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A Trial-Based Cost-Effectiveness Analysis of Bevacizumab and Chemotherapy Versus Chemotherapy Alone for Advanced Nonsquamous Non–Small-Cell Lung Cancer in China

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ABSTRACT

Background: The first-line bevacizumab plus chemotherapy resulted in a clinical efficacy for Chinese patients with advanced nonsquamous non–small-cell lung cancer (NSCLC). Some economic analyses have carried out various methods to evaluate the cost-effectiveness of bevacizumab as the first-line treatment for NSCLC in other countries. Our objective was to assess the cost-effectiveness of bevacizumab plus chemotherapy compared with chemotherapy alone for the first-line treatment of advanced nonsquamous NSCLC. **Methods:** A Markov model was applied from the perspective of the Chinese health care system to assess cost-effectiveness. It was based on the clinical trial BEYOND that compared bevacizumab plus carboplatin/paclitaxel (B+CP) with placebo plus carboplatin and paclitaxel (PI+CP) for advanced nonsquamous NSCLC. Ten-year quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated. One-way sensitivity analysis and probabilistic sensitivity analyses (PSA) were performed. **Results:** QALYs were 1.17 years in the B+CP group and 0.83 years in the PI+CP group, resulting in a difference of 0.34 years. The ICER was $130,937.09/QALY, which was far beyond the willing-to-pay threshold of $24,314/QALY. At a threshold of $130,584/QALY, addition of bevacizumab had a 50% probability of being cost-effective. **Conclusions:** Bevacizumab is not cost-effective when combined with chemotherapy for patients with advanced nonsquamous NSCLC based on the Chinese health care system, resulting in a less demand in the Chinese market.

Keywords: bevacizumab, chemotherapy, cost-effectiveness, non–small-cell lung cancer.

Introduction

Globally, lung cancer is still the leading cause of cancer-related mortality [1,2]. About 1.8 million patients were found to have lung cancer and 1.6 million patients died from this cancer in 2012 [3]. In China, the incidence and the death rate of lung cancer are growing rapidly and are ranked first in both men and women in the annual report of the China national cancer registration [4]. The majority of patients with lung cancer are found at an advanced stage, and the fact that only about 15% of lung cancers are discovered in an early phase is the main cause of the high mortality rate [1]. Non–small-cell lung cancer (NSCLC) is the most common type, accounting for around 85% of all lung cancer cases [2].

The standard first-line treatment for advanced NSCLC usually includes platinum-based doublet chemotherapy, which consists of cisplatin or carboplatin combined with gemcitabine, paclitaxel, vinorelbine, and docetaxel [5,6]. Unfortunately, many clinical studies have shown that the clinical efficacy of the above chemotherapy regimens is similar, and the death rate of NSCLC is still high. Recently, bevacizumab and other molecular targeted agents have provided a new treatment regimen for advanced NSCLC.

Bevacizumab is a monoclonal antibody that selectively inhibits vascular endothelial growth factor (VEGF) [7]. So far bevacizumab is the only antiangiogenic agent received approval as the first-line treatment for in selected patients with NSCLC [8]. Bevacizumab, usually in combination with platinum-based doublet chemotherapy, treats advanced NSCLC. Addition of bevacizumab to chemotherapy has longer progression-free survival (PFS) and overall survival (OS) than chemotherapy alone [9].

