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Cost-Utility Analysis of Pembrolizumab Combined with Gemcitabine and Cisplatin in the Treatment of Advanced Biliary Tract Cancer

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Abstract

Background: The latest KEYNOTE-966 trial shows that compared with conventional chemotherapy, pembrolizumab treatment significantly improves the overall survival benefit of patients with advanced Biliary Tract Cancer (BTC). The purpose of this study was to compare the economics of pembrolizumab combined with chemotherapy as a first-line treatment for advanced BTC.

Methods: A partition survival model was established to simulate the life-long survival benefit and cost consumption of patients. Obtain efficacy and safety data from the KEYNOTE-966 trial and local cost and resource use data from online databases and published studies. The results were expressed as total cost, incremental cost, life years, Quality-Adjusted Life Years (QALYs), incremental QALYs, and Incremental Cost-Effectiveness Ratio (ICER). The stability of the model was tested by single-factor sensitivity and probability sensitivity analysis.

Results: The results of basic analysis showed that compared with traditional chemotherapy, patients in the pembrolizumab group could obtain 0.295 QALYs more, cost $349,307.329 more, and the incremental cost-effectiveness ratio ICER was $1,182,369.991/QALY, which was much higher than the Willingness to Pay Threshold (WTP), that is, three times China's per capita gross domestic product in 2021 ($33,471.3). Single-factor sensitivity analysis showed that the price of pembrolizumab had a great influence on ICER value. The results of probability sensitivity analysis showed that when the WTP value was 3 times of 2021 GDP, the probability of pembrolizumab being economical was 0.

Conclusion: When the WTP threshold is 3 times China's per capita GDP in 2021, the first-line treatment of advanced biliary tract cancer with a pembrolizumab regimen is not economical compared with traditional chemotherapy regimens.

Keywords: Pembrolizumab; Gemcitabine; Biliary tract cancer; Cost-utility analysis; Chemotherapy

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Introduction

Biliary System Tumors (BTCs) are a group of heterogeneous and invasive tumors originating from the biliary system, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer. Intrahepatic cholangiocarcinoma is considered to be the primary intrahepatic malignant tumor second only to hepatocellular carcinoma. Although it accounts for 3% of malignant tumors of the digestive system [1], its incidence continues to increase in different populations in Asia, Europe, Latin America, Australia, and other regions [2], and the prognosis is extremely poor. The 5-year survival rate of gallbladder cancer is only 5% to 10%, and that of biliary tract cancer is 10% to 40%. Thorough surgical resection is the only opportunity to cure. However, only 10% of patients have the chance of surgical resection [3]. Even after surgical resection, the recurrence rate is as high as 60%. Therefore, patients have urgent clinical needs [4].

Systemic chemotherapy has always been the main treatment for advanced biliary tract cancer. A randomized three-phase study of ABC02 used Gemcitabine Plus Cisplatin (GEMCIS) as a standard first-line regimen for advanced biliary tract cancer. Compared with gemcitabine monotherapy, GEMCIS showed a significant improvement in overall survival and progression-free survival [5]. The efficacy of anti-PD-1/PD-L1 antibody combined with chemotherapy or other targeted therapy for BTC is significantly better than that of traditional chemotherapy. Among them, the effect of anti-PD-L1 antibody durvalumab combined with CisGem in the first-line treatment of BTC is significant, and it has been recommended by the NCCN guidelines in 2022 [6].

Pembrolizumab, a monoclonal Antibody (mAb), binds to the Programmed Death 1 (PD-1) receptor and blocks its interaction with its ligands Programmed Death Ligand 1 (PD-L1) and Programmed Death Ligand 2 (PD-L2) [7]. It has been shown that its monotherapy is active in many tumor types and hematological malignancies. The preliminary results of the 028b KEYNOTE-1 study conducted in selected PD-L1-positive tumor patients showed that pembrolizumab has controllable anti-tumor activity and safety in patients with advanced/metastatic BTC [8]. It was approved by the U.S. Food and Drug Administration in 2014 and has been widely used. Pembrolizumab has been approved by the drug regulatory authorities in China for the treatment of first-line and second-line Non-Small Cell Lung Cancer (NSCLC) patients. In addition, the indications of pembrolizumab include nasopharyngeal carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and so on. At present, the price of the drug in China is 4,479.5 yuan/ml, which is not included in the national medical insurance.

