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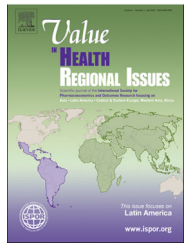

Cost-Effectiveness of Sorafenib Monotherapy and Selected Combination Therapy with Sorafenib in Patients with Advanced Hepatocellular Carcinoma

Jung-Chen Ho, MSc[1,2], *Meng-Lun Hsieh*[3,4], *Po-Heng Chuang, MD*[5], *Vivian Chia-Rong Hsieh, PhD*[6,*]

[1]*Department of Public Health, China Medical University, Taichung, Taiwan;* [2]*Central Division, National Health Insurance Administration, Ministry of Health and Welfare, Taiwan;* [3]*Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan;* [4]*School of Chinese Medicine, China Medical University, Taichung, Taiwan;* [5]*Division of Hepatogastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan;* [6]*Department of Health Services Administration, China Medical University, Taichung, Taiwan*

ABSTRACT

Objectives: To evaluate the cost-effectiveness of sorafenib treatment in combination with other therapies versus sorafenib monotherapy among patients with advanced hepatocellular carcinoma (HCC) who are enrolled in Taiwan's National Health Insurance. **Methods:** A Markov model was constructed to simulate treatment outcomes and direct medical costs of sorafenib combination therapy and monotherapy from the perspective of the healthcare payer in Taiwan. Both life-years (LYs) and quality-adjusted life-years (QALYs) were used to measure treatment outcomes, and all costs were expressed in 2014 New Taiwan dollars (NT$). Model parameters were acquired primarily using data from population-based administrative databases: the Cancer Registry, National Health Insurance Research Database, and the Death Registry. Willingness-to-pay (WTP) threshold was set at three times the per capita gross domestic product at NT $2,133,930. Deterministic and probabilistic sensitivity analyses were conducted. **Results:** For advanced HCC patients, sorafenib combined with other treatments might not be a cost-effective option when compared with sorafenib therapy alone. In the base-case analysis, combination treatment with sorafenib was estimated to increase costs by NT$434,788 compared with monotherapy, with a gain of 0.1595 QALYs. The resulting incremental cost-effectiveness ratio (ICER) was NT$2,725,943 per QALY gained. Results were sensitive to health utility values and monthly costs accrued in the progression-free survival state of the combination therapy group. **Conclusions:** Our evidence from Taiwan demonstrated that while sorafenib in combination with other therapeutic approaches might improve treatment outcome when compared with sorafenib monotherapy, its ICER exceeded the WTP threshold and was considered not cost-effective.

Keywords: combination therapy, cost-effectiveness analysis, hepatocellular carcinoma, monotherapy, sorafenib.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, ranking as high as second or third in the top leading causes of cancer deaths, with the majority of incident cases in East Asia and sub-Saharan Africa [1]. In Taiwan, it has had one of the highest incident rates among cancers since 2012, with an age-adjusted incidence rate of 30 per 100,000 owing to highly prevalent chronic hepatitis B and C infections [2–5]. Because the prognosis of HCC is very poor (overall mortality-to-incidence ratio of 0.95), together with the high incidence, HCC is a significant disease burden in Taiwan.

Treatment approaches to HCC is complex, as they can depend on various factors. One dominant system of algorithm is the Barcelona Clinic Liver Cancer (BCLC) staging system that divides HCC patients into early, intermediate, advanced, and terminal stages [6,7]. For early stage (BCLC 0, A) patients, first-line treatments are typically surgical resection, liver transplantation, or local ablation, which present the best survival outlooks. Unfortunately, because of the "silent" nature of the disease, more than 60% of patients are diagnosed with extensive tumor, and in most patients with advanced HCC the tumors are not suitable for curative therapy [8–10]. For intermediate (BCLC B) stage with multinodular HCC, chemoembolization is recommended. Sorafenib is a molecular targeted therapy used for patients in advanced (BCLC C) stage with portal invasion and Child–Pugh A or B, whereas supportive care is suggested for patients in terminal (BCLC D) stages.

Currently, sorafenib is the first-line systemic treatment indicated for patients with advanced HCC and preserved liver

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* *Address correspondence to:* Vivian Chia-Rong Hsieh, Department of Health Services Administration, China Medical University, Taichung 404, Taiwan.

E-mail: hsiehchiarong@gmail.com

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function (Child–Pugh A or B), or those who failed after locoregional therapy. It is a small molecule tyrosine kinase inhibitor specifically targeting the Raf kinase and VEGFR intracellular kinase pathway [11,12]. Previous phase III clinical trials showed that sorafenib significantly improves the overall survival of advanced HCC patients relative to supportive care in both Western and Asia-Pacific regions [13,14]. Even though sorafenib was found to improve survival significantly, the prognosis for patients with advanced HCC remains poor, with a median overall survival rate of 6.5 to 10.7 months [13,14]. Therapies with sorafenib as a single agent in practice have resulted in side effects that led to discontinuation of treatment or dose reductions [15,16]. Thus, there has been growing interest in combining sorafenib with other therapeutic methods such as chemoembolization to improve treatment effectiveness [17–20]. Some of studies have even illustrated that the improvements in both progression-free survival and overall survival achieved with sorafenib combination therapy are superior to those using monotherapy [17]. However, the results remain controversial.

