A Cost-Effectiveness Analysis of Atezolizumab and Bevacizumab Verses Sorafenib in Patients With Advanced Hepatocellular Carcinoma

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Research Article

Keywords: cost-effectiveness analysis, immune checkpoint inhibitors, antivasculotherapy, atezolizumab plus bevacizumab, sorafenib, hepatocellular carcinoma

Posted Date: August 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-761908/v1>

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Abstract

Background: Several studies have evaluated the cost-effectiveness of treatment for advanced hepatocellular carcinoma (HCC), but the economics of atezolizumab plus bevacizumab (Ate plus Beva) remains unclear.

Method: A three-state Markov model was established to simulate the life-time cost and effectiveness of advanced liver cancer, which included costs and health outcomes. Medical costs were sourced from Red Book, Healthcare Cost and Utilization Project (HCUP) and literatures. Also, the utility values of health state were derived from references. The primary outcomes were measured by life-years (LYs), quality-adjusted life-years (QALYs), incremental cost-benefit ratio (ICER) and incremental net-health benefit (INHB). The robustness of the model was verified by one-way and probabilistic sensitivity analysis.

Results: Ate plus Beva generated a gain of 0.84 QALYs (1.17 LYs), an additional incremental cost of \$242,447.40 per patient as compared with sorafenib, which resulted in the ICER of \$288,663.09/QALY (\$206,906.76/LY) at the willingness-to-pay (WTP) threshold of \$150,000/QALY, and the INHB was -0.78/QALY. The sensitivity analysis demonstrated that the ICER was most affected by the price of atezolizumab.

Conclusion: From the U.S. health care payer perspective, compare with sorafenib, Ate plus Beva regimen seems unlikely to be cost-effective in advanced HCC patients at a WTP threshold of 150,000 /QALY. If the price of atezolizumab was reduced by 75%, the probability of atezolizumab being cost-effective was over 50% at the WTP threshold.

Impacts On Practice

- The information provided by this analysis serves as a reference for decision makers to choose a more economical treatment.
- Drug manufacturers could adjust atezolizumab acquisition cost to make it more economically acceptable.

Introduction

According to the "Worldwide Epidemiology of Liver Cancer in 2018", liver cancer is the sixth most pervasive cancer and the fourth leading cause of cancer-related mortality events in the world. Hepatocellular carcinoma (HCC) accounting for 75–85% of primary liver cancer[1, 2]. Treatment options for advanced HCC are limited. Only sorafenib was approved by the Food and Drug Administration (FDA) as a first-line treatment for patients with advanced HCC over the past decade[3].

Recently, immunotherapy is considered as a new therapeutic strategy due to the specific inflammatory properties and potential immunogenicity of HCC tumors. Atezolizumab selectively binds to programmed death-ligand 1 (PD-L1) and blocks its interaction with programmed death 1 (PD-1) and B7.1 receptors,

thus reversing PD-L1/ PD-1 mediated immunosuppression[4]. Bevacizumab has been proved to treat HCC with overexpression of vascular endothelial growth factor (VEGF) because of its anti-angiogenesis and inhibition of tumor cell growth[5, 6]. Recently, based on the pivotal evidence from the IMbrave150, phase 3 randomized trial (ClinicalTrials.gov number, NCT03434379), the U.S. FDA has approved atezolizumab combined with bevacizumab for patients with unresectable HCC patients who have not previously received systemic treatment. In the clinical trial, the overall survival (OS) at 12 months was 67.2% for atezolizumab plus bevacizumab (Ate plus Beva) and 54.6% for sorafenib, and the median progression-free survival (PFS) was improved by 2.5 months in Ate plus Beva regimen (6.8 months vs 4.3 months; hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.47–0.76; $p < .001$)[7].

Both atezolizumab and bevacizumab are novel antineoplastic agents with high drug prices. At present, immunotherapy in combination with antivasculotherapy has become a rising cancer treatment option[8]. The dual-novel combination of immune checkpoint inhibitors (ICIs) and bevacizumab would undoubtedly pose considerable economic burden for patients with advanced HCC and medical reimbursement. The purpose of this study is to evaluate the cost-effectiveness of Ate plus Beva versus sorafenib for the treatment of advanced HCC from the U.S. health care payer perspective, so as to provide references for decision makers.

Aim of the study

Based on the pivotal evidence from the IMbrave150, phase 3 randomized trial (ClinicalTrials.gov number, NCT03434379), this study attempted to compare the cost-effectiveness of atezolizumab plus bevacizumab with sorafenib in treatment-naïve patients with unresectable HCC from the U.S. health care payer perspective.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Methods

Patient Characteristics and Treatments

Clinical information for the cohort of patients simulated in our study was derived from comprehensive NCT03434379 study, mainly screening patients of treatment-naïve histologically or cytologically documented locally advanced metastatic or unresectable HCC (or both). Two first-line interventions were included in model: 1) Every 3 weeks, patients in Ate plus Beva regimen received an intravenous injection of atezolizumab at a dose of 1200mg and bevacizumab at a dose of 15 mg/kg. 2) patients in sorafenib regimen were treated with sorafenib 400mg twice daily. Patients continued to receive assigned drugs until disease progression or unacceptable toxicity. According to the comprehensive NCT03434379 study, 58.6% and 66.1% of patients in the Ate plus Beva and sorafenib regimens received subsequent

treatments, respectively[7]. The available subsequent treatment options included tyrosine kinase inhibitors (cabozantinib and regorafenib), immunotherapy (ranibizumab) and chemotherapy regimens (oxaliplatin, 5-fluorouracil and leucovorin) on the basis of the National Cancer Comprehensive Network (NCCN) Guidelines. Every patient received the best supportive care (BSC) after subsequent therapies failure, until death.

Model structures

A state-transition Markov model was constructed to simulate the costs and effectiveness of treatment of HCC from the perspective of U.S. health care payer (Fig. 1). This kind of simulating the life course of the patient through the mathematical model could avoid the qualification review of the institutional review board. The Markov model included three distinct and mutually exclusive health states: progression-free survival (PFS), progressive disease (PD), and death. All patients first entered the PFS state to receive first-line treatment and could transfer between different states (Fig. 1).

Only direct medical cost was considered in our study. The model cycle length was 3 weeks with a lifetime time horizon. We adjusted the costs for inflation based on the consumer price index to reflect the U.S. dollars (USD) exchange rate in 2020, and discounted the costs and outcomes at a rate of 3% per year. The primary outcomes measures of this model were total cost, life-years (LYs), quality-adjusted LYs (QALYs), incremental cost-effectiveness ratio (ICER) and incremental net-health benefit (INHB). The model and statistical analysis were implemented in TreeAge Pro 2017 software (TreeAge, Williams-town, MA).

Model Survival and Progression Risk Estimates

The transition probabilities in states for Ate plus Beva and sorafenib were estimated based on Kaplan-Meier (K-M) curves of the NCT03434379 trial[7]. The GetData software was used to extract the PFS and OS probabilities from the published PFS and OS curves reported in the NCT03434379 trial and pseudo individual patient data (IPD) was generated by using a statistics algorithm derived from Guyot et al[7, 9]. We used five survival distributions (Log-logistic, Log-normal, Weibull, Exponential, and Gamma) to fit the pseudo IPD. According to the Akaike information criterion (AIC), we selected the log-logistic distribution for the OS curve in the sorafenib regimen and the Log-normal distribution for the rest of the survival curves because they provided the goodness simulation for the pseudo IPD we use (Supporting Table 2 for the AICs). Background mortality rates for each group were estimated based on 2017 life tables in the U.S. [10].

Cost and Health Utility Estimates

We only considered direct medical costs in our study, including the cost of the drug acquisition and disease management in PFS and PD, grade ≥ 3 severe adverse events (SAEs) management, BSC, follow up and terminal care. The drug prices were obtained from the Red Book. According to NCCN guideline recommendations: body weight of 70 kg, body surface area of 1.86 m² were employed to calculate the drug injection doses of patients^[11]. Based on the international Classification of diseases-10 (ICD-10)

codes, the costs of grade ≥ 3 SAEs and terminal care were extracted from the database of the Healthcare Cost and Utilization Project (HCUP) (Table S2). Meanwhile, disease management costs, BSC and follow-up administration fees were referred from the previously published literatures on pharmacoeconomics[12, 13](Table 1).

In Markov models, QALYs are usually expressed in terms of utility values, and are computed based on survival time and health-related quality of life (QoL). Health utility values were from published articles on pharmacoeconomics of HCC. In detail, we assigned a value of 0.76 for first-line therapy, 0.68 for second-line treatment and 0 for death (Table 1)[14]. Notably, the loss of utility values were closely related to SAEs (grade ≥ 3). Eight SAEs (Hypertension, Proteinuria, Decreased appetite, Anemia, Blood bilirubin increase, Thrombocytopenia, Hyponatremia, Diarrhea) related with higher incidence rates ($\geq 5\%$) were enrolled in the model (Supplementary Table 1).

Sensitivity analyses

Univariate sensitivity analysis and probabilistic sensitivity analysis (PSA) were used to explore the robustness of the model. In the univariable sensitivity analysis, each relevant parameter was adjusted up and down within plausible ranges. The maximum and minimum values of these variables were obtained from the literatures and credible intervals. When data was unavailable in the case, a benchmark value of $\pm 20\%$ was used (Table 1). The univariate sensitivity analysis results were presented in a tornado diagram, as shown in Fig. 3. For PSA, we performed Monte Carlo simulation of 100,00 repetitions, where an appropriate distribution of each model parameter in the model was assigned. In PSA, we continuously reduced the price of atezolizumab to explore the optimal economics of the regimen. When the price of atezolizumab was discounted by 75%, Ate plus Beva regimen being cost-effective was more than 50% (Fig. 2).

Results

Base-case analyses

For HCC patients, the projected life expectancy of patients in Ate plus Beva regimen was 3.46 LYs, with 1.17 LYs more than sorafenib alone (Table 2). Moreover, patients receiving Ate plus Beva gained 2.70 QALYs, which was 0.84 QALYs more than that of sorafenib. The Ate plus Beva regimen required an extra expenditure about \$242,447.40, which resulted in an ICER of \$288,663.09/QALY and the INHB was -0.78/QALY compared with sorafenib (Table 2). This result indicated that Ate plus Beva was not cost-effective at a WTP threshold of \$150,000/QALY in the U.S.[15].

Sensitivity analyses

The tornado diagram (Fig. 3) visualized the outcomes of univariate sensitivity analysis, which revealed that the most influential variable for ICER was the price of atezolizumab. The model was also sensitive to the price of bevacizumab, the alteration of utility values in PD and PFS, etc. However, no matter how the

key parameters altered within their specified range, none of them led to the ICER below the WTP of \$150,000/ QALY, indicating that parameters had a moderate impact on results (Fig. 3).

The acceptability curve (CEAC) suggested that Ate plus Beva had a 0.6% chance of being cost-effective compared with sorafenib at the WTP threshold (Fig. 2). Simultaneously, the suitable price of atezolizumab was explored to make the Ate plus Beva regimen more economical than that of sorafenib (Table 3). If the price of atezolizumab were reduced by 75%, the probability of atezolizumab being cost-effective was over 50% at the WTP of \$150,000 per QALY.

Although restricting the second-line treatment regimens to tyrosine kinase inhibitors produced a lower ICER, the ICER remained >\$150,000/QALY. When assuming the chemotherapy and immunotherapy were selected as the second-line treatment options, it only had a minor influence on the ICER (Table 3).

Discussion

By 2030, one million people will die of liver cancer, which becomes the second leading cause of death after pancreatic cancer from the World Health Organization's annual projections. In fact, over the past 30 years, the incidence of HCC has increased two to threefold in the U.S.[16]. There is no doubt that as the number of HCC patients increasing, there will be a heavy financial burden to the U.S. fiscal expenditure and the medicare reimbursement. Sorafenib is the first-line targeted drug approved for advanced HCC. However, more and more studies have shown that sorafenib has limited survival benefits and associate with severe adverse reactions (SAEs), which damaged patients' quality of life[3]. Recent years, the treatment of advanced HCC has changed dramatically. After 10 years of failed research, there has been an upsurge of targeted therapy and immunotherapy options in both first-line and second-line treatments, changing the way we treated advanced HCC patients. Currently, several cancer immunotherapies targeting the PD-1/PD-L1 pathway were being assessed in patients with advanced HCC[6]. However, some researches demonstrated that PD-1 inhibitors monotherapy did not significantly improve OS. ICIs were not recommended to work alone in patients with HCC. At present, the combination of immunotherapy and antiangiogenic drugs is highly appraised by researchers and clinical physicians[17, 18].

HCC patients were often associated with inflammatory responses, which exacerbated the adverse effects on normal and immune cells. Recent studies have shown that tumor cells have unique neovascular structures that might lead to drug leakage, making it difficult for antitumor drugs and immune cells to reach the tumor site. Anti-VEGF therapies have long been proposed to normalize blood vessels and improve the effectiveness of immunotherapy, which suggested the combination of immunosuppressive and antiangiogenic drugs might have synergistic effects[17]. In the comprehensive NCT03434379 study, the immunotherapy in the Ate plus Beva regimen significantly extended both the OS and PFS[7]. Although the potential use of Ate plus Beva would raise hope for patients, unfortunately, the high price came with a heavy financial burden on healthcare services and society. Obviously, governments and health care systems around the world would have to consider whether part of this therapy's cost should be borne.

The U.S. reimbursement department paid more and more attention to the cost and cost-effectiveness of drug interventions[12]. An economic evaluation is warranted to determine the optimal choices of first-line treatments for HCC patients in terms of both efficacy and cost.

Based on our model, the ICER for Ate plus Beva versus sorafenib was evaluated as \$288,663.09/ QALY. The probabilistic sensitivity analyses showed a high likelihood that Ate plus Beva would be considered not cost-effective at a WTP threshold of \$150,000/QALY. Currently, there are only two pharmacoeconomic studies about atezolizumab combination with anti-angiogenic therapies. Those showed that atezolizumab plus bevacizumab and chemotherapy was not cost-effective in patients with non-small-cell lung cancer from the perspective of the U.S., which were consistent with our research. Meanwhile, we noted that the price of atezolizumab had the most significant impact on univariate sensitivity analysis results, which suggested that the high cost of ICIs for HCC was an insurmountable problem, especially in a country like the U.S., which lack a powerful governing body to constrain the growth of drug costs[19].

Spending on cancer drugs would be the main reason for an increase in medical insurance expenditure from \$36 trillion in 2018 to nearly \$60 trillion in 2027, according to the estimate of the U.S. Centers for Medicare and Medicaid Services. As the concept of "financial toxicity" was gradually accepted by the public, the increasing cost of medical care would inevitably impose an economic burden on government departments and society. Meanwhile, we must consider the financial impact on individual patient. Given the high cost of health care, it might lead to lower patient compliance and so that be a risk factor for early mortality[20].

In this study, we sought to explore the possibility of cost-effectiveness of immunotherapy for patients with HCC. First, we conducted a structural sensitivity analysis of second-line treatment regimens after first-line treatment progression for HCC patients. The tyrosine kinase inhibitors, immunotherapy, or chemotherapy regimens were used as the subsequent treatment options in our model, which led to a much higher ICER value than the WTP threshold. When only TKIs were used as second-line therapy, a lower ICER value was produced. Unfortunately, even in this case, Ate plus Beva was not found to be cost-effective. Next, we assumed the price of atezolizumab would decrease to warrant the cost-effectiveness and the affordability of Ate plus Beva regimen. The cost-effectiveness probability of atezolizumab would exceed 50% when the price of atezolizumab decreased by 75% at the WTP of \$150,000 per QALY. Finally, biomarker based patient selection might help to maximize the efficacy of ICIs and exclude patients who may not benefit from or even be harmed by ICIs. Several potential biomarkers have been proposed in HCC, including PD-L1 expression, tumor mutation load (TMB) and genome-specific changes[21]. If these biomarkers were employed to select favorable patients, the economics of the Ate plus Beva regimen would likely be improved greatly.

It was worth mentioning that two health economics outcome indicators were evaluated in our study: the ICER and INHB analysis. The INHB studies were used for linear transformations of the ICER analysis. This statistical linear structure made the calculation and interpretation of replacement intervals, hypothesis tests, and acceptable curves easy to understand. Meantime, the INHB analysis was an excellent way to

analyze uncertainties in the Markov model, and one of the differences of INHB from the ICER analysis was the inclusion of "patient preferences"[22]. The pharmacoeconomic evaluation results of the combined group were double-verified, which further enhanced the reliability of our results.

As other cost-effectiveness analyses, there were some limitations to this study. First, our study was based on a phase 3 randomized controlled trial, which might not be the best reference to guide real-world patients' treatments. The actual resources used in disease processes and clinical practice cannot be fully replicated in our model. Drug doses were calculated based on the average body weight of an American, which varied from person to person. The data of registered participants in the NCT03434379 trial were from all over the world, not only from the U.S., but also from Asia[7]. Nonetheless, the sensitivity analyses results demonstrated that body weight was not the main factor and had little impact on ICER. Second, the utility values of this model referred to that of previously published literatures due to the lack of studies about QoL in HCC patients with atezolizumab immunotherapy. The utility values (0.76 for PFS state and 0.68 for PD state) applied in our model were close to a pharmacoeconomic study of another ICI ramucirumab for HCC patients, in which utility scores under PFS state was set to 0.778, and the utility under PD state was 0.688[23], which supported the usability of the utility values in the model. In the routine clinical practice of specific schemes, an EQ-5D questionnaire should be used to investigate the quality of life of patients, so as to make the results more accurate in future studies. Finally, this research ignored the costs of third-line and fourth-line treatments because the number of patients receiving the above treatments was very few in the NCT03434379 trial. Only 3.3% and 0.3% of patients received third-line and fourth-line treatments in Ate plus Beva regimen, 11.5% and 2.4% patients in sorafenib regimen, respectively[7]. In addition, no standard therapy in third-line and fourth-line treatments was recommended in the NCCN Guidelines. Therefore, in the model, it was assumed that these patients received the BSC after disease progression. Although it might cause some bias, the sensitivity analysis demonstrated a minor influence on ICER.

Conclusions

From the US health care payer perspective, atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma has high incremental cost and modest incremental life benefit at a WTP threshold of 150,000/QALY. Cutting the current price of atezolizumab by 75% could increase the probability of cost-effectiveness over 50%. This research indicates that the new effective regimen is not cost-effective, which expects to provide information and references for medical decision makers and price setters. Nevertheless, the results do not imply that patients should receive the less clinical benefit treatment strategies.

Declarations

Source of Funding

This work was supported by the Natural Science Foundation of Fujian Province (2019J01446) and the Startup Fund for Scientific Research, Fujian Medical University (2018QH1091).

Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Note

Meiyue Li and **Peili Lin** contributed equally to the study, **Xiuhua Weng** and **Shen Lin** are all the corresponding author of the study.

Conflicts of Interest and Source of Funding

On behalf of all authors, the corresponding author states that there is no conflict of interest.

This work was supported by the Natural Science Foundation of Fujian Province (2019J01446) and the Startup Fund for Scientific Research, Fujian Medical University (2018QH1091).

Author contributions

Meiyue Li: conceptualization, methodology, writing-original draft **Peili Lin :** validation, writing-review editing, funding acquisition **Shaohong Luo and Xiaoting Huang:** formal analysis, writing-review editing **Xiaoja Huang and Dongni Nian:** software, formal analysis **Shen Lin and Xiuhua Weng:** methodology, writing-review editing, funding acquisition