On April 16th, 2023, the clinical research plenary meeting of the 2023 American Association for Cancer Research (AACR) annual meeting announced the final analysis results of the phase III KEYNOTE-966 study of the PD-1 immune checkpoint inhibitor pembrolizumab combined with chemotherapy as the first-line treatment of advanced Biliary Tract Cancer (BTC). This is the first and only published global multicenter phase III clinical study of PD-1 monoclonal antibody combined with chemotherapy as first-line treatment for advanced biliary tract malignancies. It is also another phase III clinical study showing that pembrolizumab combined with chemotherapy as first-line treatment for advanced malignant tumors can bring significant OS benefits. The KEYNOTE-966 study showed that compared with chemotherapy, the use of pembrolizumab in the treatment of BTC patients has a longer overall survival and a longer-lasting anti-tumor response. This trial demonstrates the clinical efficacy and controllable safety of pembrolizumab compared with traditional chemotherapy [9]. Although pembrolizumab has shown superior clinical benefits, the economics of its treatment for BTC need to be further studied. Therefore, in this study, an economic analysis was performed on the first-line treatment of patients with advanced biliary tract tumors using pembrolizumab combined with gemcitabine and cisplatin compared with gemcitabine and cisplatin monotherapy.

Material and Methods

Patients and intervention

This study was conducted after the phase III clinical trial (KEYNOTE966) report. The target population of this study was patients with histologically proven unresectable locally advanced or metastatic extrahepatic cholangiocarcinoma (including mixed hepatocellular carcinoma and cholangiocarcinoma), gallbladder cancer or intrahepatic cholangiocarcinoma. According to the KEYNOTE966 trial [9], a total of 533 patients were treated with pembrolizumab combined with gemcitabine and cisplatin, and 536 patients were treated with placebo combined with gemcitabine and cisplatin. According to the ESCORT clinical study and guidelines, 200 mg of pembrolizumab or saline placebo was injected intravenously on the first day of every 3 weeks, and gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 were administered intravenously on the first and eighth days of every 3 weeks. All treatments continue until disease progression or unacceptable toxicity occurs in the patient. Pembrolizumab and placebo were limited to 35 cycles, and cisplatin was limited to 8 cycles. There is no limit on the number of cycles of gemcitabine.

Model structure

Based on the KEYNOTE966 trial, a partition survival model was established, which included three states: Progression-Free Disease (PFS), Progressive Disease (PD), and death (Figure 1). These three states are mutually exclusive [10]. In one model cycle, only one state can be converted to another state or remain unchanged. PFS can be converted to PD state, and both PFS and PD states may be converted to death state. The relative 5-year survival rate of patients diagnosed with metastatic disease was 8% or lower. Therefore, the time range of the model is set to 10 years [11]. The model period is set to 1 month to facilitate model operation and parameter calculation. The output of the model includes long-term cost, Quality-Adjusted Life Years (QALYs), and Incremental Cost-Effectiveness Ratio (ICER). TreeAge Pro 2020 software package was used to construct the model and perform statistical analysis.

Clinical data

The clinical efficacy and safety data of pembrolizumab combined with gemcitabine and cisplatin were mainly from the KEYNOTE966

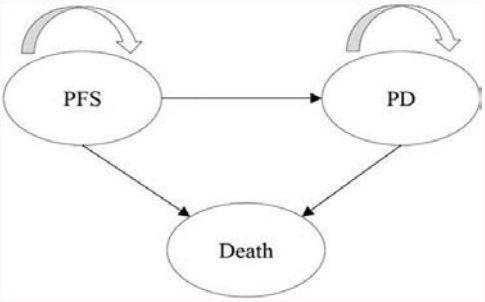

Figure 1: Model structure.

Table 1: Survival parameters.