There are a number of economic analyses in which a series of methods were adopted to evaluate bevacizumab as the first-line treatment for advanced nonsquamous NSCLC in several countries [10]. Among them, two cost-effectiveness analyses suggested that bevacizumab combined with carboplatin and paclitaxel was not cost-effective when compared with using only carboplatin and

Conflicts of Interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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paclitaxel [11,12]. One study reported that bevacizumab added to carboplatin and paclitaxel was not cost-effective when compared with using only cisplatin and pemetrexed [13]. Two studies confirmed that bevacizumab added to cisplatin and gemcitabine was cost-effective when compared with using only cisplatin and pemetrexed [14,15]. Accordingly, the cost-effectiveness of bevacizumab plus chemotherapy compared with chemotherapy alone remains controversial. Currently, no literature about the cost-effectiveness of bevacizumab based on the trial from China was found. Therefore, we performed a cost-effectiveness analysis of bevacizumab added to chemotherapy compared with chemotherapy alone for patients with advanced nonsquamous NSCLC. Our study on cost-effectiveness was based on the BEYOND trial, which was a muticenter clinical trial in China, and its result was consistent with the practical situation of the Chinese patients [16].

Materials and Methods

The data and information for this study were derived from the BEYOND trial in China [16]. A Markov model was developed to assess the cost-effectiveness of bevacizumab plus chemotherapy versus chemotherapy alone for the advanced nonsquamous NSCLC.

Model Structure

A Markov decision model of advanced nonsquamous NSCLC was used to evaluate the 10-year clinical and economic outcomes. The time horizon of 10 years can reflect disease progression and allow the survival data from two different treatments to be obtained. The decision model consisted of three mutually exclusive health statuses: progression-free survival (PFS), disease progression (DP), and death (Fig. 1). At the beginning of the model, all patients were in the PFS health status and received one of the two treatments:

1. Placebo (PI) plus six cycles of carboplatin (area under the curve = 6) intravenously (IV) and paclitaxel (200 mg/m^2) IV (CP) on day 1 of each cycle (PI+CP);
2. CP plus bevacizumab (B) (15 mg/kg) IV on day 1 of each cycle until disease progression, or unacceptable toxicity, or death (B+CP).

Each cycle lasted for 3 weeks for both groups. With time, the patients could have remained in the PFS status or moved to the DP status due to disease progression, or they could have died. Patients at the DP status could have retained the DP status or died. Patients who died from advanced NSCLC or any other cause belonged to the death status, which was the final status.

We built a Markov model to estimate the clinical costs, and life expectancy (LY) and quality-adjusted life year (QALY) gained from the clinical trial. The outcomes of both treatments were presented as incremental cost-effectiveness ratios (ICERs).

Collection and Analysis of Clinical Data

The efficacy data originated from a randomized, double-blind, placebo-controlled, multicenter, phase β clinical trial [16]. We used R 2.11.1 (R Foundation, Wien, Austria) to simulate Weibull distributions, which were suitable for the Kaplan-Meier PFS and OS curves from BEYOND trial, and calculated time-dependent transition probabilities for each cycle. The validity of the Markov model can be confirmed by comparing PFS and OS rates obtained from the Markov model–based BEYOND trial. The results are presented in Table 1. We calculated the time-dependency transition probability among PFS, DP, and death by using two key parameters of scale (λ) and shape (γ), according to the formula as follows:

$$p(t) = 1 - \exp\{\lambda(t-1)^{\gamma} - \lambda t^{\gamma}\}$$

where the scale parameter (λ) is relevant to the measurement unit of time and the shape parameter (γ) defines the hazard function to change with increasing time [17].

