First-line atezolizumab plus chemotherapy in treatment of extensive small cell lung cancer: a cost-effectiveness analysis from China

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Abstract

Background: IMpower 133 trial first confirmed the efficacy and safety of adding atezolizumab or placebo to first-line treatment with chemotherapy in patients with extensive-stage small-cell lung cancer (SCLC). While, overprice limited its broad use in clinical. The aim of this study was to evaluate the cost-effectiveness of atezolizumab plus chemotherapy in treatment of extensive SCLC as first line in China.

Methods: A Markov model was established by extracting data from the IMpower 133 trial with untreated extensive SCLC patients. Utility values were obtained from published studies, and the costs were acquired from real world and literature. Additionally, sensitivity analyses based on a willingness-to-pay (WTP) threshold were performed to identify the uncertain parameters of Markov model.

Results: Total costs of atezolizumab group were $48,129, while cost of chemotherapy alone was just $12,920 in placebo group. The quality-adjusted life-years (QALYs) in atezolizumab group was just 0.072 higher than that in placebo group (0.858 QALYs *vs.* 0.786 QALYs). The cost-effectiveness ratio between atezolizumab combination with chemotherapy and chemotherapy alone was $489,013/QALY in China. The net benefit of placebo group was significantly higher than atezolizumab group. One-way sensitivity analyses highlighted that utilities of the progression-free survival (PFS) and progression disease state in placebo group were the most influential parameter.

Conclusions: Atezolizumab combination therapy was not more cost-effective than chemotherapy alone at a WTP threshold of $25,929/QALY in China.

Keywords: Cost-effectiveness; Immunotherapy; Chemotherapy; Small cell lung cancer

Introduction

Extensive-stage small cell lung cancer (SCLC), a devastative lung malignancy, has a poor prognoses with a median overall survival of approximately 10 months.[1] Despite a high initial response rate to first-line chemotherapy, recurrence is rapid in the vast majority of cases, usual resulting in death within only a few months.[2] In the past two decades, there has been little progress in the treatment of SCLC. Fortunately, SCLC has a high mutation burden,[3] indicating that these tumors may be more immunogenic and benefit from immune-checkpoint inhibitors.

Immune checkpoint inhibitors work by either inhibiting the programmed death/ligand 1 (PD-1/PD-L1) receptor or the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor. PD-1 inhibitors pembrolizumab and nivolumab, PD-L1 inhibitor atezolizumab and CTLA-4 inhibitor ipilimumab have been approved by the United States Food and Drug Administration (FDA) as a therapy for multiple tumors, such as non-SCLC and melanoma. Clinical outcomes have been observed in the treatment of extensive-stage SCLC; however, single application of these immunotherapies has not resulted in significantly improved outcomes.[4-6] Studies indicate that suitable chemotherapies that involve PD-1/PD-L1 blockade and optimize the tumor immune microenvironment may enhance the antitumor immunity of PD-1/PD-L1 inhibitors.[7] Clinical activity of several immunotherapies has been observed in patients with refractory or metastatic SCLC; however, a phase 3 study of ipilimumab plus chemotherapy showed no improvement in efficacy in the first-line treatment of extensive-SCLC.[6] Fortunately, the IMpower 133 study has provided initial confirmation that combining atezolizumab with cytotoxic therapy is beneficial and potentially necessary to improve the survival of extensive-stage SCLC.[8] The median overall survival (OS) of atezolizumab combined with chemotherapy

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group was 2 months longer, and the 1-year OS rate was approximately 13% higher (51.7% *vs*. 38.2%) than that of a chemotherapy plus placebo group.

However, the exorbitant price of these novel therapies poses a major challenge to healthcare systems. Atezolizumab, priced at $11,470 per 1200 mg for each cycle, is not a financially feasible option for most. Cost-effectiveness analyses have been used to quantify the clinical benefits as well as the potential cost associated with the new therapies. In the current study, we performed a cost-effectiveness analysis to assess the economic effects of first-line atezolizumab combined with chemotherapy *vs*. chemotherapy plus placebo in China.