Kaplan-Meier	Best fitting	Survival parameters
OS for pembrolizumab	Log-logistic	Shape = 1.79886, scale = 12.70996
PFS for pembrolizumab	Log-normal	Meanlog = 1.79624, sdlog = 1.09585
OS for placebo	Log-logistic	Shape = 1.78259, scale = 11.03387
PFS for placebo	Log-normal	Meanlog = 1.67386, sdlog = 1.00081

Table 2: Model input parameters.

Model input	Base value	Range	Distribution	Reference
Drug costs				
Pembrolizumab (100mg)	2449.79	1959.83-2939.75	Gamma	Menet
Gemcitabine (200mg)	15.36	0.32-46.59	Gamma	Menet
Cisplatin (30mg)	2.9	2.62-3.82	Gamma	Menet
Fluorouracil (100mg)	20.11	19.7-24.13	Gamma	Menet
Folinic acid (250mg)	68.61	54.89-82.33	Gamma	Menet
Oxaliplatin (50mg)	27.27	12.64-40.05	Gamma	Menet
Irinotecan (40mg)	56.94	4.07-136.10	Gamma	Menet
Capecitabine (500mg)	1.02	0.26-3.76	Gamma	Menet
SAE management cost				
Anemia	5.23	4.18-6.28	Gamma	[20]
Neutropenia	63.17	50.54-75.80	Gamma	[20]
Leukopenia	176.6	141.28-211.92	Gamma	[20]
Thrombocytopenia	165.97	132.78-199.16	Gamma	[20]
Other costs				
Terminal care	1742.78	1394.22- 2091.34	Gamma	[19]
Follow up	98.71			[19]
Incidence of SAE in Pembrolizumab plus				
Anemia	28%	0.22-0.34	Beta	[9]
Neutropenia	49%	0.39-0.59	Beta	[9]
Leukopenia	12%	0.10-0.14	Beta	[9]
Thrombocytopenia	18%	0.14-0.22	Beta	[9]
Utility and disutility				
PFS	0.76	0.608-0.912	Beta	[15]
PD	0.68	0.544-0.816	Beta	[15]
U-Anemia	0.073	0.0584-0.0876	Beta	[16]
Disutility of leukopenia	0.09	0.072-0.108	Beta	[16]
Disutility of Neutropenia	0.09	0.072-0.108	Beta	[16]
Disutility of thrombocytopenia	0.65	0.52-0.78	Beta	[16]
Discount	5%	0%-8%		[18]

clinical trial. Use GetData Graph Digitizer 2.26 (http://www.getdata-graph-digitizer.com) to obtain the survival point of the Kaplan-Meier curve. R software was used for the individual-level data of patients and then fitted by Log-normal distribution, Weibull distribution, Gompertz distribution, Exponential distribution, and Log-logistic distribution. According to the lowest value of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) [12], the best-fitting distribution was selected. The fitting results are shown in Table 1. Finally, the fitting extrapolation of the OS curve and PFS curve conforms to the Log-logistic distribution and Log-normal distribution, respectively, as shown in Figure 2, 3.

Cost and utility

This study only considered direct medical costs, including drug, follow-up, best supportive care, post-progressive treatment drugs, and Severe Adverse Event (SAE) treatment costs. The average body surface area of the patients in the model was 1.72 m^2 (1.5-1.9 m^2) [13]. The unit cost of drugs is obtained from the Minenet database (menet.com) and converted into US dollars. The treatment regimen, the proportion of patients using each regimen, and the incidence of serious adverse events were extracted from the KEYNOTE966 trial [9], and only grade ≥ 3 adverse reactions were considered. Forty-three percent of the patients in the group received subsequent chemotherapy, 5% received immunotherapy, and 8% received other treatments. The proportion of patients receiving various treatments in the chemotherapy group was 43%, 7%, and 9%, respectively. However, there is no specific follow-up treatment drug in the trial. Therefore, according to the NCCN and CSCO guidelines of BTC, it is assumed that pembrolizumab (immunotherapy), FOLFOX (chemotherapy), irinotecan + capecitabine (other treatments) are used as follow-up treatment drugs [14].