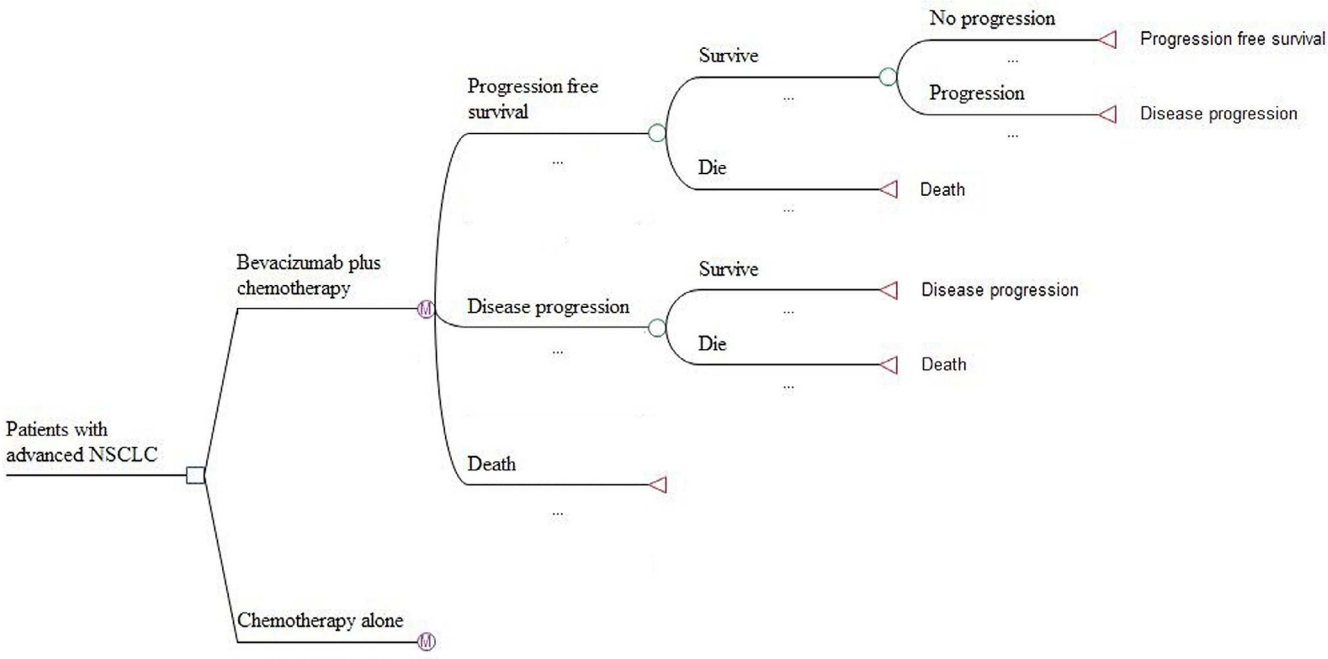

Fig. 1 – Markov model tree structure of bevacizumab plus chemotherapy versus chemotherapy alone for the advanced nonsquamous non–small-cell lung cancer.

Table 1 – Weibull regression model fitted to the Kaplan-Meier survival curve in the trial.

Treatment	Scale, mean (SE)	Shape, mean (SE)	Adjusted R^2	Correlation coefficient
Progression-free survival				
B+CP	0.00367 (0.00051)	2.00337 (0.04986)	0.99554	−0.98931
PI+CP	0.00474 (0.00099)	2.26582 (0.08833)	0.99368	−1.00000
Overall survival				
B+CP	0.00350 (0.00025)	1.48026 (0.02012)	0.99666	−0.99711
PI+CP	0.00444 (0.00061)	1.54682 (0.04015)	0.98907	−0.99923

B+CP, bevacizumab plus carboplatin/paclitaxel; PI+CP, placebo plus carboplatin/paclitaxel.

Costs

In our study, medical costs data were from the perspective of Chinese health care system, and only direct costs were considered. Main medical costs in the PFS state included treatment costs, and the costs of adverse drug reactions (ADR) treatments. The treatment costs mainly included the drug costs (carboplatin, paclitaxel, and bevacizumab) and the drug administration costs.

The drug costs were calculated by multiplying the unit prices of drugs by the number of cycles administered. The patients in the PI+CP group received carboplatin (area under the curve = 6) IV and paclitaxel (200 mg/m^2) IV plus placebo on day 1 of each cycle, and the patients in the B+CP group received the same chemotherapy regimen plus bevacizumab (15 mg/kg) IV on day 1. The bevacizumab was used until disease progression, or unacceptable toxicity, or death. The patients received carboplatin and paclitaxel for up to 6 cycles unless disease progression, or unacceptable toxicity, or death. We assumed apatient as an example who was 57 years old, with 65 kg weight, 1.72 m^2 body surface area, and 70 ml/min creatinine clearance [11,18]. We assumed that no drug was wasted.

