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Bevacizumab in Treatment of High-Risk Ovarian Cancer—A Cost-Effectiveness Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Bevacizumab • Cost-effectiveness analysis • Ovarian cancer • Markov chain

Abstract

Objective. The objective of this study was to evaluate a cost-effectiveness strategy of bevacizumab in a subset of high-risk advanced ovarian cancer patients with survival benefit.

Methods. A subset analysis of the International Collaboration on Ovarian Neoplasms 7 trial showed that additions of bevacizumab (B) and maintenance bevacizumab (mB) to paclitaxel (P) and carboplatin (C) improved the overall survival (OS) of high-risk advanced cancer patients. Actual and estimated costs of treatment were determined from Medicare payment. Incremental cost-effectiveness ratio per life-year saved was established.

Results. The estimated cost of PC is $535 per cycle; PCB + mB (7.5 mg/kg) is $3,760 per cycle for the first 6 cycles and then $3,225 per cycle for 12 mB cycles. Of 465 high-risk stage IIIC (>1 cm residual) or stage IV patients, the previously reported OS after PC was 28.8 months versus 36.6 months in those who underwent PCB + mB. With an estimated 8-month improvement in OS, the incremental cost-effectiveness ratio of B was $167,771 per life-year saved.

Conclusion. In this clinically relevant subset of women with high-risk advanced ovarian cancer with overall survival benefit after bevacizumab, our economic model suggests that the incremental cost of bevacizumab was approximately $170,000.

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Implications for Practice: The financial burden of cancer care has more than doubled in the past decade. The use of bevacizumab for ovarian cancer has not been shown to be cost-effective. In this economic analysis in a subset of high-risk advanced ovarian cancer patients with survival benefit, we showed that adding bevacizumab was near cost-effective based on current benchmarks. With limited health care resources, future clinical trials should incorporate a prospective collection of costs, long-term treatment toxicity, and quality of life.

Introduction

Epithelial ovarian cancer is the most lethal gynecologic malignancy. Despite good initial responses to chemotherapy, 75% of ovarian cancer patients ultimately succumb to their cancer because of disease progression [1]. Consequently, there is a strong impetus to investigate new therapies to improve the outcome of patients with this aggressive cancer.

Bevacizumab, a humanized vascular endothelial growth factor-neutralizing monoclonal antibody, inhibits tumor angiogenesis and has been shown to be active in epithelial ovarian cancer [2–5]. In the International Collaboration on Ovarian Neoplasms trial (ICON 7), the investigators randomly assigned 1,528 ovarian cancer patients to carboplatin (C) and paclitaxel (P) every 3 weeks for 6 cycles versus this same regimen with bevacizumab (B), and maintenance bevacizumab (mB) continued for 12 additional cycles or until disease progression. These investigators found that bevacizumab improved the progression-free survival (PFS) in ovarian cancer patients. In a post hoc subset analysis of 465 high-risk stage IIIC (>1 cm residual) or stage IV patients, the overall survival after PC was 28.8 months compared with 36.6 months in those who underwent PCB + mB (hazard ratio [HR] = 0.64; 95% confidence interval [CI] = 0.48–0.85; $p = .002$). Addition of B increased PFS from 10.5 to 16.0 (HR = 0.73; 95% CI = 0.60–0.93; $p = .002$). Based on the findings of ICON 7 and the Gynecologic Oncology Group trial 218 (GOG 218), the addition of bevacizumab to chemotherapy recently received regulatory

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Table 1. Markov model parameters: paclitaxel and carboplatin with or without bevacizumab and maintenance bevacizumab

Parameter	Value
Median PFS (months)	
PC	10.5
PCB + mB	15.9
Median overall survival (months)	
PC	28.8
PCB + mB	36.6
Hazard ratio	
PFS	0.68 (95% CI: 0.55–0.85)
Overall survival	0.64 (95% CI: 0.48–0.85)
Severe complication rate	
PC	0.2 (0.1–0.3)
PCB + mB	0.2 (0.1–0.3)
Complication cost	$2,000 each occurrence

Abbreviations: B, bevacizumab; C, carboplatin; CI, confidence interval; mB, maintenance bevacizumab; P, paclitaxel; PFS, progression-free survival.

approval in the European Union [6–9]. In recurrent and resistant ovarian cancer patients, the OCEAN and AURELIA investigators recently demonstrated that bevacizumab combined with chemotherapy improved the progression-free survival versus chemotherapy alone. Despite these results, submission to the U.S. Food and Drug Administration has been deferred because of concerns about overall survival.

