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Cost-effectiveness analysis of axicabtagene ciloleucel as a second-line treatment for diffuse large B-cell lymphoma in China and the United States

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Na Li*, **Jianying Lei***, **Jiahao Zhang**, **Hongfu Cai**, **Bin Zheng**, **Ting Yang**, **Maobai Liu** and **Jianda Hu**

Abstract

Background: Axicabtagene ciloleucel (Axi-cel) is the first Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) product approved in China for treating adult patients with relapsed or refractory large B-cell lymphoma after receiving second-line or above systemic therapy. However, it cannot be widely used in clinical practice due to its high price.

Objectives: To evaluate the economic value of Axi-cel fully in countries at different stages of economic development, this article, from the perspective of the medical and health system in China and the United States, evaluated the cost-effectiveness of Axi-cel in the second-line treatment of diffuse large B-cell lymphoma (DLBCL).

Design: Cost effectiveness analysis of Axi-cel in the treatment of relapsed or refractory large B-cell lymphoma (LBCL).

Methods: Based on the clinical trial data of ZUMA-7, a short-term decision tree and a long-term semi-Markov partitioned survival model were constructed to evaluate the cost-effectiveness of the two strategies. This model was cycled for 40 years in 1-month cycles. In this article, only direct medical costs were considered. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to assess the robustness of the base-case results.

Results: In the baseline cost-effectiveness analysis, Axi-cel was associated with more quality-adjusted life year (QALY; 2.72 *versus* 1.46) and greater costs overall ($180,501.55 *versus* $123,221.34) than standard second-line chemotherapy in China. Moreover, the incremental cost-effectiveness ratio (ICER) of the Axi-cel group was $45,726.66/QALY, which was greater than the threshold of $37,654.5. To achieve cost-effectiveness, the price of Axi-cel must be reduced appropriately. In the United States, Axi-cel was associated with more QALYs (2.63 *versus* 1.74) and greater costs overall ($415,915.16 *versus* $289,564.34). The ICER for the Axi-cel was $142,326.94/QALY, below the set threshold of $150,000.

Conclusion: Axi-cel is not a cost-effective option as second-line therapy for treating DLBCL in China. However, In the United States, Axi-cel has shown a cost-effectiveness advantage as a second-line treatment for DLBCL.

Keywords: axicabtagene ciloleucel, cost-effectiveness, large B-cell lymphoma, Markov model, second-line treatment

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Correspondence to:
Jianda Hu
Fujian Medical University Union Hospital, No. 29 Xinquan Road, Fuzhou 350001, China.

The Second Affiliated Hospital of Fujian Medical University, Quanzhou, China
drjiandahu@163.com

Maobai Liu
Fujian Medical University Union Hospital, No. 29 Xinquan Road, Fuzhou 350001, China.

The School of Pharmacy, Fujian Medical University, Fuzhou, China
liumaobai@163.com

Na Li
Jianying Lei
Jiahao Zhang
Hongfu Cai
Bin Zheng
Fujian Medical University Union Hospital, Fuzhou, China

The School of Pharmacy, Fujian Medical University, Fuzhou, China

Ting Yang
Fujian Medical University Union Hospital, Fuzhou, China

*These authors share first authorship.

Introduction

Malignant lymphoma is a highly heterogeneous hematological tumor, including Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Among Chinese patients with malignant lymphoma, the proportion of NHL is much higher than that of HL. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for about 30%.[1] The prevalence of DLBCL is increasing yearly,[2] which has brought a severe economic burden to society.

The primary clinical treatment for DLBCL is standard chemotherapy, which has a high curative effect. However, due to the high heterogeneity of DLBCL in immunophenotype and molecular genetics, the long-term prognosis of chemotherapy is not good.[3] Studies have shown that about two-thirds of patients with DLBCL experience long-term remission after first-line therapy.[4] If patients with DLBCL who have relapsed or failed first-line therapy are eligible for autologous stem cell transplantation (ASCT), salvage chemotherapy is further used after ASCT.[5] However, about half of the patients still have disease relapse or are insensitive to chemotherapy regimens after the above treatment and then develop relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL).[6]

Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) is an emerging cancer treatment method that has substantially affected lymphoma. Axicabtagene ciloleucel (Axi-cel) is one of the CAR-T products on the market. On April 1, 2022, Axi-cel was approved by the Food and Drug Administration (FDA) as the world's first CAR-T drug for the second-line treatment of R/R DLBCL. The approval was based on the clinical trial data of ZUMA-7 (NCT03391466). The ZUMA-7 study demonstrated that[7] at a median follow-up of 24.9 months, compared with standard of care (SOC) salvage chemoimmunotherapy, Axi-cel substantially improved the event-free survival of patients with R/R LBCL, extended by 6.3 months (8.3 *versus* 2.0 months). The remission rate (83% *versus* 50%) and 2-year overall survival (OS; 61% *versus* 52%) were also higher in the Axi-cel group than in the standard care group.