Since the KEYNOTE966 study did not collect quality-of-life information, the utility values of PFS and PD status used in this study were derived from published literature [15]. At the same time, this study also considered the negative effects of severe adverse drug reactions [16] (Table 2).

Taking the World Health Organization and the "Chinese Pharmacoeconomic Evaluation Guide 2020" as a reference, this study selected three times China's per capita GDP as the willingness to pay

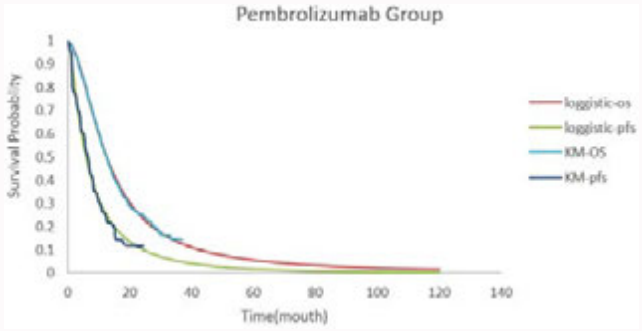

Figure 2: Fit curve of the pembrolizumab group.

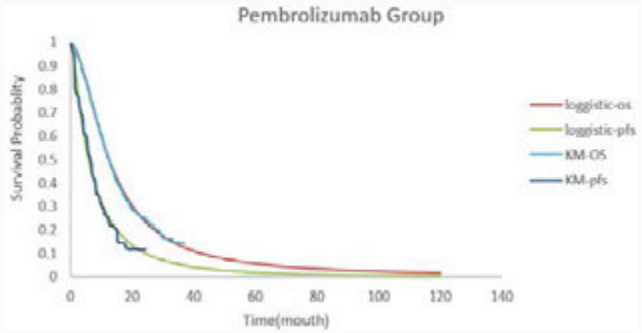

Figure 3: Fitting curve of the placebo group.

threshold [17,18]. According to the data of China's per capita GDP of 80,976 yuan in 2021 shown on the official website of the National Bureau of Statistics, the WTP threshold was set to USD 33,471.30/QALY. The discount rate is 5%.

Sensitivity analysis

In this study, single-factor sensitivity analysis (DSA) and Probability Sensitivity Analysis (PSA) were performed to verify the stability of the model results. In DSA, the upper and lower limits of the variables are set according to the upper and lower limits of the variables (the drugs used in the study are set according to the price provided by the rice network, and the other parameters are used as the upper and lower limits of the mean ± 20%. The discount rate is 0% to 8% [18]. Calculate the impact of a single variable change on the ICER value one by one, and draw a tornado map based on the calculation results. The horizontal axis of the cyclone diagram represents the influence range of each parameter on ICER, and the vertical axis represents the parameter name. The degree of influence of the factors that affect the evaluation results decreases from top to bottom. In PSA, it is assumed that the cost parameter obeys the gamma distribution, and the incidence of AE and utility parameters follow the β distribution. In addition, all survival parameters are evaluated by Cholesky decomposition. 1,000 Monte Carlo iterations were performed to evaluate the uncertainty of the overall model [19,20]. According to the Monte Carlo simulation results, the cost-effectiveness scatter plot and the cost-effectiveness acceptable curve were drawn.