The drug administration costs were estimated by multiplying the prices of drug administration each cycle by the number of cycle administered. Because ICERs depended on the difference of clinical outcomes and costs, it was proper to remove any same items between the two regimens such as the costs of clinical follow-up, CT, biochemical test, and the adjunctive care.

The costs of treating ADRs focused on neutropenia, anemia, thrombocytopenia, and diarrhea. Their costs were obtained from the literature published [17,19,20].

In this analysis, starting from seventh cycle in the PFS state, the patients in the B+CP group received bevacizumab only as the maintenance treatment, whereas those in the PI+CP group were administrated best support care, whose costs were obtained from the literature published [18]. There is a Bevacizumab Patient Assistance Program (BPAP) provided by Roche China, which makes bevacizumab available to eligible patients. According to the BPAP, the cost of bevacizumab for three cycles should be considered. Therefore, the economic analyses covered the importance of BPAP for bevacizumab. The costs of the DP state per circle was referred from the public paper [21].

In this model, the costs were shown in U.S. dollar ($), and the price year was 2016. In this study, the discount rate of costs was 3% annually [22].

Utility Values

The health state utility values were derived from the public literature that described the health state utilities of Chinese patients with NSCLC. The health utilities were 0.80 in the PFS state and 0.32 in the DP state and were used for all patients of both groups [23].

Sensitivity Analysis

One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed to reflect uncertainty of the parameters in the model.

One-way sensitivity analysis examined the impact of singe variable concerning the outcome of ICER while other variables kept constant. Its outcome was presented in a tornado diagram. The parameters contained the cost data, the rate of ADR, the utility values, and discount rate. The ranges of the parameters were obtained from the public literature. When data were not available from the public literature, a range of ±20% of the base-case value was adopted. The willing-to-pay (WTP) threshold was $24,314 (triple the per capita GDP of China), according to the recommendation of the World Health Organization [24]. The range and distributional assumptions of each key parameter were shown in Table 2.

PSA considered the influences of all variables on the model parameter uncertainty. The parameters were assessed through the Monte Carlo method to run 1000 replicated outcomes, which were presented in acceptability curve and scatter diagram of ICER.

Results

Base Case

In the model, the median PFS and OS were 9.58 and 24.93 months in the B+CP group compared with 6.32 and 18.33 months in the PI+CP group. In the clinical trial, the median PFS and OS were 9.2 and 24.3 months in the B+CP group compared with 6.5 and 17.7 months in the PI+CP group. Median PFS and OS values gained by our model were slightly different from those in the clinical trial data, indicating the reliability of the Markov model.

We used TreeAge Pro Suit 2011 (TreeAge Software Inc, Williamstown, MA) to assess a 10-year clinical outcomes and costs of bevacizumab plus chemotherapy versus chemotherapy alone for the advanced NSCLC. The base-case outcomes discounted at 3% per year were exhibited in Table 3. The discounted LY was 2.33 years (28.0 months) in the B+CP group and 1.72 years (20.6 months) in the PI+CP group, with a tolerance of 0.61 years. QALYs were 1.17 years (14 months) in the B+CP group and 0.83 years (10 months) in the PI+CP group, with a difference of 0.34 years. Thereby, it was demonstrated that the life quality was improved when bevacizumab was added to chemotherapy.

The cost of the PI+CP group was $40,993.49. For the B+CP group, the total cost without and with BPAP was $85,512.10 and $50,148.54, respectively. The ICER without BPAP was $130,937.09, which was far beyond the WTP threshold of $24,314. The ICER with BPAP was $26,926.62, which was slightly more than the WTP threshold.

