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Bevacizumab in recurrent, persistent, or advanced stage carcinoma of the cervix: Is it cost-effective?☆

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Abstract

Objective—Evaluate the cost-effectiveness of incorporating bevacizumab into the treatment regimen for recurrent, persistent, or advanced stage carcinoma of the cervix following publication of a recent phase III trial that demonstrated an overall survival (OS) benefit with the addition of bevacizumab.

Methods—A cost-effectiveness decision model was constructed using recently published results from a Gynecologic Oncology Group phase III study, comparing a standard chemotherapy regimen (Chemo) to the experimental regimen (Chemo + Bev) consisting of the standard regimen + bevacizumab. Costs and adverse events were incorporated and sensitivity analyses assessed model uncertainties.

Results—The cost of Chemo + Bev was \$53,784 compared to \$5,688 for the Chemo arm. The 3.7 month OS advantage with Chemo + Bev came at an incremental cost-effectiveness ratio (ICER) of \$155K per quality-adjusted life year (QALY). Chemo + Bev becomes cost-effective with an ICER \$100K in sensitivity analysis when the cost of bevacizumab is discounted >37.5% or the dose is reduced from 15 to 7.5 mg/kg, an effective dose in ovarian cancer.

Conclusions—With an ICER of \$155K/QALY, the addition of bevacizumab to standard chemotherapy approaches common cost-effectiveness standards. Moderately discounting the cost of bevacizumab or using a smaller dose significantly alters its affordability.

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Keywords

Cervical cancer; Bevacizumab; Cost-effectiveness

Introduction

Recurrent, persistent, or advanced cervical cancer is usually considered an incurable disease and patients generally have a poor response to chemotherapy. Patients face the dilemma of pursuing aggressive chemotherapy with meager response rates, optimizing quality of life through supportive care, or a combination thereof. Multiple phase III collaborative group trials have been performed in an effort to identify a superior cytotoxic treatment regimen, with platinum-containing doublets generally considered the standard treatment regimen [1,2]. The recent publication of the Gynecologic Oncology Group (GOG) 240 study demonstrated a significant 3.7 month improvement in overall survival (OS) with the addition of bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor, to either cisplatin and paclitaxel or paclitaxel and topotecan in patients with recurrent, persistent or advanced stage primary cervical cancer [3]. The 17-month median OS in the bevacizumab-containing arms of GOG 240 represents a 30.7% improvement in OS compared to the best alternative regimen [3]. As bevacizumab-containing regimens are predicted to become the standard of care, the unprecedented survival benefit may be overshadowed by the reality that a 17-month OS remains a poor prognosis. While embracing the benefit of bevacizumab, many providers are left with lingering questions about the added toxicity and cost of this new, ultimately palliative regimen.

A foundational tenet of medical ethics is social justice, the concept of equitably distributing limited healthcare goods [4,5]. With healthcare spending in the United States unsustainably high at greater than 15% of the gross domestic product (GDP), looming spending cuts will likely result in magnified attention to the concept of social justice [6]. Expensive therapies yielding limited benefits for few patients will be culled. Cost-effectiveness analyses will play a crucial role in determining the current healthcare practices that are aligned with the fiscal restructuring of the healthcare system. To this end, the use of bevacizumab in ovarian cancer has been evaluated with cost-effectiveness models, all of which have highlighted the economic infeasibility of current bevacizumab regimens [7,8]. However, with the promising results of GOG 240, our current study seeks to determine whether the addition of bevacizumab to standard chemotherapy is cost-effective when used in the treatment for recurrent, persistent, or advanced cervical cancer.

Methods

Model

A decision-analysis model was constructed using TreeAge Pro software (TreeAge Software Inc., Williamstown, MA) (Fig. 1) to evaluate two of the four treatment arms in GOG 240. Arm 1 (Chemo) included the standard chemotherapy regimen of cisplatin and paclitaxel. Arm 2 (Chemo + Bev) included the standard chemotherapy regimen in arm 1 with the addition of bevacizumab. For simplicity sake, and since the model was specifically assessing

the cost-effectiveness of bevacizumab, only the cisplatin containing regimen was incorporated into the model and not the topotecan regimen that was also part of GOG 240. Although OS was similar between topotecan- and cisplatin-containing arms with or without bevacizumab, in the absence of a contraindication to cisplatin, the cisplatin-paclitaxel-bevacizumab regimen is likely preferred as the GOG 240 trial demonstrated this regimen offered significantly better progression free survival and ease of administration (one infusion day versus three infusion days per cycle) with more complete responses compared to the topotecan-paclitaxel-bevacizumab regimen [3]. Costs incurred for treatment and adverse events were applied to each arm in the model with the overall cost calculation of chemotherapy based on the average number of chemotherapy cycles used for each arm from GOG 240 [3]. Rates of salvage bevacizumab (Table 1) were applied to each arm based on the rates published in GOG 240 with the assumption that 6 cycles of salvage therapy were used [3]. Effectiveness was measured as quality-adjusted life year (QALY) and based on median OS (Table 1), which was obtained from published results of GOG 240 [3]. Quality of life (QOL) data were collected in GOG 240, and there were no significant differences reported between the arms [3]. Each strategy was compared with regard to life expectancy and costs using an incremental cost effectiveness ratio (ICER), and results were presented using costs per QALY. ICER is a numerical value comparing two regimens and indicating how much it would cost to gain a unit in effectiveness. Sensitivity analyses were performed to account for uncertainties in assumptions and inputs. Sensitivity analysis tests the model's validity over a range of possible values of a clinical variable in an effort to identify values at which these changes would modify the outcome of the model. When estimates for certain outcome variables contain uncertainties, a sensitivity analysis helps validate the model's results and clarify the strength of any interpretation.