Scenario analysis

In this study, three different scenarios were considered: (1) To explore the impact of the price of pembrolizumab on the economy of pembrolizumab combined with chemotherapy, the price of pembrolizumab was reduced by 50% and 80%, respectively; (2) pembrolizumab charity assistance project has been implemented in the treatment of several tumors. The specific programs are as follows: Patients use 2 courses of pembrolizumab injection, which can be assisted for 2 courses after being approved by the foundation. After 2 courses of treatment, the foundation could continue to assist until the disease progressed, and the patients were treated with pembrolizumab injections for no more than 24 months. In this study, we hypothesized that this method of assistance was also used after pembrolizumab was approved for advanced BTC in China, and analyzed ICERs in all groups of patients receiving and not receiving charitable assistance. (3) The TOPAZ1 test proved that durvalumab combined with chemotherapy has significant clinical benefits for advanced biliary tract cancer [21]. It is similar to KEYNOTE966 in many aspects and is also compared with the gemcitabine plus cisplatin chemotherapy group. Due to the lack of head-to-head clinical trials of pembrolizumab combined with chemotherapy and durvalumab combined with chemotherapy, this study used the survival data of the pembrolizumab group as a control and used the HR derived from the results of Network Meta-Analysis (NMA) to calculate the survival data of the durvalumab group for indirect comparison. The study used R software (https://www.r-project.org) to call the gemtc package for Bayesian NMA. The fitting degree of the fixed effect and random effect models was judged according to the value of the Deviation Information Criterion (DIC). If the DIC difference between the two models is greater than 5, the model with a smaller DIC value is selected. If the DIC difference is less than or equal to 5, it means that the fitting degree of the two models is the same, and the model with smaller I^2 is selected. Log-logistic distribution is the best for OS data, and Log-normal distribution is the best for PFS data. Two parameters of Log-logistic distribution can be obtained by fitting: Shape parameter (γ) and scale parameter (λ). The shape parameter of the durvalumab group = the shape parameter of the pembrolizumab group, and the scale parameter of the durvalumab group = HR × the scale parameter of the pembrolizumab group [22]. The survival rate of the durvalumab group was calculated according to the above formula.

Results

Basic situation analysis

According to the calculation results of the mean value, in the partition survival model, the incremental cost of the pembrolizumab group relative to the placebo group was $349,307.3293, the incremental utility was about 0.295 QALYs, and the ICER was $1,182,369.991/QALY, which was higher than the WTP threshold of $33471.3/QALY, indicating that the pembrolizumab group was not economical for first-line treatment of biliary malignancies.

Sensitivity analysis

The results of the one-way sensitivity analysis are shown in Figure 4. The main factor that has a greater impact on ICER is the cost of pembrolizumab. The incidence of thrombocytopenia in

Table 3: Basic results of cost-utility analysis.

Treatment	Cost	QALY	Incremental cost	Incremental QALY	ICER
Pembrolizumab group	3,76,310.61	3.44	3,49,307.33	0.3	11,82,369.99
Placebo group	27,003.28	3.15			

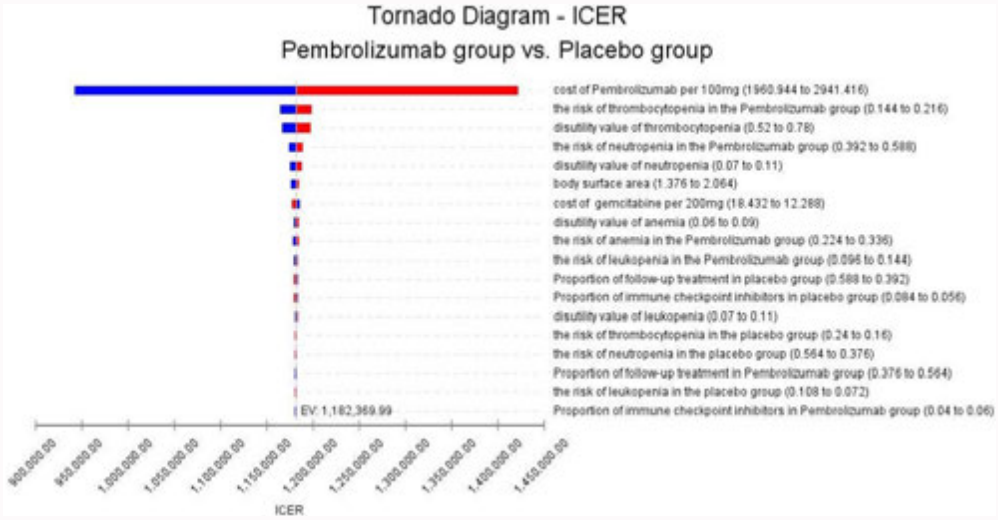

Figure 4: Tornado diagram for univariate sensitivity analysis.