The financial burden of cancer care has more than doubled in the past decade, totaling more than $90 billion annually [10]. As such, there is an increased focus on cancer therapies that are both efficacious and cost-effective [11–17]. A recent cost-effectiveness analysis on addition of B to chemotherapy under GOG 218 found an incremental cost-effectiveness ratio (ICER) of $479,712 per progression-free life-year saved [11]. As such, these authors concluded that the addition of B was not cost-effective. In contrast, our current study used data from a clinically relevant subset of high-risk patients from ICON 7 with an overall survival advantage. In addition, the ICON 7 trial incorporated B at half dose and for a shorter duration compared with GOG 218, which influenced costs. Using an economic model previously described, we evaluated the incremental cost-effectiveness ratio of the ICON 7 regimen in high-risk patients in whom an overall survival benefit was suggested [18].

Methods

Using a Markov model, we performed a cost-effectiveness analysis based on the treatment schema and outcomes of the ICON 7 study from a health care system perspective. Because this was an unplanned retrospective analysis of the ICON 7 study, we did not need to receive institutional review board approval. The structure of the Markov model comprised three mutually exclusive states: treatment/stable, progression, and death. Patients who had severe complications (with or without stable disease) were allowed to return to treatment or proceed to discontinuation. Those who voluntarily withdrew from the treatments entered the stable state. The treatment consisted of six cycles, and if responsive to the treatment, three additional cycles were added. The duration of the Markov model was 46 months corresponding to the follow-up duration in the study. The Monte Carlo simulation analysis was based on 9,999 probability samples of parameters. Patients could switch to a different state at the end of each cycle based on the transition probabilities estimated from the hazard rates of progression-free survival and overall survival and the rate of complications based on the study. The hazard rate for disease progression was estimated based on the median survival time using the following formula: hazard rate $= -\ln(0.5)/(\text{median overall survival time})$. Markov state transition probabilities for disease progression were obtained from the hazard rate using the following formula: probability $= 1 - \exp(-\text{hazard rate per cycle})$.

Table 2. Estimated costs per treatment cycle: paclitaxel and carboplatin with or without bevacizumab and maintenance bevacizumab

Regimen	Cost
PC	$535 per cycle
PCB + mB	$3,760 per cycle first 6 cycles and $3,225 per cycle for 12 maintenance cycles

Abbreviations: B, bevacizumab; C, carboplatin; mB, maintenance bevacizumab; P, paclitaxel.

Costs of drugs were derived from the average Medicare wholesale prices from the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco. To represent a typical American patient, we used the estimated average age of diagnosis for ovarian cancer in the U.S. Costs for major complications (such as severe hypertension and neutropenia) were estimated based on the adverse events reported in the ICON 7 report. These costs, along with those for discontinuation and chemotherapy, were added episodically and incorporated into the total accrued for treating patients.

The primary measurement was ICER expressed as the cost per life-year saved using the following equation: $\text{ICER} = (\text{cost}_A - \text{cost}_B)/(\text{efficacy}_A - \text{efficacy}_B)$. One-way sensitivity analysis was performed to assess the impact of various parameters including median progression-free survival, overall survival, hazard ratios between two treatment arms, complication rates, and utility and cost parameters assuming the range and distributions described in Table 1. For the multiway probability sensitivity analysis, a two-stage random simulation was used: first to randomly choose a set of parameters from the parameter distributions, and then to perform a simulation based on the chosen parameter values. The probability sensitivity analysis was based on 9,999 samples. The model was implemented using TreeAge Pro Suite 2009 (TreeAge Software Inc., Williamstown, MA, http://treeage.com).

Results

Using a body weight and surface area of the average U.S. woman diagnosed with ovarian cancer (63 years old), the estimated cost of PC is $535 per cycle; PCB + mB (7.5 mg/kg) is $3,760 per cycle for the first 6 cycles and then $3,225 per cycle for 12 mB cycles [19]. The actual and estimated costs of treatment per cycle were then calculated based on Medicare payment for administration of chemotherapy (Table 2).

