Cost-effectiveness analysis of transcatheter arterial chemoembolization with or without sorafenib for the treatment of unresectable hepatocellular carcinoma

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BACKGROUND: Transcatheter arterial chemoembolization (TACE) and TACE in combination with sorafenib (TACE-sorafenib) have shown a significant survival benefit for the treatment of unresectable hepatocellular carcinoma (HCC). Adopting either as a first-line therapy carries major cost and resource implications. The objective of this study was to estimate the relative cost-effectiveness of TACE against TACE-sorafenib for unresectable HCC using a decision analytic model.

METHODS: A Markov cohort model was developed to compare TACE and TACE-sorafenib. Transition probabilities and utilities were obtained from systematic literature reviews, and costs were obtained from West China Hospital, Sichuan University, China. Survival benefits were reported in quality-adjusted life-years (QALYs). The incremental cost-effectiveness ratio (ICER) was calculated. Sensitive analysis was performed by varying potentially modifiable parameters of the model.

RESULTS: The base-case analysis showed that TACE cost $26 951 and yielded survival of 0.71 QALYs, and TACE-sorafenib cost $44 542 and yielded survival of 1.02 QALYs in the entire treatment. The ICER of TACE-sorafenib versus TACE was $56 745 per QALY gained, which was above threshold for cost-effectiveness in China. Sensitivity analysis revealed that the major driver of ICER was the cost post TACE-sorafenib therapy with stable state.

CONCLUSION: TACE is a more cost-effective strategy than TACE-sorafenib for the treatment of unresectable HCC.

(*Hepatobiliary Pancreat Dis Int 2017;16:493-498*)

KEY WORDS: hepatocellular carcinoma; transcatheter arterial chemoembolization; TACE in combination with sorafenib; cost-effectiveness

Introduction

Hepatocellular carcinoma (HCC) is one of the most common solid malignancies globally, especially in East Asia where there is a higher prevalence of chronic viral hepatitis.[1] Curative treatments for HCC include surgical resection, liver transplantation and local ablative therapy. Although these treatments confer superior survival, only approximately 30% of patients present with early-stage tumors and undergo potentially curative therapies in practice.[2] Most HCC patients are diagnosed at Barcelona Clinic Liver Cancer (BCLC) B (intermediate) and C (advanced) stages, and few meaningful therapeutic options are available at this point.[3] Patients with unresectable HCC (intermediate and advanced-stage disease) usually receive transcatheter arterial chemoembolization (TACE) or systemic therapies.[2]

TACE has been playing an important role in the treatment algorithm for patients with multifocal or large intrahepatic lesions who are not eligible for curative treatments.[4] Survival benefits have been proved for unresectable HCC as compared with best supportive care in several randomized controlled trials.[2, 5] The median survival for patients with intermediate-stage HCC is 16.0 months without treatment, and 20.0 months with TACE therapy.[6] Two meta-analyses found that TACE significantly improved 2-year survival compared with non-active treatment for unresectable HCC, although the magnitude of the benefit is relatively small.[7, 8] Nevertheless, TACE induces ischemic or hypoxic changes that result in increased vascular endothelial growth factor

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doi: 10.1016/S1499-3872(17)60009-2
Published online April 24, 2017.

(VEGF) expression in the residual surviving cancerous tissue.[9] Elevations in serum VEGF are associated with poor prognosis in patients with HCC.[10] The consequent increase in angiogenesis may promote tumor growth, thereby limiting the potential for long-term disease control with TACE.