Table 4: Scenario analysis results.

	Cost	Incermental cost	LY	QALY	Incermental QALY	ICER
The price of Pembrolizumab has been reduced by 50%						
chemotherapy group	25,511.83		4.15	3.15		
Pembrolizumab group	1,97,680.17	1,72,168.34	4.53	3.44	0.3	5,82,772.43
The price of Pembrolizumab has been reduced by 80%						
chemotherapy group	24,616.96		4.15	3.15		
Pembrolizumab group	90,501.91	65,884.95	4.53	3.44	0.3	2,23,013.89
PAP						
chemotherapy group	23,578.24		4.15	3.15		
Pembrolizumab group	86,120.22	62,541.97	4.53	3.44	0.3	2,51,873.27
Compared with durvalumab						
Pembrolizumab group	3,76,310.61		4.53	3.44		11,82,369.99
Durvalumab group	5,56,261.52	1,79,950.91	4.54	3.45	0.01	17,32,234.52

the monoclonal antibody group and the negative utility value of thrombocytopenia will also have a certain impact on ICER. The results of single factor sensitivity analysis showed that the ICER of pembrolizumab was always higher than that of WTP in China, regardless of how the variables changed, and the basic analysis results were robust.

Probability sensitivity analysis

After 1000 Monte Carlo simulations, the cost-effectiveness scatter plot (Figure 5) and the cost-effectiveness acceptable curve of the probabilistic sensitivity analysis can be obtained (Figure 6). It can be seen from Figure 5 that most of the ICER values are in the first quadrant and above the threshold line, suggesting that the probability that the pembrolizumab treatment regimen is economical at this time is 0. It can be seen from Figure 6 that under the threshold of 3 times per capita GDP (USD 33471.30), the probability of pembrolizumab being economical is 0. With the gradual increase of WTP value, the probability of pembrolizumab being economical gradually increased. When the WTP increases to 106 times per capita GDP, the treatment of biliary tract cancer will be economical.

Scenario analysis

The results of scenario analysis showed that when the price of pembrolizumab was reduced by 50% (Table 4) and 80%, the ICER of the pembrolizumab group and the placebo group was $582,772.43/QALY and $223,013.89/QALY, respectively, which was still higher than the current WTP in China. This regimen is still not economical for first-line treatment of advanced biliary tract cancer in China.

With the implementation of the charitable relief plan (incremental cost of USD 62,541.97, calculated ICER of USD 251,873.27/QALY), incremental cost and ICER decreased significantly. However, ICER is still much higher than WTP. The results showed that, whether or not there was a charitable assistance program, pembrolizumab plus chemotherapy was not an economical treatment strategy.

The total treatment costs of the durvalumab combined chemotherapy regimen and pembrolizumab combined chemotherapy regimen were USD 556,261.52 (3.45 QALYs) and USD 376,310.61 (3.44 QALYs), and the corresponding ICER values were 1,732,234.52 and 1,182,369.99, respectively. These analyses suggest that at the Chinese WTP threshold of $33,571.3/QALY, neither the durvalumab regimen nor the pembrolizumab regimen is an economical treatment strategy. Although the pembrolizumab group received less than 0.01 QALYs, it reduced the cost by $179,950.91, which was a more economical choice.

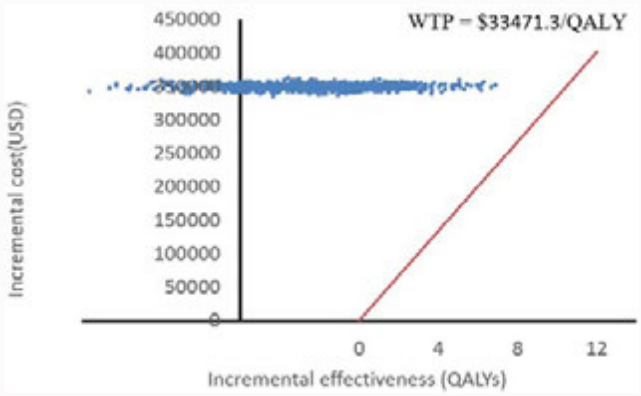

Figure 5: Scatter plot.

