces evidence-based guidance and advice for health, public health and social care practitioners in England and Wales, published a reappraisal in 2010 that concluded Sorafenib is not cost-effective because of considerable uncertainty about its overall survival benefit, and it was unclear how long patients would take this drug[57].

What this study adds?

To our knowledge, the present study is the first retrospective economic evaluation of clinical data associated with Sorafenib treatment of patients with HCC in Thailand. Moreover, the outcomes of different modalities administered to patients with advanced HCC and select patient subgroup provide new insights that will facilitate the design of improved treatment strategies for patients with advanced disease. Our study provides a rationale for conducting comparative studies of clinical data gathered from medical institutions throughout Thailand, which likely will reveal further information that decision-makers and stakeholders can translate to clinical practice.

Acknowledgements

We would like to extend our special thanks to Chulabhorn Royal Academy for kind assistance and support towards the success and accomplishment of this research study.

Potential conflicts of interest

The authors declare no conflict of interest.

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