Camrelizumab In Patients With Advanced Non-Squamous Non-Small-Cell Lung Cancer: A Cost-Effective Analysis In China

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Research Article

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Abstract

Background Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against programmed cell death 1 (PD-1) that shows effective antitumor activity with acceptable toxicity in multiple tumor types. The Camel trial demonstrated that camrelizumab plus chemotherapy significantly prolonged the median progression-free survival (PFS) and median overall survival (OS) versus chemotherapy alone in patients with advanced non-squamous non-small-cell lung cancer (NSCLC). Because of a rapid cancer burden increase in China, our study was conducted to investigate the cost-effectiveness of the two strategies in chemotherapy-naïve patients with advanced non-squamous NSCLC.

Methods A Markov simulation model was generated based on the Camel trial. The two simulated treatments included camrelizumab plus chemotherapy (CC) and chemotherapy alone (CA). Utility was derived from published literature, and costs were calculated based on those at our hospital in Chengdu, China. Incremental cost-effectiveness ratios (ICERs) were calculated to compare the cost-effectiveness of the two treatment arms.

Results The total costs were \$64,874.51 and \$13,531.38 for CC and CA treatment, respectively. The CC treatment produced 1.19 quality-adjusted life years (QALYs), and the CA treatment produced 0.96 QALYs. Hence, patients who were in the CC group spent an additional \$51,343.44 and generated an increase of 0.23 QALYs, resulting in an ICER of \$223,232.35 per QALY. Currently, in China, CC treatment is not cost-effective when considering a willingness-to-pay (WTP) threshold of \$28,130 per QALY gained.

Conclusions For chemotherapy-naïve patients with advanced non-squamous NSCLC, camrelizumab plus chemotherapy is not considered a cost-effective therapy versus chemotherapy alone in China.

Introduction

Lung cancer has become one of the most common cancers, the leading cause of cancer-related death worldwide and the most commonly diagnosed cancer in Chinese males[1, 2]. The most common type of lung cancer is non-small-cell lung cancer (NSCLC). More than 30% of patients with NSCLC have locally advanced disease at the time of diagnosis, with a 5-year survival rate of 18%[3, 4]. The standard of care for patients with advanced NSCLC is mainly platinum-based doublet chemotherapy[3]. The treatment paradigm of advanced NSCLC has been changed by immune checkpoint inhibitors (ICIs) in recent years. For example, ipilimumab, a fully human anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, and nivolumab, a fully human anti-programmed cell death 1 (PD-1) antibody, are ICIs that result in few adverse events and improved efficacy in patients with NSCLC[5, 6]. The significant overall survival (OS) benefit was observed with nivolumab plus ipilimumab comparing with chemotherapy as first-line treatment in patients with NSCLC[7]. Pembrolizumab, as first-line monotherapy, improves OS and progression-free survival (PFS) in patients with untreated metastatic NSCLC with a programmed death ligand 1 (PD-L1) expressing [8].

Camrelizumab is a selective, humanized, high-affinity IgG4 kappa monoclonal antibody against PD-1 that shows great tumor response with acceptable toxicity in multiple tumor types[9].

As the outcomes from the CameL trial presented, camrelizumab plus chemotherapy (CC) treatment showing a clinically meaningful and statistically significant improvement in PFS versus chemotherapy alone (CA) in all patients with advanced non-squamous NSCLC without sensitive epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations[10, 11]. In practice, given the high price of camrelizumab, whether camrelizumab plus chemotherapy is a cost-effective option in China is unknown. Because of a rapid cancer burden increase in China nowadays, our study was vanuable to investigate the cost-effectiveness of CC versus CA in chemotherapy-naive patients with advanced non-squamous NSCLC.

Methods

Clinical outcomes

Clinical results were extracted from the CameL trial[11]. A total of 412 chemotherapy-naive patients who had histologically confirmed advanced non-squamous NSCLC without sensitive EGFR and ALK alterations were randomly allocated at a 1:1 ratio to the CC group (205) and the CA group (207). Patients in the CC group received intravenous camrelizumab (200 mg) plus carboplatin (area under the curve [AUC], 5 mg/mL per min) and pemetrexed (500 mg/m²) on day 1 every 3 weeks, followed by maintenance therapy with camrelizumab plus pemetrexed. Patients in the CA group received intravenous carboplatin (AUC 5 mg/mL per min) and pemetrexed (500 mg/m²) on day 1 every 3 weeks, followed by maintenance therapy with pemetrexed alone. The median duration of treatment was 34.1 weeks in the CC group and 19.7 weeks in the CA group. For the first 54 weeks, CT scans were conducted every 6 weeks and every 12 weeks thereafter. Laboratory examinations were performed every 3 weeks and every month during treatment and 90 days after treatment, respectively. Among the 412 patients, both PFS and OS were significantly prolonged in the CC group comparing with the CA group (PFS, 11.3 months vs 8.3 months, p = .0001; OS, 27.9 months vs. 20.5 months) (Table 1).