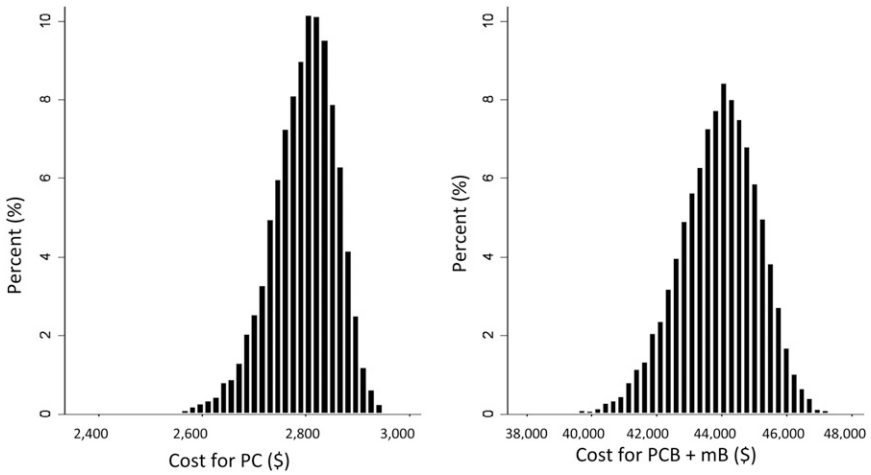

Figure 1. Distributions of total treatment costs of paclitaxel and carboplatin with or without bevacizumab and maintenance bevacizumab. $ in U.S. dollars.

Abbreviations: B, bevacizumab; C, carboplatin; mB, maintenance bevacizumab; P, paclitaxel.

Of 465 patients with stage IIIC (>1 cm residual) or stage IV disease, the median progression-free survival after combination chemotherapy (n = 234) was 10.5 months, and the addition of B (n = 231) improved this by an additional 5.4 months (HR = 0.68; 95% CI = 0.55–0.85). Moreover, the addition of B improved the median overall survival by nearly 8 months (28.8 months vs. 36.6 months, HR = 0.64; 95% CI = 0.48–0.85; p = .002). To provide an economic model to estimate the incremental cost of B, we also incorporated the rate of severe complications and an estimated cost of occurrence (Table 1). A multiway probability sensitivity analysis was performed based on 9,999 samples showing the distributions of costs for the two regimens (Fig. 1).

With nearly an 8-month improvement in overall survival, the ICER of B was $167,771 per life-year saved (95% CI = $95,582–$550,077) (Fig. 2). Using a maximum ICER threshold of $200,000 per life-year saved to consider an intervention as a value at which most health care systems approve new therapeutic options, the ICER of B is cost-effective [20, 21]. In a willingness-to-pay threshold of $200,000, approximately 37% of samples suggested that the addition of B was cost-effective (Fig. 3). In our sensitivity analysis, the ICER was most sensitive to the hazard rate for difference in overall survival between the two regimens (Fig. 4). For example, an 8-month difference in overall survival (from 28.8 months OS reported in the PC arm of the ICON 7 study to 36.6 months in the PCB + mB arm) resulted in nearly a $1 million change of ICER per life-year saved (Fig. 4).

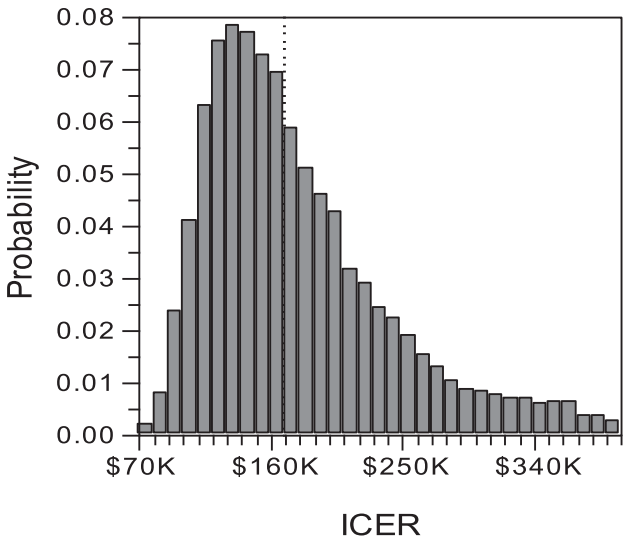

Figure 2. Incremental cost-effectiveness ratio of paclitaxel and carboplatin with or without bevacizumab and maintenance bevacizumab.