ZUMA-7 demonstrated the safety and efficacy of Axi-cel in the second-line setting for patients with DLBCL. However, due to the high cost of Axi-cel, which is priced at 1.2 million BMR, popularizing it clinically in China is challenging. However, the economic situation of different countries considerably affects drug choice.

This article evaluated the cost-effectiveness of Axi-cel in the treatment of relapsed or refractory large B-cell lymphoma (LBCL) from the perspective of the medical and health system in China and the United States.

Methods

Our study followed the Consolidated Health Economic Evaluation Reporting Standards guidelines for economic evaluations.[8]

Study populations and interventions

This study was based on patient characteristics from the ZUMA-7 clinical trial: adults who have received adequate first-line therapy but have relapsed or failed to respond to treatment. Two treatment options were included: (1) SOC that included rituximab, ifosfamide, carboplatin, and etoposide (R-ICE); rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP); rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP); and rituximab, etoposide, cytarabine, and cisplatin (R-ESHAP) and (2) Axi-cel regimens. Conditioning chemotherapy of cyclophosphamide and fludarabine was used before a single infusion of Axi-cel. (A detailed treatment strategy is shown in eTable 1 in the Supplemental material.) Furthermore, only a minority of patients (36%) in the SOC arm received high-dose chemotherapy with ASCT, and at least 56% of patients in the SOC arm used CAR-T therapies as a subsequent treatment.

Model structure

A decision-analytic model was developed by TreeAge Pro 2022 software to estimate the cost-effectiveness of standard second-line and Axi-cel regimens. Based on patients' survival statistics and the treatment strategies' course, the model's cycle length was 1 month.

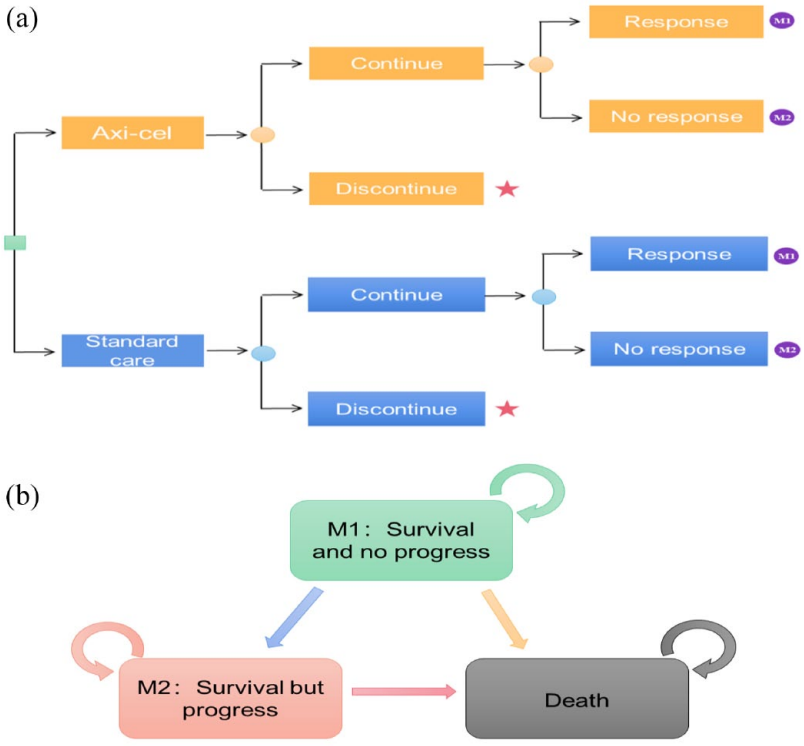

Figure 1. Decision tree model (a) and semi-Markov partitioned survival model (b).
M, Markov.
M1: The patient was treated effectively and entered the Markov model.
M2: Abandon the original treatment for various reasons, switch to other standard treatments, and enter the Markov model.