Methods

This economic analysis was based on a literature review and an experimental model and did not require approval from an institutional review board or ethics committee.

Clinical parameters

Clinical patient characteristics and outcomes are from the IMpower 133 trial. The criteria of enrolling patients includes the following: (1) adults with histologically or cytologically confirmed extensive SCLC; (2) the presence of measurable lesions; (3) an Eastern Cooperative Oncology Group performance-status score of 0 or 1; (4) had not received previous systemic treatment; and (5) patients with treated asymptomatic central nervous system metastases were also eligible. Key exclusion criteria were a history of autoimmune disease or previous treatment with CD137 agonists or immune-checkpoint blockade therapies.

A total of 403 patients with untreated extensive-stage SCLC were randomly assigned to the atezolizumab combined with chemotherapy group (atezolizumab group, $n = 201$) or placebo plus chemotherapy (placebo group, $n = 202$). Untreated extensive-stage SCLC patients received four 21-day cycles of carboplatin and etoposide with atezolizumab (1200 mg per cycle) or placebo, followed by maintenance atezolizumab therapy (1200 mg per 21 days) or placebo, until the occurrence of intolerable toxic effects or disease progression according to RECIST. Clinical prognostic data are shown in Supplementary Table 1, http://links.lww.com/CM9/A113. Tumor assessments were conducted at screening, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter until the occurrence of PD according to RECIST. After PD, patients who continued the trial regimen continued to undergo tumor assessments every 6 weeks until the regimen was discontinued.

We used R for statistical computing. Kaplan-Meier survival data were extracted from survival curves using GetData Graph Digitizer software (Digital River GmbH, Inc., Germany). The transition probabilities between progress-free and progressive disease states were based on the PFS curve. The probabilities of transitioning from either state to death state calculated based on the OS data. We used Weibull survival models to fit the survival curves. Weibull parameters including scale and shape were used to obtain time dependency transition probabilities with the following two formulas: $P = 1 - \text{Exp}(-r \times t)$; $pt = 1 - \text{Exp}$ [Scale $\times$ $(t_0 - u)$^shape-scale $\times$ (t_0)^shape], where p is the probability at time t, r is the survival rate, u is the length of the Markov cycle, t_0 is the current cycle number, and pt is the transition probability.

Markov model

We established a Markov model to evaluate the cost-effectiveness of different treatment strategies. The Markov model of each therapeutic involved three mutually transferable health states: PFS, progressive disease (PD), and death.[9] All patients were defined in the PFS state in the beginning and subsequently survived or died; patients who survived either remained in the PFS state or transferred to the PD state. Patients who transferred to the PD state either remained or died.[10] A cycle length of transition probabilities was 21 days based on the period of chemotherapy. The cost and utility values were calculated at a 3% annual discount rate.

The primary endpoints of the cost-effectiveness analysis were quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER). Secondary endpoints were the average cost-effectiveness ratio (average CE) and net benefit (willing-to-pay [WTP] benefit-costs).

Costs inputs

Only direct medical costs were considered in this study, including drug cost and cost of adverse events ≥ grade 3, tests cost, supportive care cost, and disease management cost. Tests cost included computed tomography, magnetic resonance imaging, single-photon emission computed tomography, and other blood tests. Disease management cost consists of the cost of progression-free state and PD state. Currently no listing of atezolizumab (Tecentriq; Genentech, Inc., USA) in the mainland of China, so we used its pricing at $11,470 per 1200 mg in Hong Kong, China. Other drug costs were extracted from drug price query website in China, and tests costs were indirectly obtained from published literature.[9] Cost parameters estimated in 2019 United States dollars are shown in Supplementary Table 2, http://links.lww.com/CM9/A113.

Health state utilities

Quality-adjusted life years (QALYs) were used to quantify the health condition of patients. Health state utilities represented life quality of patients based on disease state and adverse effects, ranged from 0 to 1. Utility values were all obtained from published literatures.[10-12] We only extracted the utilities of adverse events with ≥grade 3. Utilities are summarized in Supplementary Table 3, http://links.lww.com/CM9/A113.