Abbreviations: B, bevacizumab; C, carboplatin; ICER, incremental cost-effectiveness ratio; mB, maintenance bevacizumab; P, paclitaxel.

Discussion

The cost of U.S. health care has increased to unsustainable levels. In fact, experts expect that health care expenditures will account for up to one fourth of the gross domestic product in 2014. Accordingly, the costs of cancer care have more than doubled in the past decade, with an estimated annual spending of more than $90 billion [10]. As such, there is an increased focus on cancer therapies that are both efficacious and cost-effective [11–17].

In a recent cost-effectiveness analysis, the addition of bevacizumab to standard chemotherapy with paclitaxel and carboplatin resulted in an ICER of $479,712 per progression-free life-year saved [11]. Based on these results, the investigators concluded that the addition of B to standard chemotherapy in advanced ovarian cancer patients was not cost-effective. Moreover, their analysis demonstrated that the cost-effectiveness of B is primarily dependent on drug costs. Nevertheless, this study used the GOG 218 data in which there was no suggestion of an overall survival benefit. In addition, this trial incorporated B at a higher dose and for a longer duration, which influenced costs. In this study, we evaluated the ICER of the ICON 7 regimen in high-risk ovarian cancer patients for whom an overall survival benefit was suggested.

Despite finding no overall survival benefit in the total patient cohort, the investigators of the ICON 7 study found an overall survival benefit in a subset of high-risk or stage IIIC (>1 cm residual) or stage IV patients (HR = 0.64; 95% CI = 0.48–0.85; p = .002). The corresponding 1-year overall survival rates increased from 86% to 92%. Although the combination of B and chemotherapy for ovarian cancer recently received

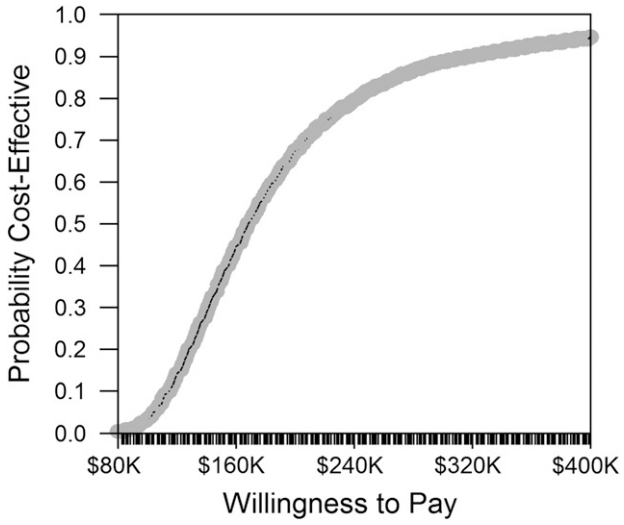

Figure 3. Cost-effectiveness acceptability curve of paclitaxel and carboplatin with bevacizumab and maintenance bevacizumab.

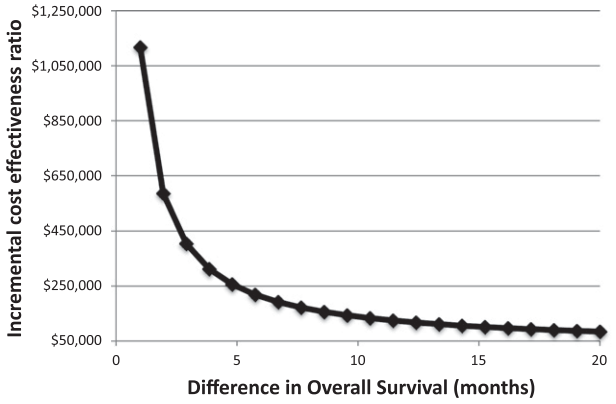

Figure 4. Sensitivity analysis based on difference in overall survival.

regulatory approval in the European Union, the U.S. Food and Drug Administration submission has been deferred because of concerns about overall survival [5–7, 11]. However, there are no reports that have evaluated the incremental increase in costs based on the overall survival found in this high-risk subgroup of patients from ICON 7. In this current analysis, we found that the ICER of adding B was $167,771 per life-year saved using this updated analysis of ICON 7 with an overall survival advantage and at a lower dose for a shorter duration compared with GOG 218. Nevertheless, we were able to demonstrate that only 37% of the simulations were cost-effective using a willingness to pay of $200,000. However, if the willingness to pay were increased to $300,000, the majority of simulations (approximately 80%) were cost-effective.