The model consisted of a short-term decision tree and a long-term semi-Markov partitioned survival model (Figure 1). The first part of the model is a decision tree model, which branches into two main axes (Axi-cel and standard second-line chemotherapy) at the decision nodes and extends backward. Patients assigned Axi-cel may discontinue treatment due to considerable adverse reactions and deaths. Survival and disease response rates also varied among patients eligible to receive complete Axi-cel and subsequent therapy.

The second part of the model is the Markov partitioned survival model. For each treatment strategy, after completing initial therapy, patients in the model would transition into the following health states: survival and no progress, survival but progress, and death. The patient enters the model from the survival and no progress state. When the patient enters a state of survival but progresses, they can only maintain the *status quo* or die. At this point, the current drugs would be replaced by other regimens. In clinical trials,[7] the mean age of patients was 60 years. After 40 years of simulation, the surviving patient is about 100 years old, and this age is assumed to be the end of life. Therefore, the time horizon of this simulation is 40 years.

Model input

Transition probabilities. The model's OS and progression-free survival (PFS) parameters were derived from the experiment ZUMA-7. In this article, the OS and PFS curves were digitally extracted by GetData Graph Digitizer 2.0 software. RStudio was used to obtain the survival rate of patients in different periods. The survival curve was estimated and fitted to summarize survival data through the research method of Hoyle and Henley.[9] Seven parameter survival distributions (Gompertz, exponential, gamma, Weibull [AFT], Weibull [PH], log-logistic, and log-normal) were used to refit the survival dates.[10] The fitting of parameter distribution to the data was evaluated

Table 1. Health utility value.

	Value	Distributed
Utility of survival and no progress	0.83	Beta
Utility of survival but progress	0.71	Beta
Disutility of chemotherapy	−0.42	Beta
Disutility of ASCT	−0.3	Beta
Disutility of Axi-cel	−0.15	Beta

ASCT, autologous stem cell transplantation; Axi-cel, axicabtagene ciloleucel.

by the Akaike information criterion and the Bayesian information criterion. Moreover, the distribution function with the best goodness of fit was selected to extrapolate the survival curve. The probability of transitioning from survival and no progress status to death status was based on the age-specific mortality rates for the general population published by the National Bureau of Statistics.[11] The formula is $r = -\ln(1 - P)/t$, where P is the annual mortality rate. The formula calculates the probability of death per cycle (1 month): $1 - \exp(-r \times 30/365)$. The specific values are shown in eTable 2 and eFigure 1 in the Supplemental material.

Utilities. Health outcomes were expressed as quality-adjusted life years (QALYs), which were obtained by multiplying health utility value by the life years. Utility values ranged from 0 to 1, representing death and perfectly healthy. The utility values for survival and no progress and survival but progress statuses were based on the Norwegian Medicines Agency single technology assessment.[12] The negative utilities associated with treatments were also considered, including CAR-T, chemotherapy, and ASCT[12,13] (Table 1).

Cost. From the medical and health system's perspective, this article only considered direct medical costs consisting of drug costs, clinical monitoring costs, grade 3 or greater adverse events (AEs) with high incidence rates (including anemia, neutropenia, and thrombocytopenia), follow-up, and physical examination costs. In addition, patients receiving CAR T-cell therapy as a subsequent treatment were costed with the same assumptions as in the second line. Studies have shown that the four regimens included in standard second-line chemotherapy are equally clinically selected.[7] Therefore, the cost of standard treatment regimens was taken from the average of four types of chemotherapy. The body surface areas of Chinese and American patients are about 1.72 and 1.86 m^2, respectively.[14,15]

In China, the cost of the chemotherapy strategy adopted the Diagnosis-Related Group (DRG) payment standard[16] of Fujian Province, China, which covered all the treatment expenses of patients undergoing chemotherapy. The cost of ASCT also adopted the DRG payment standard[17] of Fujian Province, China. The cost of Axi-cel injection (Yikaida) was obtained from the notice of proposed listing announced by the Guangdong Provincial Drug Trading Center.[18] The winning bid prices in each province in 2021 were queried on 'Yaozhi.com' to obtain the cost of the remaining pretreatment drugs.[19] China's clinical testing and management costs referred to the research by Zhu *et al.*[20] The costs of AEs for CAR-T referred to the study by Luo *et al.*[21] and were converted based on incidence.[7] Follow-up and physical examination data were collected after expert consultation.