The results indicated that the BPAP sharply reduced the cost of the progression-free stage for the bevacizumab strategy

Table 2 – Ranges and distribution assumptions of key parameters for sensitivity analysis for the patients with advanced nonsquamous NSCLC in China (data are in 2016 U.S. dollars).

Parameter	Base case	Range	Source	Distribution	Reference
Drug costs					
Carboplatin per 100 mg	11.11	8.89–13.34	±20%	Log-normal	
Paclitaxel per 30 mg	144.28	115.42–173.13	±20%	Log-normal	
Bevacizumab per 100 mg	300.90	240.72–361.08	±20%	Constant	
Administration costs in the PFS per cycle					
B+CP group (≤6 cycle)	48.83	39.07–58.60	±20%	Gamma	
B+CP group (>6 cycle)	20.90	16.72–25.08	±20%	Gamma	
PI+CP group (≤6 cycle)	34.86	27.89–41.84	±20%	Gamma	
Cost of best supportive care	1415.40	1022.8–2021.5	Low–high	Log-normal	[18]
Cost of DP for both groups per cycle	1209.96	967.97–1451.95	±20%	Gamma	[20]
Costs of ADR events					
Neutropenia	461.5	415.4–507.7	Low–high	Log-normal	[19]
Anemia	531.7	478.5–584.9	Low–high	Log-normal	[19]
Thrombocytopenia	3395.0	3017.5–3804.6	Low–high	Log-normal	[20]
Diarrhea	5.18	4.14–6.22	±20%	Log-normal	[17]
Risks for serious ADR events					
Neutropenia in B+CP group	0.23	0.184–0.276	±20%	Beta	
Neutropenia in PI+CP group	0.28	0.224–0.336	±20%	Beta	
Anemia in B+CP group	0.07	0.056–0.084	±20%	Beta	
Anemia in PI+CP group	0.11	0.088–0.132	±20%	Beta	
Thrombocytopenia in B+CP group	0.07	0.056–0.084	±20%	Beta	
Thrombocytopenia in PI+CP group	0.09	0.063–0.108	±20%	Beta	
Diarrhea in B+CP group	0.01	0.008–0.012	±20%	Beta	
Diarrhea in PI+CP group	0.03	0.024–0.036	±20%	Beta	
Body surface area (m^2)	1.72	1.5–1.9	Low–high	Normal	[18]
Weight (kg)	65	52–78	±20%	Normal	[18]
Utility					
PFS	0.80	0.64–0.96	±20%	Beta	[23]
DP	0.32	0.26–0.38	±20%	Beta	[23]
Discount rate (%)	3	0–8	Fixed in PSA	Constant	[22]

ADR, adverse drug reaction; DP, disease progression; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; PSA, Probabilistic sensitivity analysis.

Table 3 – Base case results discounted at 3% per year.

Results	B+CP	PI+CP
Effectiveness		
Life expectancy (years)	2.33	1.72
PFS of life expectancy	0.87	0.58
DP of life expectancy	1.46	1.14
QALYs	1.17	0.83
PFS of QALY	0.70	0.46
DP of QALY	0.47	0.37
Lifetime costs without BPAP, $		
PFS	55,485.88	17,444.71
DP	30,026.22	23,548.78
Total cost	85, 512.10	40,993.49
ICER($/QALY)	130,937.09	
Lifetime costs with BPAP, $		
PFS	20,122.32	17,444.71
DP	30,026.22	23,548.78
Total cost	50,148.54	40,993.49
ICER ($/QALY)	26,926.62	

BPAP, Bevacizumab Patient Assistance Program; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

($35,363.56). Bevacizumab added to chemotherapy was not cost-effective based on commonly cited WTP threshold of $24,314 [24].