Sensitivity analysis

We performed a one-way sensitivity analysis to assess the impact of each parameter on model outputs. The ranges were set as ±20% for utilities and ±30% for costs [Table 1]. For the probabilistic sensitivity analysis, a

Table 1: Cost and utility parameters.

Parameters	Base-case value	Minimum	Maximum	Standard error
Drug cost ($/cycle)				
Atezolizumab group	12,439	8707.3	16,170.7	3731.7
Placebo group	969	678.3	1259.7	290.7
AE cost ($/cycle)				
Atezolizumab group	48	33.6	62.4	14.4
Placebo group	47	32.9	61.1	14.1
PD state cost	847	592.9	1101.0	254.1
Examination cost	441	308.7	573.3	132.3
Healthy state utility				
Progression-free state				
Atezolizumab group	0.611	0.489	0.733	0.122
Placebo group	0.607	0.486	0.728	0.121
PD state	0.321	0.257	0.385	0.064

AE: Adverse effects; PD: Progression disease.

Table 2: Results of cost-effectiveness analysis.

Groups	QALYs	Costs ($)	IncrEff	IncrCost ($)	ICER ($/QALY)
Atezolizumab	0.858	48,129	0.072	35,209	489,013
Placebo	0.786	12,920	0	0	0

ICER: Incremental cost-effectiveness ratio; IncrCost: The increase of cost; IncrEff: The increase of effectiveness; QALYs: Quality-adjusted life-years.

Monte Carlo simulation was performed with 1000 iterations and each parameter was fitted to a specific distribution: a beta distribution for utilities and lognormal distribution for costs.[13,14] The WTP threshold was set to three times the per capita GDP of China in 2019: $25,929/QALY. The results are described as cost-effectiveness acceptability curves.

Results

Base case analysis

Compared to chemotherapy alone, combination with atezolizumab yielded an additional survival benefit of 2 months (12.3 months *vs.* 10.3 months, $P = 0.007$). And the occurrence rate of adverse effects ≥grade 3 was not significantly different between the atezolizumab and placebo groups (58.1% *vs.* 57.7%, $P > 0.05$).

Total costs incurred were $48,129 in the atezolizumab group and $12,920 in the placebo group, resulting in a cost difference of $35,209. However, the QALYs in atezolizumab group was just 0.072 higher than that in placebo group (0.858 QALYs *vs.* 0.786 QALYs). The ICER between atezolizumab combined with chemotherapy and chemotherapy alone was $489,013/QALY in China [Table 2].

Sensitivity analysis

Results of the one-way sensitivity analysis indicated that the values of the PFS and PD state in the placebo group were the most influential parameter [Figure 1]. A probabilistic sensitivity analysis with Monte Carlo simulations revealed that atezolizumab combined with chemotherapy was not cost-effective at a WTP threshold of $25,929/QALY in China, compared with chemotherapy alone.