Table 1. Clinical efficacy, baseline input costs and baseline transition probability base on the CameL trial

Parameters	CC group	CA group
Costs per month \$		
Camrelizumab	3065.17(3678.20-2452.14)	-
Chemotherapy	1006.68(1208.02-805.35)	805.63(966.76-644.51)
Hospitalization	25.81(30.97-20.65)	15.22(18.26-12.18)
[†] AEs	58.19(69.83-46.55)	63.22(75.87-50.58)
Tests	201.95(242.34-161.56)	166.98(200.37-133.58)
Cost of PFS	4357.80(5229.36-3486.24)	1051.05(1261.26-840.84)
Cost of PD	183.68(220.42-146.95)	249.92(299.91-199.94)
utility		
[‡] PFS	0.65	0.65
[§] PD	0.47	0.47
Discount rate, %	3	

[†]AEs, adverse events; [‡]PFS, progression-free survival; [§]PD, progressive disease

Model structure

A Markov model was used to assess the cost and effectiveness associated with the two treatments from the Chinese payer perspective. The disease process included 3 states: PFS, progressive disease (PD) and death. Patients with advanced non-squamous NSCLC were assumed to be in the PFS state until progression, and then they could either enter the PD state or the death state; however, patients in the PD state could either remain in the same state or enter the death state (Fig. 1). GetData Graph Digitizer software was used to extract the survival curve from published OS and PFS curve from the published CameL trial. Pseudo-individual patient data were generated using the algorithm derived by Hoyle et al, while Weibull distributions were fitted to both groups (Fig. 2A and 2B). Based on the fitted curve, we can estimate the time-dependency transition probability in each cycle as the following formula: $P(t \rightarrow t+1) = 1 - \exp[\lambda(t)\gamma - \lambda(t+1)\gamma]$, where t equals the current cycle number in Markov model[12]. The cycle length was 1 month, and this model defined the time horizon as 10 years. Health outcomes were measured by quality-adjusted life years (QALYs) and were programmed in TreeAge Pro software version 2019 (TreeAge Software LLC, Williamstown, Massachusetts). We assumed that patients in the 2 groups received docetaxel after PD based on clinical guidelines[13].

Costs and utility

In this analysis, we considered only direct costs, including hospitalization, costs for drugs, radiology and laboratory tests and treatments for all grades of AEs. The prices of all the drugs were based on the price in our hospital in Chengdu, China. We assumed a mean body surface area and a body weight of 1.64 m² and 65 kg, respectively[14]. All costs were measured in US dollars (USD) based on the exchange rate on Dec. 27, 2020 (1 USD = 6.46 CHY). Health utility scores were 0.65, 0.47 and 0 in the PFS state, PD state and death state, respectively[15]. The annual discount rate of 3% was calculated.

Sensitivity analysis

One-way probabilistic sensitivity analyses were performed to examine the impact of input factors on the model. Key parameters were used within a range of ± 20% to explore their impacts on the incremental cost-effectiveness ratios (ICERs). Treatments were considered cost-effective if the ICERs were lower than the willingness-to-pay (WTP) threshold. According to the WHO recommendations for cost-effectiveness analysis, the threshold of \$28,130 per QALY was defined as 3-fold the gross domestic product (GDP) per capita of China[16]. In addition, probabilistic sensitivity analysis was performed using Monte Carlo simulation, which included 1,000 iterations to further address the uncertainty of all the input parameters.

Results

Baseline analysis

The total costs were \$64,874.51 and \$13,531.38 for CC and CA treatment, respectively. The CC treatment produced 1.19 quality-adjusted life years (QALYs), and the CA treatment produced 0.96 QALYs. Hence, patients who were in the CC group spent an additional \$51,343.44 and generated an increase of 0.23 QALYs, resulting in an ICER of \$223,232.35 per QALY. (Table 2).

Table 2. Results of base-case analysis of CC and CA group

Result	CC group	CA group
Cost (\$)	64,874.51	13,531.38
Incremental costs		51,343.44
Effectiveness ([†] QALYs)	1.19	0.96
Incremental effectiveness		0.23
[‡] ICER (\$/QALY)		223,232.35

[†]QALY, quality-adjusted life year; [‡]ICER, Incremental cost-effectiveness ratio.

Sensitivity analyses

The results of the one-way sensitivity analysis are displayed in tornado diagrams (Fig. 3). The utility of PD was the most sensitive parameter influencing the results. The second sensitive parameter was the cost of camrelizumab, which ranged from \$2,452.14 to \$3,678.17 with ICERs ranging from \$190,107.80 to \$270,060.62 per QALY, which was well above the WTP threshold. Changing other parameters may somehow result in different results but has little impact on the ICER. Thus, considering the current WTP threshold of \$28,130, the acceptable curve shows camrelizumab plus chemotherapy is not cost-effective for chemotherapy-naïve patients with advanced non-squamous NSCLC in China (Fig. 4). All of the scatter points are located above the WTP threshold, implying the same results (Fig. 5).