For the United States, drug costs were derived from the 'Centers for Medicare & Medicaid Services'.[22] The cost of AE treatment was based on scholars' research, such as Roth and exchange rate conversion.[23] Follow-up and administrative costs referred to the results of a pharmacoeconomic study.[24] Costs for ASCT came from Pelletier *et al.*[25] See Table 2 for details.

Statistical analysis

The model in this study simulated 40-year disease course outcomes with both regimens. Patient QALYs, total life years, and associated direct costs were predicted; $150,000 was set as the American population's willingness to pay (WTP). The Chinese population lacks a prescribed WTP, so this work referred to the World Health Organization's recommendations that considered three times China's per capita gross domestic product (GDP) in 2021 as China's WTP. According to the National Bureau of Statistics website, China's per capita GDP in 2021 is ¥80,976. Three times the per capita GDP is ¥242,928, which is $37,654.5 based on the

Table 2. Costs in China and the United States.

	Price ($)	Range of sensitivity analysis	Distribution	Sources
China				
Standard treatment				
DRG	2801.80	2240.8–3362.2	Gamma	Fujian Provincial Healthcare Security Bureau[16]
ASCT	30,439.01	24,351.21–36,526.81	Gamma	Fujian Provincial Healthcare Security Bureau[17]
Axi-cel				
Axi-cel injection	180,323.70	144,258.90–216,683.40	Gamma	Guangdong Medicine Exchange[18]
Pretreatment	2567.00	2053.60–3080.40	Gamma	YAOZH[19]
Clinical monitoring	2745.00	2196.00–3294.00	Gamma	Zhu *et al.*[20]
Adverse events	1612.56	1290.04–1935.07	Gamma	Luo *et al.*[21]
Follow-up (yearly)	246.70	197.36–296.04	Gamma	Expert consultation
United States				
Standard chemotherapy				
Chemotherapy drugs	6202.53	4962.02–7443.04	Gamma	Centers for Medicare & Medicaid Services[22]
Adverse events	12,996.08	10,396.86–15,595.30	Gamma	Roth *et al.*[23]
Manage	28,050.00	22,440.00–33,660.00	Gamma	Lin *et al.*[24]
ASCT	182,395.36	145,916.29–218,874.43	Gamma	Pelletier *et al.*[25]
Axi-cel				
Axi-cel injection	399,000.00	312,000.00–468,000.00	Gamma	Centers for Medicare & Medicaid Services[22]
Pretreatment	9283.58	7426.86–11,140.30	Gamma	Centers for Medicare & Medicaid Services[22]
Adverse events	11,914.43	9531.54–14,297.32	Gamma	Roth *et al.*[23]
Manage	31,000.00	24,800.00–37,200.00	Gamma	Lin *et al.*[24]
Follow-up				
Axi-cel (month 1)	2300.00	1840.00–2760.00	Gamma	Lin *et al.*[24]
Axi-cel (months 2–12)	180.00	144.00–216.00	Gamma	Lin *et al.*[24]
SOC (year 1)	150	120.00–180.00	Gamma	Lin *et al.*[24]
All therapies				
Follow-up (year 2)	130.00	–	Gamma	Lin *et al.*[24]
Follow-up (year 3)	60.00	48.00–72.00	Gamma	Lin *et al.*[24]
Follow-up (year 4)	30.00	24.00–36.00	Gamma	Lin *et al.*[24]
Follow-up (year 5)	15.00	12.00–18.00	Gamma	Lin *et al.*[24]

ASCT, autologous stem cell transplantation; Axi-cel, axicabtagene ciloleucel; DRG, Diagnosis-Related Group; SOC, standard of care.

Table 3. Baseline cost-effectiveness analysis data.