One-Way Sensitivity Analysis

The tornado diagram (Fig. 2) shows the one-way sensitivity analysis on the net health benefit of B+CP versus that of PI+CP. We obtained sensitive parameters, including mean weight, cost of bevacizumab, utility of PFS, utility of DP, cost of best supportive care per cycle, and discount rate in a descending order. Among them, mean weight was the most sensitive parameter.

Probabilistic Sensitivity Analysis

We conducted PSA to examine the probabilities of meeting the ICER thresholds. The scatter plot (Fig. 3) shows that most of the 1000 simulation iterations were located in the northeast quadrant (combination of bevacizumab treatment resulted in QALYs gained at extra costs compared with chemotherapy alone), whereas the other iterations fell in the northwest quadrant (combination of bevacizumab treatment resulted in QALYs loss at extra costs compared with chemotherapy alone).

We conducted the cost-effectiveness acceptability curves under different WTP by using a Monte Carlo simulation (Fig. 4). At a threshold of $130,584/QALY, bevacizumab plus chemotherapy has a probability of 50% of achieving cost-effective.

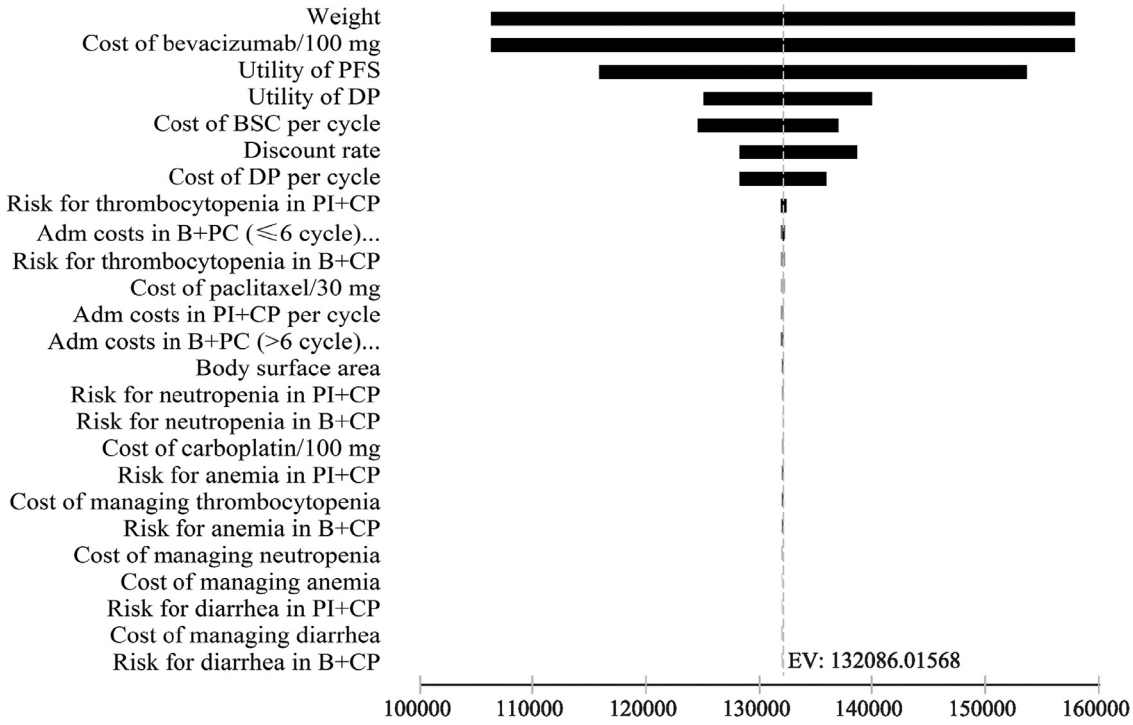

Fig. 2 – ICER Tornado Diagram. Adm, administration; B+CP, bevacizumab plus carboplatin and paclitaxel; BSC, best supportive care; DP, disease progression; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PI+CP, placebo plus carboplatin and paclitaxel.