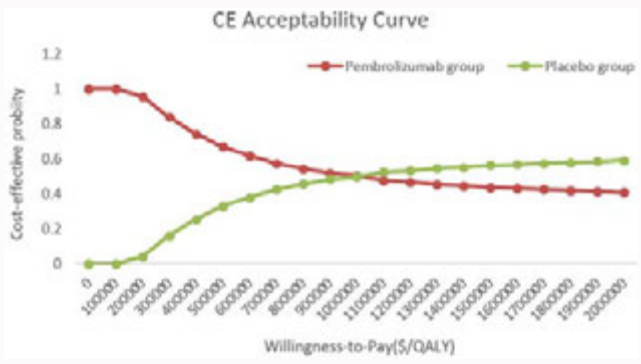

Figure 6: Cost-effectiveness acceptability curves under different thresholds.

Discussion

Tumor immunotherapy, especially PD-1/PD-L1 immune checkpoint inhibitors, has made rapid progress in the field of tumor therapy in recent years and has become another important tumor treatment after surgery, radiotherapy, and chemotherapy. In the past decade, gemcitabine combined with cisplatin was usually the first-line treatment option for patients with advanced biliary tract cancer. However, the benefits of patients using traditional chemotherapy were very limited, with a median OS of only 11.7 months. The TOPAZ-1 trial reported exciting clinical results in the treatment of biliary tract cancer with durvalumab combined with chemotherapy. Compared with standard chemotherapy, durvalumab combined with chemotherapy significantly improved OS and PFS in patients with advanced biliary tract cancer, marking a milestone breakthrough in the treatment of advanced biliary tract cancer. After the TOPAZ-1 test, KEYNOTE966 verified the effect of immune checkpoint inhibitors targeting PD1 and PDL1 combined with chemotherapy in the treatment of advanced biliary tract cancer. Compared with patients treated with chemotherapy alone, patients treated with pembrolizumab combined with GemCis had mOS (12.7 *vs.* 10.9 months; HR: 0.83; 95% CI, 0.72-0. 95; p=0.0034) and mPFS (6.5 *vs.* 5.6 months; HR: 0.87; 95% CI, 0.76-0. 99) were significantly prolonged. However, there are still some problems to be solved before clinicians can formally apply this immunotherapy combined chemotherapy regimen to the clinical practice of patients with advanced biliary tract cancer.

In 2016, China's medical expenditure on biliary tract cancer was 1.66 billion yuan, and the overall economic burden of management of patients with advanced biliary tract cancer increased over time [23]. The high cost of immune checkpoint inhibitors also brought a heavy economic burden to patients and their families. Some patients were forced to give up because they could not afford the treatment of immune checkpoint inhibitors. Therefore, clinicians must choose the appropriate treatment by weighing the relative costs and benefits of immune checkpoint inhibitors. Through a literature search, it is found that there is no relevant economic research on the treatment of advanced biliary tract cancer with pembrolizumab combined with chemotherapy at home and abroad. This is the first study to discuss the cost-effectiveness of pembrolizumab combined with chemotherapy compared with traditional chemotherapy in the first-line treatment of advanced biliary tract cancer. Therefore, the results of this study are of great significance to decision-makers.

Our results showed that the ICER of the pembrolizumab regimen was much higher than the WTP we set. This means that under the current economic conditions, although the pembrolizumab regimen can bring significant clinical benefits, it is not economical for most patients due to its relatively high sales price. On the other hand, based on China's national conditions, whether a higher WTP threshold should be used as an evaluation standard for tumor drugs remains to be further explored. The cost-effectiveness acceptable curve showed that with the increase of the threshold, the economic possibility of pembrolizumab can be further improved, but the conclusion of the model did not change. China had begun to coordinate drug procurement nationwide to reduce drug costs. Several Chinese-made PD-1 inhibitors, including carrelizumab and sintilimab injections, were included in medical insurance with a price reduction of >60%. The cost-effectiveness of PD-1 inhibitors will increase with price adjustment. Further analysis of the price of pembrolizumab showed that pembrolizumab combined with chemotherapy was only economical when the price of pembrolizumab fell to $102.74/100 mg or more.