Treatment plan	Total cost ($)	Incremental total cost ($)	QALYs	Incremental QALYs	ICER
China					
Standard treatment	123,221.34		1.46		
Axicabtagene ciloleucel	180,501.55	57,280.21	2.72	1.25	45,726.66
United States					
Standard treatment	289,564.34		1.74		
Axicabtagene ciloleucel	415,915.16	126,350.82	2.63	0.89	142,326.94

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

annual average exchange rate (1:6.4512)[26] of the US dollar to the RMB in 2021. The incremental cost-effectiveness ratio (ICER), which is the cost of gaining one QALY, was calculated. ICER was compared with the WTP of the two countries separately to measure the economics of the treatment options. QALYs and costs in China were discounted at 5%, and those in the United States were discounted at 3% annually.[27]

Sensitivity analysis

To assess the robustness of the base-case results, one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were conducted. One-way sensitivity analysis was performed to explore uncertainties that may have influenced the outcome of the evaluation, including costs, health utility, and disease probability. The variation range of all parameters was set as 20% up and down. The results of the one-way sensitivity analysis were reported *via* a tornado diagram.

In addition, PSA was performed based on Monte Carlo simulations. For each strategy, 1000 Monte Carlo model iterations were performed using gamma distribution for cost and beta distribution for transition probabilities and utility value. A cost-effectiveness acceptability curve (CEAC), which describes the possibility of the cost-effectiveness of treatment strategies changing with WTP,[28] was constructed.

Results

Baseline cost-effectiveness analysis

This article obtained the incremental cost and effectiveness of different regimens with the lowest cost treatment strategy as the baseline. The results of the baseline cost-effectiveness analysis are summarized in Table 3.

In the Chinese treatment setting, following quality of life adjustment, patients receiving Axi-cel have 2.72 QALYs, and those receiving standard chemotherapy have 1.46 QALYs. Total treatment-related costs were $180,501.55 for Axi-cel and $123,221.34 for SOC. However, for the SOC arm, subsequent treatment costs represented nearly 82% of the total treatment-related costs. Axi-cel resulted in an additional 1.25 QALYs at the cost of $45,726.66/QALY gained.

In the United States, compared with patients receiving standard chemotherapy, the QALYs (2.63 *versus* 1.74) and overall costs ($415,915.16 *versus* $289,564.34) were higher for those receiving Axi-cel. However, Axi-cel resulted in an additional 0.89 QALYs at the cost of $142,326.94/QALY gained.

Sensitivity analysis

Univariate sensitivity analysis. The tornado diagram displayed the magnitude of ICER change for all influential parameters. The most sensitive variables of the American model were the cost of Axi-cel medicine, the utility of survival and no progress, the discount rate, and the cost of subsequent treatment patterns in the SOC arm (Figure 2(a)). In the Chinese setting, the Axi-cel treatment cost, subsequent treatment patterns in the SOC arm, and the utility of survival and no progress were the most influential variables that affected the model results (Figure 2(b)).