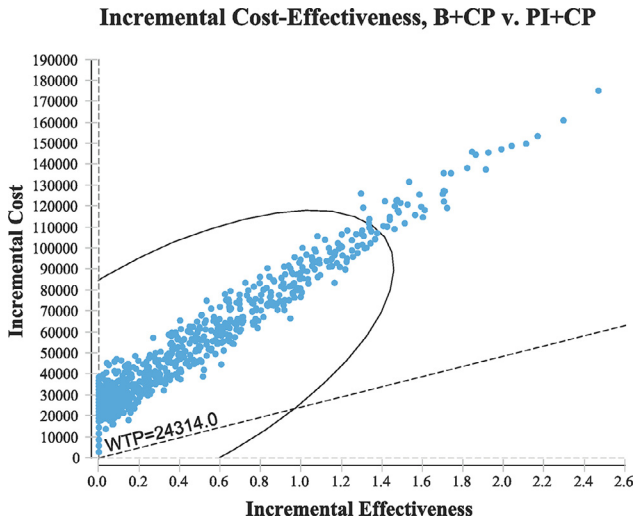

Fig. 3 – Incremental cost-effectiveness scatter plot. WTP, willingness to pay.

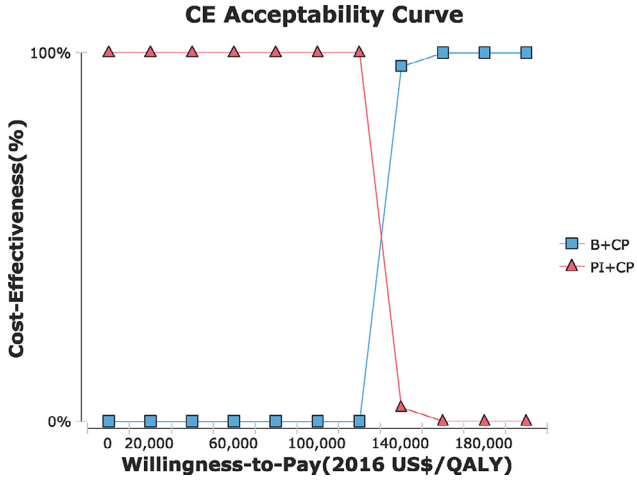

Fig. 4 – Cost-effectiveness acceptability curve of bevacizumab plus chemotherapy versus chemotherapy alone.

Discussion

We performed a cost-effectiveness analysis of bevacizumab-chemotherapy compared with chemotherapy alone as first-line therapy for advanced nonsquamous NSCLC based on the clinical BEYOND trial [16]. At the base case, compared with chemotherapy alone, bevacizumab strategy could prolong life expectancy by approximately 0.61 years (7.3 months) and the QALY by approximately 0.34 years (4.1 months), respectively. For bevacizumab strategy without BPAP and with BPAP, compared with chemotherapy alone, the total incremental costs were approximately $44,518.61 and $9,155.05, respectively, and the ICERs were $130,937.09 and $26,926.62, respectively. One-way sensitivity analysis revealed that the cost of bevacizumab was the important parameter for net health benefit. Thus, with a significant decrease in the cost of bevacizumab, the ICER would be largely reduced accordingly.

Several public economic studies assessed the cost-effectiveness of bevacizumab used to treat the advanced nonsquamous

Table 4 – The economics studies of bevacizumab as first-line chemotherapy in advanced nonsquamous NSCLC.

Country	Intervention	Comparator	ICER	Reference
USA	Bev/Car/Pac	Car/Pac	$560,000/QALY	[11]
Vietnam	Bev/Car/Pac	Car/Pac	VND 768,732,924/QALY	[12]
USA	Bev/Car/Pac	Cis/Pem	$337,179/LY	[13]
Italy	Bev/Cis/Gem	Cis/Pem	€34919/LY	[14]
Korea/Taiwan	Bev/Cis/Gem	Cis/Pem	₩34,064,835/LYG in Korea, NT$1 607,960/LYG in Taiwan	[15]

Bev, bevacizumab; Car, carboplatin; Cis, cisplatin; Gem, gemcitabine; LY, life expectancy; Pac, paclitaxel; Pem, pemetrexed.