In this study, three different scenarios were set up to better analyze the economy of pembrolizumab in different application scenarios. In Scenario Analysis 1, due to policies such as China's health insurance negotiations in recent years, drug prices have declined significantly. Therefore, this study compared the economy of pembrolizumab when it was reduced by 50% and 80%. Unfortunately, even with an 80% price reduction, there was still a gap between the cost of the pembrolizumab and the current WTP, which meant that the clinical efficacy and safety advantages of the combination chemotherapy regimen of Pembrolizumab were still difficult to make up for its economic deficiencies while its price was greatly reduced. In Scenario Analysis 2, to improve the accessibility and standardization of tumor immunotherapy in Chinese cancer patients, reduce the economic burden of patients, and prolong the life of patients. In September 2018, the China Primary Health Care Foundation officially launched the "Key to Life-Cancer Immunotherapy Patient Assistance Project" pembrolizumab had brought better benefits to patients when applied to charitable programs, but it was still not economical. Scenario Analysis 3 showed that compared with the new first-line treatment regimen of durvalumab combined with gemcitabine and cisplatin, pembrolizumab had a comparative advantage, which reduced the treatment cost of advanced biliary cancer and was, therefore, more economical.

So far, only two studies have focused on the economic evaluation of immune checkpoint inhibitors in the treatment of patients with

advanced biliary tract cancer. Ye et al. [24] and Zhao et al. [25] used the results of the TOPAZ-1 trial to compare the relative cost-effectiveness of durvalumab combined with GemCis compared with chemotherapy alone in the treatment of advanced biliary tract cancer. The results showed that durvalumab combined with chemotherapy was not economical in the United States (ICER 381,864.39/QALY) or China (ICER 367,608.51 USD/QALY and 696,571.11 USD/QALY). Compared with the existing research, the analysis of this paper provided some advantages. First, based on the latest clinical evidence, this study was the first to perform an economic analysis of pembrolizumab in patients with advanced biliary tract cancer. Second, there might be significant differences in healthcare systems between individual countries and related patient groups, so country-specific outcomes might not be more broadly applicable. Therefore, in this report, this study evaluated the economics of the immune checkpoint inhibitor program from the perspective of Chinese payers. At the same time, the article conducted scenario analysis to compare the economics of pembrolizumab price reductions, use of aid programs, etc., and provided a valuable basis for guiding medical-related decision-making in multiple countries. Finally, the results of this study reflected the clinical status of patients with advanced biliary tract cancer, helping to promote the goal of achieving an appropriate balance between improving patient benefits and saving costs, and providing an effective reference for countries including China in the informed allocation of limited medical resources.

This study still had some limitations. First of all, because the KEYNOTE-966 study did not publish utility data, it did not clearly explain the drug regimen used in immunotherapy and chemotherapy in the follow-up treatment of patients. Therefore, this study retrieved utility data from the literature and used the drugs recommended by the guide for analysis. Due to the inconsistency of the study participants, this may cause a certain degree of bias. However, we conducted a one-way sensitivity analysis of the utility value and found that the results were not sensitive to the utility value and the drugs used after disease progression. Secondly, the KEYNOTE-966 trial did not report the dosing regimen for patients who progressed, so it was assumed that patients who were treated with pembrolizumab combined with chemotherapy had the same follow-up regimen as those who were treated with chemotherapy alone and received the best supportive treatment. Finally, this study did not include all the adverse reactions of pembrolizumab, only the adverse reactions of grade 3 or above were included, and there was a certain deviation from the real world. However, the results of single factor sensitivity analysis showed that the cost of adverse reaction treatment had little effect on the results.

Conclusion

In conclusion, when the WTP threshold is $33,471.30/QALY, the combination of pembrolizumab and chemotherapy is not cost-effective in the first-line treatment of advanced BTC. Pembrolizumab needs to be further reduced in price to improve its economy.

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