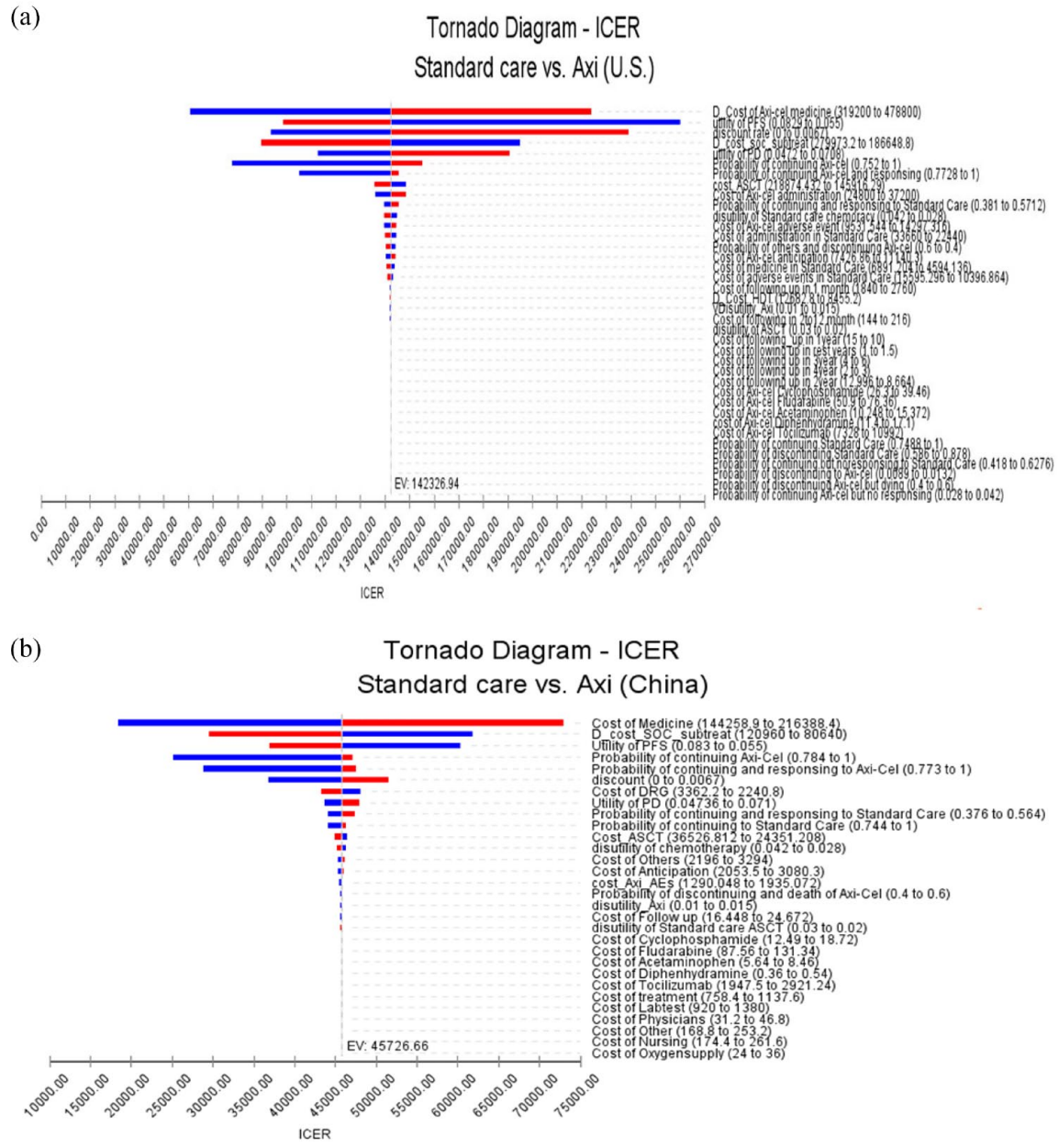

Figure 2. The tornado diagram of the United States (a) and the China (b) univariate sensitivity analysis.

Monte Carlo PSA. The CEAC showed the probability of Axi-cel's cost-effectiveness increased with increasing WTP. In the United States, at a WTP threshold of $150,000/QALY, Axi-cel was cost-effective *versus* SOC in 56.1% of the simulations. In China, the probability of Axi-cel's cost-effectiveness exceeded that of standard second-line chemotherapy at WTPs of approximately $45,000. However, at a WTP of $37,654.5, which was the threshold set in this article, the probability of Axi-cel's cost-effectiveness was 36.2%. The CEAC results are presented in Figure 3(a) and (b).

The results of the Monte Carlo simulation were shown by scattering distribution. In the American model, 56.1% of the scatter points for the Axi-cel strategy were below the threshold, that is, Axi-cel still had a small advantage over standard treatment when the threshold was $150,000/QALY. Moreover, 63.8% of the Chinese model's scatter points were above the threshold. Finally, Axi-cel's