Discussion

The clinical benefit from ICIs therapy demonstrated in clinical trials caused great excitement in both oncologists and patients. However, the wide use of these agents results in a rapid increase in health resource consumption, which is of concern to both the health system and patients. The combination therapy in the CC group provided incremental benefits at high incremental costs per QALY in our analysis. The probabilistic sensitivity analyses indicated that CC treatment would be cost-effective at a WTP threshold higher than 110,000 per QALY, which is well above the current WTP threshold in China.

Some cost-effectiveness studies investigated other ICIs, such as pembrolizumab, nivolumab and ipilimumab, as the first-line treatment in advanced NSCLC patients. These studies demonstrated that pembrolizumab monotherapy was more cost-effective than chemotherapy in the US and France; however, it was not cost-effective in the United Kingdom and China[17–22]. For patients with advanced NSCLC, atezolizumab plus bevacizumab and chemotherapy was not a cost-effective option [23], by the other hand, nivolumab plus ipilimumab were demonstrated to be a more cost-effective option than chemotherapy from the US payer perspective [24].

Despite the high price of camrelizumab in China, it still shows promising tumor response in multiple tumor types with manageable toxicities[25–29]. The incidence of treatment-related AEs of any grade was higher in the CC group than in the CA group. The treatment duration of pemetrexed was longer in the CC group due to a longer duration of maintenance therapy, which indicates a better tumor response. The median OS in the CC group was estimated to be 27.9 months (95% CI, 21.9 – not reached), and the results might be even more encouraging because only 45% of deaths occurred around the time that the median endpoint was reached. Thus, there is a high likelihood that we may have underestimated the effectiveness of CC treatment. Also, there will be a price reduction on camrelizumab in march 2021 in China, which may result in some differences on our analysis.

Given the lack of cost-effectiveness studies on camrelizumab, our research was valuable for assessing a cost-effective strategy for chemotherapy-naïve patients with advanced non-squamous NSCLC from a Chinese payer perspective. To our knowledge, this is the first study to examine the cost-effectiveness of camrelizumab plus chemotherapy versus chemotherapy alone in patients with advanced non-squamous NSCLC all over the world.

However, there were limitations to our analysis. First, our model was based on a clinical trial, which may not be completely appropriate for real-world patients. The dose of chemotherapy drugs was calculated based on the average body surface in Chinese individuals, which varies in different individuals. Second, given the lack of utility data in the Camel trial, the utilities of PFS and PD were derived from published literature, which were demonstrated to indeed affect the results. Additionally, the regimen of second-line treatment was not mentioned in the Camel trial, so we assumed that patients accepted docetaxel after PD, which was recommended in the NCCN[13]. Reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common immune-related dermatologic toxicity of camrelizumab according to the Camel trial, however, the cost of treating RCCEP was excluded from our study because its effects are mild, reversible, and predictable[29].

Conclusion

In conclusion, from the Chinese payers perspective, camrelizumab plus chemotherapy is not a cost-effective therapy comparing with chemotherapy alone in chemotherapy-naïve patients with advanced non-squamous NSCLC at current WTP of \$28,130 per QALY.

Declarations

Trial registration none reported

Authors' Contributions

Qian Xie wrote the main manuscript text and prepared 2 tables and Hanrui Zheng prepared figures 1-5. Qiu Li and Na Su designed the study. All authors reviewed the manuscript.

Ethical approval Ethical approval is not required for the study (This study was not related to any patients, please see reference14-17,20-23).

Conflicts of interest The authors have indicated that they have no conflicts of interest.

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Availability of data and material The data that supports the findings of this study are presented in this article

Code availability Not applicable

Consent to participate All the authors are consent to participate in the study

Consent for publication All the authors are consent for this article publication

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Figures

Figure 1

A Markov structure was built to compare 2 treatment strategies. Abbreviations: PFS, progression-free survival; PD, progressive disease.

Figure 2

The original Kaplan-Meier PFS (A) and OS (B) curves from the CamelL trial, Weibull distributions were fitted to the two groups. OS, overall survival; PFS, progression-free survival.

Figure 3

Tornado diagram of one-way sensitivity analyses. The impact of parameters on the ICER was listed. Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PD, progressive disease.

Figure 4

The cost-effectiveness acceptability curve showed the probability at different WTP threshold. Abbreviations: WTP, willingness to pay; QALY, quality-adjusted life year.

Figure 5

Dashed line indicates the willingness-to-pay (WTP) threshold. All of the scatter points are located above the WTP threshold, implying that camrelizumab plus chemotherapy is not a cost-effective therapy at current WTP.