NSCLC (Table 4). Goulart and Ramsey [11] and Tran and Nguyen [12] performed similar cost-effectiveness analyses to our study and reported that addition of bevacizumab to carboplatin and paclitaxel was not cost-effective when compared with only carboplatin and paclitaxel. Thus, the two studies indicated that the high price of bevacizumab led to the negative cost-effectiveness. Klein et al. reported that the combination of carboplatin, paclitaxel, and bevacizumab was not cost-effective when compared with the combination of cisplatin and pemetrexed [13]. Ahn MJ et al. and Giuliani G et al. confirmed that bevacizumab added to cisplatin and gemcitabine was cost-effective when compared with only cisplatin and pemetrexed [14,15]. Two main aspects can explain the outcomes of their cost-effectiveness analyses. First, the price of bevacizumab and that of pemetrexed were different in the United States, Italy, Korea, and Taiwan. Bevacizumab ($5.75/mg) was more expensive than pemetrexed ($4.94/mg) in the United States. Bevacizumab (₩4601.88/mg) was more expensive than pemetrexed (₩2075.70/mg) in Korea. Bevacizumab (NT$160/mg) was more expensive than pemetrexed (NT $70.42/mg) in Taiwan. Bevacizumab (€2.68/mg) was cheaper than pemetrexed (€2.75/mg) in Italy only. Second, the researchers used different doses of bevacizumab. Klein et al. used bevacizumab at a dose of 15 mg/kg for a 3-week cycle, whereas Ahn et al. and Giuliani et al. used bevacizumab at a dose of 7.5 mg/kg each cycle. The cost of bevacizumab was very important to ICER in the one-way sensitivity analysis, therefore the price and dose of bevacizumab can affect the cost-effectiveness analysis greatly.

There are three ways to improve the cost-effectiveness of bevacizumab. First, the pharmaceutical company could reduce the price of bevacizumab. The cost of bevacizumab is a very important parameter in the one-way sensitivity analysis, and reduction of the unit price of bevacizumab would lead to decreased ICER. Presently, bevacizumab is listed in China's National Drug Reimbursement Categories, which reduces the medicine cost. Moreover, the possibility of being cost-effective would be increased if WTP is improved. The cost-effectiveness analysis was conducted in order to compare the ICER by using the threshold of WTP, and to assess whether the treatment was cost-effective. WTP is triple of the per capita GDP of China and is related to the economy of a country. From the sensitivity analysis, the probability of cost-effectiveness increases with the increase in WTP. Thus, bevacizumab would be cost-effective with increasing income of residents and WTP. Finally, Roche China supports charity policy of bevacizumab more widely. The charity project of bevacizumab is available only for low-income families, and the patients will obtain this drug for free after using it to certain dose. The sensitivity analysis indicated that the BPAP sharply decreases the cost of the progression-free stage for the bevacizumab strategy. So bevacizumab would be cost-effective when increasing the intensity and scope of the charity project.

There are two main limitations in our research. First, we could not collect all the cost data of each treatment item in the BEYOND trial for our research. Among them, the cost data of best support care, DP, and treating ADRs were referred from the Chinese economic evaluation, and the cost data of drug administration were from the charge standard of three-level hospital in Shanghai [17–20]. Then, we could not obtain long-term clinical data of practice research. To figure out long-term health data, we need to design a model to deduct the survival data. In our study, we simulated the Weibull curves, which cannot accurately reflect the true characteristic of disease status change.

Conclusion

Taken together, our results indicate that bevacizumab with chemotherapy strategy was not a cost-effective option for advanced nonsquamous NSCLC.

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