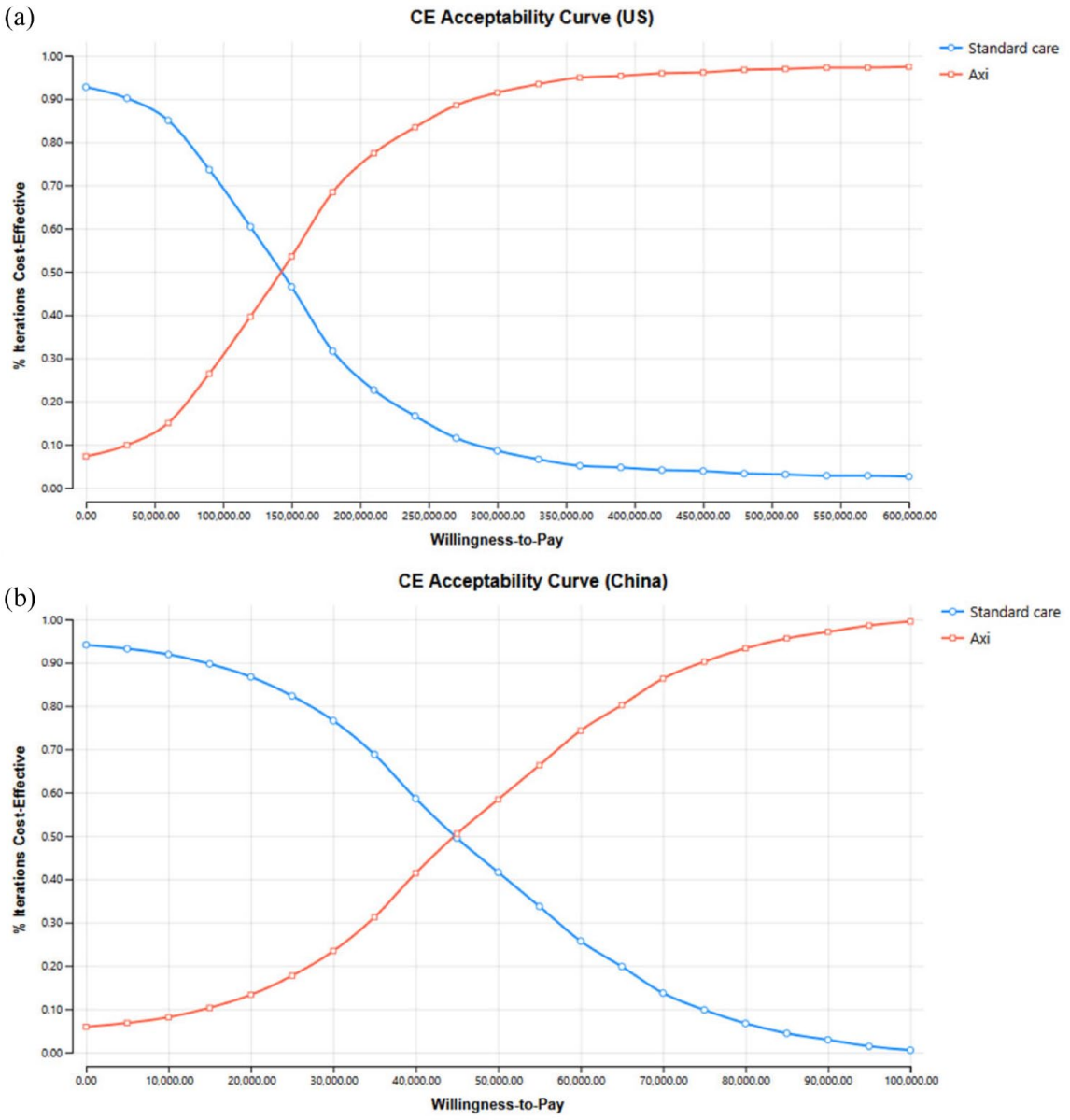

Figure 3. The cost-effectiveness acceptability curve of the United States (a) and China (b).

cost-effectiveness was less likely. The incremental cost-effectiveness scatterplots were presented in eFigure 2 in the Supplemental material.

Discussion

Following FDA approval in 2022, Axi-cel became the first CAR-T for the second-line treatment of R/R DLBCL. The ZUMA-7 clinical trial demonstrated the value of Axi-cel compared with SOC. However, due to its high price, it cannot be widely used in clinical practice. In recent years, many studies have evaluated the cost-effectiveness of Axi-cel. Scholars such as Whittington *et al.*[29] found in the long-term survival and benefit evaluation of LBCL patients over 58 years old that Axi-cel was more cost-effective than standard third-line chemotherapy. Liu *et al.*[30] concluded that Axi-cel could achieve better treatment outcomes at lower incremental costs for patients with LBCL in the United States who had received two or more systemic therapies. A follow-up study of patients with R/R DLBCL in the United States identified Axi-cel as a potentially cost-effective

alternative, affirming its excellent economic benefits.[23] The overall research trend affirms the remarkable therapeutic effect and excellent economic benefit of Axi-cel in third-line therapy. However, the economic evaluations of Axi-cel *versus* traditional second-line chemotherapy worldwide are rare. Therefore, in this article, the cost-effectiveness of Axi-cel in the second-line treatment of DLBCL was evaluated.