To our knowledge, this is the first study to identify a potential cost-effective strategy to incorporate the use of B in ovarian cancer. The ICER of B in this study cohort appears comparable to costs in colorectal cancer, but lower than either breast or lung cancer, both of which were found to be more than $200,000 (Table 3). Nevertheless, this study was limited by its use of a simplified simulation model based on reported data from a subset of a single prospective clinical trial. As such, it does not account for all possible clinical scenarios. With regard to toxicity, we did not incorporate minor complications as there was no significant difference between the two arms of the ICON 7 study. In addition, there was a lack of detailed information regarding the actual management of neutropenia, treatment delay, dose reduction, and other nonhematological complications and medication use. Furthermore, our analysis did not incorporate costs associated with subsequent treatments after progressive or recurrent disease. Moreover, there are other additional resources required that were not incorporated into our analyses such as indirect costs to patients, caregivers, and time and efforts from other health care personnel. In addition, this model assumes that the hazard rate is constant over time, which may not be appropriate for advanced ovarian cancer patients. Nonetheless, a constant hazard rate reduces the complexity of the model and is commonly used in decision analyses.

With respect to the differences in the specific regimens, it is clear that the increase in frequency of treatment associated with B will also escalate the costs from a societal and quality of life perspective. However, our model does not account for these other societal and patient-related costs beyond the therapeutic costs, which may include loss of productivity and impact on quality of life because of the greater number of infusions and associated clinic visits. In fact, prior reports have estimated that indirect medical costs may add an additional 20% to direct medical costs. It is also clear that these data are derived from a subset of patients from an ancillary study and may not be applicable to all ovarian cancer patients. Furthermore, this analysis did not account for the timing of bevacizumab administration, whether upfront or at recurrence and as extended maintenance. The costs and duration of therapy of these various clinical situations could vary considerably [5–9].

As bevacizumab combined with other chemotherapies has not been shown to be cost-effective in treating ovarian and other metastatic cancers, it may be important to use value-based

Table 3. ICERs of bevacizumab for other cancer sites

Author	Publication year	Disease type	Chemotherapy treatment	ICER of bevacizumab
Shiroiwa et al. [25]	2007	Colorectal	5-Fluorouracil/leucovorin	$145,000
Shiroiwa et al. [25]	2007	Colorectal	Irinotecan/5-fluorouracil/leucovorin	$99,000
Shiroiwa et al. [25]	2007	Colorectal	Irinotecan/5-fluorouracil/leucovorin/oxaliplatin	$113,000
Shiroiwa et al. [25]	2007	Colorectal	Bolus 5-fluorouracil/leucovorin	$141,000
Klein et al. [26][a]	2009	Lung	Cisplatin/pemetrexed	$337,179
Montero et al. [21][a]	2012	Breast	Paclitaxel	$745,000

[a]American-based health care analysis.
Abbreviation: ICER, incremental cost-effectiveness ratio.

pricing or await other competing antiangiogenic drugs to enter the market to lower costs. In this manner, these novel agents will be more cost-effective and accessible to patients [21].

The development of biomarkers to improve patient selection is needed to better define the role of the drug in ovarian cancer as in other cancers. In this manner, we can use biomarker testing to further target subset populations to enhance the quality and efficiency of health care. With emerging novel testing strategies in clinical practice, translational and cost-effectiveness studies are warranted to not only target patients who will most likely benefit from treatment with this novel drug but also decrease unnecessary toxicities that occur from using ineffective drugs while increasing the cost and disparities of cancer care in our system [22, 23]. Moreover, additional economic analyses on the cost-effectiveness of B should focus on a community practice setting rather than a prospective clinical trial setting.

Conclusion

In this economic analysis based on the subset analysis of ICON 7, we showed that the ICER of adding bevacizumab was $167,771 per life-year saved, which is near cost-effectiveness based on current benchmarks [24]. With limited health care resources, future clinical trials should incorporate a prospective collection of costs, long-term treatment toxicity, and quality of life.

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Final approval of manuscript: John K. Chan, Thomas J. Herzog, Lilian Hu, Bradley J. Monk, Tuyen Kiet, Kevin Blansit, Daniel S. Kapp, Xinhua Yu

Disclosures

Thomas J. Herzog: Morphotek, Merck (C/A); **Bradley J. Monk:** Roche/Genentech (RF, H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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