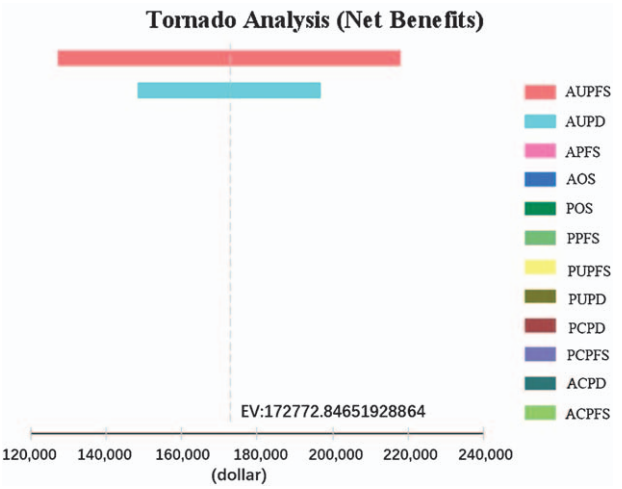

Figure 1: Tornado diagrams. Results of a one-way sensitivity analysis of the first-line atezolizumab combination group and chemotherapy alone group in China. AUPFS: The utility of atezolizumab group in PFS state; AUPD: The utility of atezolizumab group in PD state; APFS: The transition probabilities between progress-free and progressive disease states in atezolizumab group; AOS: The transition probabilities from survival state to death state in atezolizumab group; POS: The transition probabilities from survival state to death state in placebo group; PPFS: The transition probabilities between progress-free and progressive disease states in placebo group; PUPFS: The utility of placebo group in PFS state; PUPD: The utility of placebo group in PD state; PCPD: The cost of placebo group in PD state; PCPFS: The cost of placebo group in PFS state; ACPD: The cost of atezolizumab group in PD state; ACPFS: The cost of atezolizumab group in PFS state.

Discussion

There has been a lack of significant advance in the treatment of SCLC, especially in extensive-stage SCLC. PD1/PD-L1 inhibitors may result in progress in patients with extensive-stage SCLC, such as in the IMpower 133 trial, where 2-month survival benefit did result in obvious clinical significance in extensive-stage SCLC with a median overall survival of only 10 months. Even so, the limitations associated with exorbitant cost require careful consideration.

In our study, we established a Markov model to assess the cost-effectiveness of first-line atezolizumab combined with chemotherapy in patients with extensive-stage SCLC. The efficacy of atezolizumab were verified that the median OS in atezolizumab group prolonged 2 months and median PFS extended 0.9 months, compared to placebo group. Furthermore, addition of atezolizumab was not increased the occurrence rates of adverse effects. However, the WTP threshold is $25,929.00/QALY in China, leading to the analysis indicated that combination of atezolizumab is not cost-effective compared with chemotherapy alone.

In a cost-effectiveness acceptability analysis, we found that atezolizumab was only cost effective in approximately 11.5% of patients at a WTP threshold of $25,929 in China. With a discount of more than 80%, or paying through company donation/medical insurance on the list price, atezolizumab combined with chemotherapy would be cost-effective in China, compared to chemotherapy alone. These results may serve as a clinical decision-making reference for the Chinese government, pharmaceutical companies, physicians, and patients.

In addition, we found that screening the appropriate patients became increasingly important for the treatment of extensive-stage SCLC. Other randomized clinical trials have showed that tumor mutation burden (TMB) and PD-L1 expression level are promising biomarkers to identify potentially beneficial patients for PD1 or PD-L1 inhibitors. Among these patients, patients with high TMB and/or PD-L1 positive expression may be more likely to be cost-effective with the addition of atezolizumab, suggesting that maximizing the efficacy provides a way to increase the cost-effectiveness of novel therapies without adjusting the price.

In the one-way sensitivity analysis, we found that utilities were the most influential parameters. Accordingly, we considered the costs of different treatment regimens and the data from the PFS and OS curves of IMpower 133 clinical trials in this study, where utilities were extracted from the published literature and varied in different populations,[15] which resulted in the observation that diverse utilities have a critical effect on the cost-effectiveness analysis. The comparison of utilities between the atezolizumab and placebo groups was a relative value, and its influence on the overall outcome was reflected in the improvement of the effectiveness value of atezolizumab compared to placebo. The tornado analysis indicated that the effectiveness values of PFS and OS status in the atezolizumab group had a greater influence on the overall cost-effectiveness. In our study, we used utilities specific to Chinese populations for PFS and PD[16] and then subtracted the utilities of adverse effects. This approach may be a relatively objective method to assess the utilities of these two groups.

However, there are some limitations to this study. Firstly, we could not obtain the clinical data from current patients, only indirectly derived from published literature, including values for OS, PFS, and adverse effects. Secondly, we only relied on the original listed price of atezolizumab, without considering diverse health insurance policies and company discounts. Therefore, actual clinical data should be used to recalculate values after atezolizumab is officially approved for sale in the mainland of China. In the current study, we provide a decision-making reference for drug pricing and medical insurance companies. In conclusion, atezolizumab combination therapy as a first-line treatment was not more cost-effective than chemotherapy therapy alone at a WTP threshold of $25,929/QALY in China.

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Conflicts of interest

None.

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