Although sorafenib has been listed and its clinical effectiveness may be proven in Taiwan, its cost-effectiveness remains a significant issue as pharmaceutical expenditure is a major issue under a global budgetary system. Results of some economic evaluations indicated that sorafenib is not a cost-effective regimen for treating advanced HCC patients because of its high cost and related adverse events [21,22]. Treatments with sorafenib are therefore being modified or used in combination with other therapies to improve treatment outcomes. Aside from the fact that improvement in survival by means of combination therapy remains controversial, the costs of multimodal treatment also require scrutiny for decision-making purposes. In recent economic evaluations, supportive care or other therapies such as stereotactic body radiotherapy were commonly chosen as a comparator to the target therapy while their effectiveness parameters were mostly collected from clinical trials [15,21–24]. Thus, with use of real-life data, this study aimed to assess the cost-effectiveness of sorafenib treatment combined with other therapies such as surgical resection, percutaneous ethanol injection (PEI), transcatheter arterial chemoembolization (TACE), and radiotherapy versus sorafenib monotherapy for patients with advanced HCC from the payer perspective.

Methods

Data Collection

To the best of our knowledge, no clinical trial has yet investigated the two treatment options under study. Hence, we collected effectiveness and cost data from population-based administrative health care databases in Taiwan, namely the Cancer Registry, National Health Insurance Research Database (NHIRD), and the Death Registry, which were managed by the Health and Welfare Data Science Center established by the Department of Statistics, Ministry of Health and Welfare in Taiwan. Owing to the positive outcomes from randomized controlled trials (RCTs) and other studies, sorafenib was added to the reimbursement list in Taiwan in 2012. The treatment indication for advanced HCC is unresectable tumor or unsuccessful locoregional therapy, with either extrahepatic spread or macrovascular invasion in patients with Child–Pugh A liver function. As the NHI is the country's single-payer health insurance program, it covers 99.6% of Taiwan's population and contracts with 93% of hospitals and clinics [25]. It has beneficiary registration information and their detailed medical claims, including medication prescriptions and laboratory tests. Its validation and reliability are confirmed, as many existing economic appraisals have been published using this database [22,26,27].

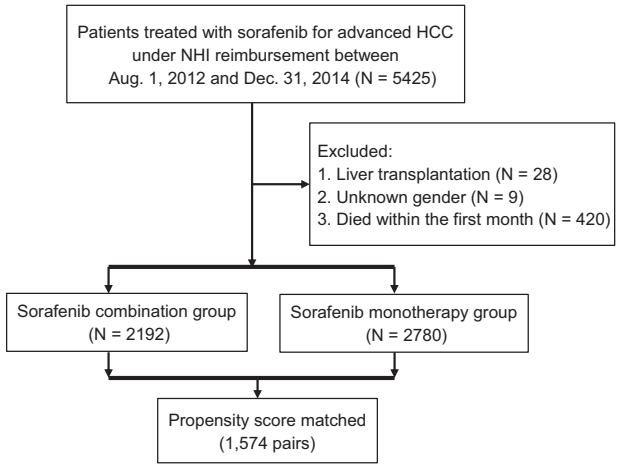

Fig. 1 – Algorithm for study subject selection. HCC, hepatocellular carcinoma; NHI, National Health Insurance.

For additional information on cancer and mortality, we linked the NHI database to the Cancer and Death Registries using unique encrypted personal identification (ID) unique to each beneficiary. The former registry contains hospital-reported diagnosed malignancies in Taiwan and the latter has information taken from death certificates issued by physicians or prosecutors. Their completeness and accuracy were also validated [28–31].

A total of 5425 advanced HCC patients who received sorafenib under the NHI reimbursement program from August 1, 2012 to December 31, 2014 were identified and retrospectively enrolled (Fig. 1). Patients who had ever undergone liver transplantation (N = 28), with unknown sex (N = 9), and those who died within the first month of sorafenib regimen (N = 420) were excluded. Two groups were further stratified: a group of 2192 patients received sorafenib in combination with other treatment methods, such as resection, PEI, TACE, and radiotherapy during the observation period (combination therapy), and a group of 2780 patients received only sorafenib (monotherapy). After propensity score matching (1:1), 1574 matched pairs remained (Fig. 1). Propensity score matching methods were used to adjust for potential confounding by baseline characteristics and estimated using a logistic regression model based on age, sex, hepatitis B, hepatitis C, ascites, liver cirrhosis, Child–Pugh class, and previous therapy with a Greedy algorithm [32] (Table 1). The study protocol has been cleared by the Research Ethics Committee at the China Medical University & Hospital (CRREC-104-080).

Model Structure

We constructed a decision analytic Markov model to simulate the health care costs and health effects associated with sorafenib combination therapy and monotherapy over a 5-year time horizon (Supplemental Fig. 1). Markov cycle length was set at 1 month. The model comprises three possible health states: progression-free survival state (PFS), progressive disease state (PD), and dead state (D). All patients began at the PFS state and transitioned to other states according to transition probabilities we derived [33,34]. Transition probabilities (TPs) were estimated from median overall survival and median time to progression in this study. The median time to event is the time at which 50% patients stayed in the original state, which we could represent using the following equation: $0.5 = 1 \times (1 - TP)^{(\text{median time to event})}$. Accordingly, TPs could be derived from the foregoing equation: