Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial

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\textbf{ABSTRACT}

\textbf{Purpose}: Malignant pleural mesothelioma (MPM) is a rare malignancy, and pemetrexed/cisplatin (PC) is the gold standard first-line regime. This study evaluated the cost-effectiveness of the addition of bevacizumab to PC (with maintenance bevacizumab) for unresectable MPM based on a phase III trial that showed a survival benefit compared with chemotherapy alone.

\textbf{Methods}: To estimate the incremental cost-effectiveness ratio (ICER) of the incorporation of bevacizumab, a Markov model based on the MAPS trial, including the disease states of progression-free survival, progressive disease and death, was used. Total costs were calculated from a Chinese payer perspective, and health outcomes were converted into quality-adjusted life year (QALY). Model robustness was explored in sensitivity analyses.

\textbf{Results}: The addition of bevacizumab to PC was estimated to increase the cost by $81446.69, with a gain of 0.112 QALYs, resulting in an ICER of $727202.589 per QALY. In both one-way sensitivity and probabilistic sensitivity analyses, the ICER exceeded the commonly accepted willingness-to-pay threshold of 3 times the gross domestic product per capita of China ($23970.00 per QALY). The cost of bevacizumab had the most important impact on the ICER.

\textbf{Conclusions}: The combination of bevacizumab with PC chemotherapy is not a cost-effective treatment option for MPM in China. Given its positive clinical value and extremely low incidence of MPM, an appropriate price discount, assistance programs and medical insurance should be considered to make bevacizumab more affordable for this rare patient population.

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare and fatal malignancy, even though its incidence has continued to increase in many countries, such as the United States, China, Russia, Western Europe and India \cite{1-8}. The incidence of malignant mesothelioma (MM) is estimated to be 2000–3000 cases each year in the United States and less than 1.5 cases per million in China \cite{9}. Only a minority of people diagnosed with localized disease are eligible for surgical resection. For advanced MPM, pemetrexed/cisplatin is the current standard first-line chemotherapy regimen, and it yields a median overall survival (OS) of only 12.1 months (13.3 months in patients receiving vitamins B12 and B9) \cite{10}.

Since pemetrexed was approved as a treatment for MPM 10 years ago, no further therapeutic advances had been made until the recent data from the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS). This randomized, controlled, multicenter phase III trial compared the addition of bevacizumab to pemetrexed/cisplatin (with maintenance bevacizumab) versus pemetrexed/cisplatin in patients with unresectable MPM, and it demonstrated a significant 2.7-month improvement for OS in the bevacizumab-containing group (18.8 vs. 16.1 months; HR = 0.77; P = 0.0167) without a negative impact on patient quality of life \cite{11}. Following the findings, bevacizumab plus pemetrexed/cisplatin has been recommended as a first-line therapy for MPM in the NCCN (The National Comprehensive Cancer Network) guidelines \cite{12}.

Although the clinical outcomes can be viewed as major progress in the treatment of MPM, median progression-free survival (PFS) up to 9.2 months means that the duration of bevacizumab use in first-line and maintenance settings will dramatically increase the costs of treatment. Therefore, it is very important to consider the health economics value of this new treatment option, especially in developing countries, such as...
China, in which bevacizumab needs to be paid for by the patient. Hence, the objective of this study was to develop a Markov model to evaluate the cost-effectiveness of bevacizumab plus pemetrexed/cisplatin chemotherapy based on the phase III trial from the perspective of a Chinese payer.

2. Materials and methods

2.1. Patients and regimens

The target population for our economic analysis reflected the study population in the phase III trial (MAPS). Recruited patients with unresectable MPM naive to chemotherapy were randomly assigned to receive 500 mg/m² pemetrexed plus 75 mg/m² cisplatin (day 1; PC) or 15 mg/kg bevacizumab (day 1) plus PC (PCB) per 21-day cycle for up to 6 cycles. After 6 cycles, bevacizumab maintenance was allowed in the PCB group until disease progression or toxic effects. Both groups were fully supplemented with vitamin B12 and B9.

2.2. Markov model

A Markov decision tree using the TreeAge Pro program (TreeAge 2011, Williamstown, MA, USA) was developed to compare the cost-effectiveness of bevacizumab chemotherapy based on the phase III trial from the perspective of a Chinese payer.

The key data of clinical outcomes were derived from the MAPS trial. Survival time was adjusted to quality-adjusted life-years (QALY) by model parameters: utility scores of health state and transition probabilities of health states. Although quality-of-life (QoL) assessments in the MAPS trial did not find reductions in Qol because of bevacizumab-related AEs, no precise utility scores were available in the original or previous MPM literature. Therefore, the utility scores in our analysis referred to the published values for non-small cell lung cancer (NSCLC) and were assumed to be similar in the same health state of the two groups, with 0.65 for PFS state, 0.47 for PD state and 0 for death.

2.4. Cost estimates

Costs were estimated from the Chinese societal perspective. Direct medical costs were associated with anticancer drugs, tests, management of grade 3–4 adverse events (AEs) and chemotherapy administration (hospitalization). No indirect or social costs were incorporated. Considering that 74.9% of patients in the bevacizumab-containing cohort and 76.0% in the chemotherapy-alone cohort received 6 cycles of platinum-based triplets or doublets and that no specific chemotherapy duration was obtained from the article, we assumed a mean of 5 chemotherapy cycles for both groups and calculated the corresponding costs for chemotherapy and bevacizumab in the combination and maintenance period. We also performed analyses in the model assuming 4 and 6 cycles. Doses of anticancer drugs were calculated according to the reported median body surface area (BSA) and weight in China [16]. Unit price for each drug or test was obtained by consulting the 2016 fee schedule of West China Hospital, Sichuan University. Moreover, we estimated costs for second-line treatment after disease progression, but other supportive care was not considered in our study. Considering that the median PFS in both groups was less than 1 year, and the median OS difference was just 2.7 months, the annual discount of costs was not considered. All costs were converted into US dollars, with an exchange rate of $1 = ¥6.8115 (Nov 11, 2016).

2.5. Sensitivity analyses

One-way sensitivity analysis was performed to address the impact of parameters on the model by varying one parameter within ± 20% of its baseline value, while other parameters were fixed. Probabilistic sensitivity analysis was conducted using Monte-Carlo simulation of 10,000 patients by simultaneous and random preset variation of parameters to evaluate optimal strategies at different hypothetical willingness-to-pay thresholds (WTP). According to the World Health Organization (WHO) guidelines for cost-effective analysis [17,18], 3 times the gross domestic product per capita (GDP) was set as WTP in our study, which was $23970.00 per QALY in China.

3. Results

3.1. Health outcomes

In the MAPS trial, the chemotherapy plus bevacizumab group achieved a better median OS of 18.8 months, while the chemotherapy-alone group had an OS of 16.1 months. Similarly, the difference in PFS of 1.9 months also favored the incorporation of bevacizumab (9.2 vs. 7.3 months). Efficacy and grade 3–4 AEs related to costs collected from the MAPS trial were shown in Table 1. Table 2 provided the monthly transition probabilities between health states according to the aforementioned equation. By analysis of the model, the overall QALY in the bevacizumab-containing group was higher than that in the che-
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