Our analysis found that the overall costs and QALYs of Axi-cel treatment were higher than standard chemotherapy in the Chinese setting. In addition, the ICER for patients receiving Axi-cel was $45,726.66/QALY, which exceeded the WTP threshold ($37,654.5). PSA demonstrated the probability of Axi-cel's cost-effectiveness was only 36.2% at a WTP of $37,654.5. These results suggested that Axi-cel is not an economical option in China's second-line treatment of DLBLC. To achieve cost-effectiveness, the price of Axi-cel should be reduced appropriately. However, Axi-cel in the United States has shown small economic suitability. Axi-cel was associated with more QALYs (2.63 *versus* 1.74) and more substantial costs overall ($142,326.94 *versus* $289,564.34). The ICER for Axi-cel was $142,326.94/QALY, below the set threshold of $150,000. In addition, PSA indicated that Axi-cel had an advantage over standard treatment when the threshold was $150,000/QALY. These results were maintained over a wide range of sensitivity and scenario analyses.

This analysis estimated incremental costs with Axi-cel were higher by $57,280.21 for China and $126,350.82 for the United States, but essential offsets were observed compared with SOC. Based on ZUMA-7, at least 56% of patients in the SOC arm used CAR-T therapies as a subsequent treatment. Subsequent treatment costs represented nearly 82% of the SOC arm's total treatment-related costs for China and nearly 80% for the United States, and that was the main reason for reducing the difference in cost between arms.

Some other reports have been published suggesting that second-line Axi-cel would be cost-effective from the US healthcare perspective. Choe *et al.*[31] conducted multiple scenario analyses and concluded that second-line Axi-cel was associated with an ICER of $99,101/QALY from the healthcare sector perspective and an ICER of $97,977/QALY from the societal perspective. Similarly, based on ZUMA-7, Perales *et al.*[32] used a mixture of cure models to extrapolate survival outcomes and concluded that second-line Axi-cel is cost-effective, with an ICER of $93,547/QALY. Our findings aligned with these results. In addition, the China perspective was considered, highlighting slight differences in drug suitability among countries at different stages of economic development.

Based on above results, the treatment options for patients with DLBCL from different national backgrounds vary. In developed countries such as the United States, Axi-cel may be more cost-effective for the second-line treatment of DLBCL. However, for patients in developing countries, using the current standard second-line treatments is more economical.

This article also has several limitations. First, the health utility uses the same value in both countries. The individual differences between patients in China and the United States cannot be distinguished in detail. Second, fully counting and calculating the specific costs of all standard second-line chemotherapy regimens took work. This article referred to the clinical treatment by Locke *et al.*[7] and took the mean value costs of four chemotherapy regimens (R-ICE, R-DHAP, R-ESHAP, and R-GDP) as input model for simulation. Third, the model designed was based on the disease progression in patients with DLBCL but can only partially cover all processes, so it was partially simplified. However, the cost of inclusion and patients' life quality were well documented. Fourth, owing to the scarcity of information on CAR-T therapies as a subsequent treatment, the estimated costs were adopted with the same assumptions as in the second line.

The original purpose of this article was to improve the treatment status of Axi-cel in China, but the results show that at its current price, Axi-cel is unsuitable for treating patients with second-line DLBCL in China. However, given the substantial clinical efficacy, an appropriate price reduction of Axi-cel is of great importance for patients in most countries.

Conclusion

In the US setting, compared with the standard second-line regimen, the Axi-cel regimen has economics for patients with DLBCL. By contrast,

Axi-cel, as second-line therapy in the treatment of DLBCL, is not a cost-effective option in China. Given the remarkable clinical efficacy, an appropriate price reduction of Axi-cel is required to benefit more patients with DLBCL.

Declarations

Ethics approval and consent to participate

Ethics approval for this study was not required per the authors' university regulations.

Consent for publication

Not applicable.

Author contributions

Na Li: Conceptualization; Funding acquisition; Writing – original draft.

Jianying Lei: Conceptualization; Software; Writing – original draft.

Jiahao Zhang: Investigation; Methodology; Software.

Hongfu Cai: Investigation; Methodology; Software.

Bin Zheng: Formal analysis; Validation; Visualization.

Ting Yang: Formal analysis; Validation; Visualization.

Maobai Liu: Project administration; Supervision; Writing – review & editing.

Jianda Hu: Project administration; Supervision; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Data were derived from published literature data and local data.

ORCID iD

Na Li https://orcid.org/0000-0002-5529-0127

Supplemental material

Supplemental material for this article is available online.

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