Sorafenib (Nexavar) is an oral multikinase inhibitor that restrains tumor angiogenesis and cell proliferation by way of VEGFR-2 and platelet-derived growth factor receptor. It was a standard first-line systemic agent for advanced HCC. Two randomized, multicenter, phase III trials demonstrated that sorafenib could extend the overall survival (OS) in patients with advanced HCC.[11, 12] Owing to the significant antiangiogenic effect of sorafenib and the limitation of TACE, it is rational to combine TACE with sorafenib (TACE-sorafenib) to decrease post TACE angiogenesis. This is an attractive strategy to improve the efficacy of TACE therapy and potentially delay HCC progression. A phase II study using TACE-sorafenib reported a significantly longer time to progression (TTP) in patients with HCC compared to the placebo group (9.2 vs 4.9 months), with no unexpected side effects.[13] Another phase II study of TACE-sorafenib for HCC in Asia (START) indicated that this combined therapy was well tolerated and effective.[14] A systematic review concluded that the combination of TACE with sorafenib was likely to improve OS and TTP versus TACE monotherapy for the treatment of unrespectable HCC.[15]

Both TACE and TACE-sorafenib therapies have shown significant clinical benefits for unresectable HCC. However, large financial outlay is needed for treating a large number of patients with unresectable HCC. Thus, the decision to adopt either therapy as a first-line option carries major implications with respect to costs and expectations for quality healthcare. The aim of this study was to estimate the relative cost-effectiveness of TACE alone and TACE-sorafenib therapy for treating unresectable HCC via a decision analytic model from the Chinese perspective of healthcare system.

Methods

Patients and model structure

A Markov model (TreeAge Software, Williamstown, MA, USA) was conducted to simulate a cohort of patients with unresectable HCC. They underwent TACE or TACE-sorafenib and followed over a time horizon of their remaining life expectancy (Fig. 1). Including criteria of unresectable HCC patients are listed as follows: (i) histologically or clinically confirmed HCC; (ii) categorized as BCLC stage B or C (according to the BCLC staging system); (iii) no main portal vein thrombosis or extrahepatic metastasis; (iv) Child-Pugh class A or B liver function and adequate hematologic/clotting and renal function; (v) aged at least 18 years old, and Eastern Cooperative Oncology Group (ECOG) performance status: 0-2. The study was approved by the Research Ethics Committees of West China Hospital, Sichuan University. Patients with unresectable HCC were hypothetical cohort derived from literatures. Clinical data, utilities and transition probabilities were primary based on literature reviews, and costs were calculated based on the records.

The hypothetical cohort of patients occupied one health state and moved to another according to transition probabilities during each model cycle (Table 1). The length of model cycle was one month and the time horizon chosen for the current analysis was a lifetime. Monthly transition probabilities were derived from cu-

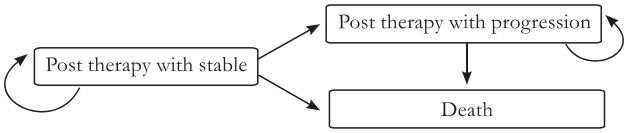

Fig. 1. Overview of the Markov models. Simulation represents the transitions of the hypothetical cohorts through various health states from commencement of stable state to death.

Table 1. Transition probabilities used in the model

Parameters	Base case value	References
Post TACE 1-year cumulative survival rate (%)	51	[2, 5, 8, 17-21]
Probability of post TACE with stable to death*	0.0577	-
Post TACE the median TTP (mon)	7.8	[22, 23]
Probability of post TACE with stable to HCC progression#	0.0850	-
Post TACE the median time of stable to HCC progression (mon)	6.6	[13, 14, 24-28]
Probability of recurrent HCC to death post TACE	0.0997	-
Post TACE-sorafenib the median OS (mon)	20.4	[24-26]
Probability of post TACE-sorafenib with stable to death#	0.0334	-
Post TACE-sorafenib the median TTP (mon)	13.8	[13, 14, 26-28]
Probability of post TACE-sorafenib with stable to HCC progression#	0.0490	-
Post TACE-sorafenib the median time of stable to HCC progression (mon)	6.6	[13, 14, 24-28]
Probability of recurrent HCC to death post TACE-sorafenib#	0.0997	-

*: Using the assumption of a declining exponential approximation of life expectancy, the monthly probability was derived from 2-year cumulative survival by using the formula: 1-(prob)1/12, where prob is 1-year cumulative survival; #: Monthly probability of health states were estimated using the formula: 1- (0.5)(1/median time to event). TACE: transcatheter arterial chemoembolization; HCC: hepatocellular carcinoma; TTP: time to progression; OS: overall survival.