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Tables

Table 1
Ranges and distributions of parameters used in sensitivity analyses

Parameters	Base-case values	Min	Max	Distributions	Source
Cost (\$) per cycle					
Atezolizumab	9192	7353.6	11030.4	Gamma	[11]
Bevacizumab	8367.87	6694.30	10041.44	Gamma	[11]
Sorafenib	10656.64	8525.31	12787.97	Gamma	[11]
Regorafenib	13737.2	10989.76	16484.21	Gamma	[11]
Cabozantinib	19708.8	15767.04	23650.56	Gamma	[11]
Ramucirumab	6662.04	5329.63	7994.45	Gamma	[11]
Oxaliplatin	154.7	123.76	185.64	Gamma	[11]
Fluorouracil	77.26	61.81	92.71	Gamma	[11]
Leucovorin	145.6	116.48	174.72	Gamma	[11]
BSC	659.8	494.73	823.86	Gamma	[12]
Terminal care	2470.45	1974.78	2962.17	Gamma	[24]
Follow up	504.86	403.89	605.83	Gamma	[13]
Hypertension	8743.78	7424.41	10063.32	Gamma	[24]
Proteinuria	4424.76	3914.59	4936.63	Gamma	[24]
Decreased appetite	11101.34	8187.88	14014.8	Gamma	[24]
Anemia	7125.38	7033.75	7213.27	Gamma	[24]
Blood bilirubin increase	9042.98	8384.91	9702.75	Gamma	[24]
Thrombocytopenia	9940.24	9591.91	10288.57	Gamma	[24]
Hyponatremia	7463.17	7378.68	7547.49	Gamma	[24]
Diarrhea	7046.16	6905.4	7186.92	Gamma	[24]
Disease management in PFS	3467.54	2774.03	4161.05	—	[25]
Disease management in PD	2600.66	2080.53	3120.13	—	[25]

BSC: best supportive care, **PFS:** progression-free survival, **PD:** progressive disease, **BSA:** body surface area

Parameters	Base-case values	Min	Max	Distributions	Source
Utility value					
PFS	0.76	0.61	0.91	Beta	[26]
PD	0.68	0.54	0.82	Beta	[26]
Disutilities					
Decreased appetite	0.078	0.0624	0.0936	Beta	[27]
Anemia	0.1250	0.1	0.15	Beta	[19]
Thrombocytopenia	0.25	0.2	0.3	Beta	[28]
Hyponatremia	0.1910	0.1528	0.2292	Beta	[19]
Diarrhea	0.047	0.0376	0.0564	Beta	[28]
Body weight (kg)	70	40	160	Gamma	[29]
Discount rate (%)	3	0	5	Fixed	[30]
BSA (m2)	1.82	1.6	2.04	Gamma	[30]
BSC: best supportive care, PFS: progression-free survival, PD: progressive disease, BSA: body surface area					

Table 2
Summary of cost and effectiveness results

Regimen	Ate-Beva	Sorafenib	Incremental
Total cost, (\$)	483673.34	241225.94	242447.40
Total LYs	3.46	2.29	1.17
Total QALYs	2.70	1.86	0.84
ICER, (\$)			
per LY	—	—	206906.76
per QALY	—	—	288663.09
Ate-Beva: atezolizumab plus bevacizumab, LY: life year, QALY: quality-adjusted life year, ICER: incremental cost effectiveness ratio			

Table 3
Results for structural sensitivity analyses and summary of univariable and PSA

Parameters	Incremental Cost (US\$)	Life- Years Gained	Incremental QALYs	ICER* (US\$/QALY)	Probability of Cost- Effectiveness (%)
Second-line treatment options ICER					
Tyrosine kinase inhibitor	200996.3	1.17	0.84	239310.5	4.8
Chemotherapy	245864.3	1.17	0.84	287724.7	0.8
Immunotherapy	226953.8	1.17	0.84	270216.1	1.3
Assumption cost in the United States					
Atezolizumab at full cost	242447.4	1.17	0.84	288663.1	0.6
Atezolizumab at 25% cost	205116.4	1.17	0.84	244216.0	4.0
Atezolizumab at 50% cost	167785.4	1.17	0.84	199768.9	17.6
Atezolizumab at 75% cost	130454.5	1.17	0.84	155321.9	50.7
Atezolizumab at 80% cost	122988.3	1.17	0.84	146432.5	55.2
Atezolizumab at 90% cost	108055.9	1.17	0.84	128653.7	68.1

Figures

Image not available with this version

Figure 1

Image not available with this version

Figure 2

Figure 2

Image not available with this version

Figure 3

Figure 3

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [RevisedCHEERSChecklistOct13.pdf](#)
- [Supplementarymaterial.docx](#)