Adverse event rates

Adverse event rates were assigned based on GOG 240 results (Table 1) [3]. Only major adverse events (grade 3–4) whose incidence varied significantly between treatment arms were modeled and included gastrointestinal (GI)/genitourinary fistula (GU), thromboembolic events and hypertension. The incidence of grade 4 or higher neutropenia was significantly higher in the bevacizumab-containing regimens; however, no difference in febrile neutropenia rates were observed suggesting this may be a clinically insignificant observation. Costs for grade 4 or higher neutropenia were not accounted for in the model because the GOG 240 report does not associate any chargeable intervention for this adverse event such as growth factor support or chemotherapy delays [3].

Costs

Costs for each arm were in 2013 US dollars and were obtained through publically available databases (Table 2). When necessary, costs were adjusted for inflation to 2013 US dollars using the medical component of the Consumer Price Index (<http://www.bls.gov/cpi>) publicly accessible inflation data tables [9]. Publically available Medicare reimbursement data (<https://www.cms.gov>) were used to determine the chemotherapy costs incurred for each arm and were calculated for a 70 kg hypothetical woman with a body surface area (BSA) of 1.76 m², and included costs of administration, pre-medications, outpatient physician visit, and the cost of the chemotherapeutic agent estimated from 2013 CPT and J codes [10]. The

dose of bevacizumab in the base case model was 15 mg/kg as used in the GOG 240 study [3].

Costs of major adverse events were estimated using the cost of hospitalization for each condition (Table 2). Inpatient costs were obtained using *International Classification of Diseases, Ninth Revision* (ICD-9) codes to search the 2009 national database of the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project Nationwide Inpatient Sample (<http://www.hcupnet.ahrq.gov>) for mean costs of hospitalization [11]. Because the rate of GI and GU fistula was approximately 3% each in the chemo + bev arms, a composite GI/GU fistula cost representing the sum of half the cost of each fistula type was created. The composite GI/GU fistula cost was modeled based on the combined rates of GI and GU fistula reported in GOG 240 [3]. The costs of adverse events associated with receipt of salvage bevacizumab are not modeled since the rates of such events were not published with the GOG 240 manuscript.

Sensitivity analysis

One-way sensitivity analyses were performed by varying treatment costs, adverse event rates and costs, and the percentages of patients receiving salvage bevacizumab for each arm. Specifically, costs and rates were varied between 50 and 200% of the base case estimates. Sensitivity analysis was also performed by modeling a bevacizumab dosage of 7.5 mg/kg, which has provided improved survival outcomes in a phase III ovarian cancer trial [12].

Results

Base case

The Chemo arm, least effective in GOG 240 with a median OS of 13.3 months, was the least costly arm with an average regimen cost of \$5,688. Chemo + Bev arm had an average regimen cost of \$53,784 and an OS of 17 months. The 3.7 month improvement in OS seen in the Chemo + Bev arm came at an ICER of \$155K/QALY (Table 3).

Sensitivity analysis

Cost: The ICER for Chemo + Bev was greater than the willingness-to-pay threshold of US \$100K based on current costs, and thus not cost-effective. However, the ICER met the common willingness-topay threshold of \$100K/QALY when the cost of bevacizumab was discounted to 62.5% of the original cost (Fig. 2). This discounting would decrease the cost of chemotherapy for the Chemo + Bev arm from \$49,831 to \$32,311 for the regimen.

Adverse events: The ICER was insensitive to changes in the percentage of or costs for adverse events.

Dose and rate of bevacizumab: When the dose of bevacizumab was decreased to 7.5 mg/kg for the Chemo + Bev arm, the cost of chemo-therapy decreased from \$49,831 to \$26,472, and the ICER became cost-effective with an ICER of \$92K/QALY. When considering rates of salvage bevacizumab, the model was relatively insensitive to variation such that the percentage of patients on the Chemo arm transitioning to salvage bevacizumab had to be

48% or higher (only 6.5% received salvage bevacizumab in GOG 240 and the base case) before the Chemo + Bev arm became cost-effective.

Discussion

The addition of bevacizumab to standard chemotherapy regimens has repeatedly demonstrated improved outcomes, generally an improvement in progression-free survival, in multiple phase III trials in gynecologic malignancies, most recently in a GOG trial evaluating its use in recurrent, persistent, or advanced stage cervical cancer [3,12,13]. Despite these improved outcomes, cost-effectiveness studies have consistently suggested that bevacizumab is not a cost-effective therapy [7,8]. While our model predicts that the addition of bevacizumab to standard chemotherapy in the treatment of recurrent carcinoma of the cervix as utilized in GOG 240 is not cost-effective when applying a \$100K ICER willingness-to-pay threshold, the \$155K ICER is the most cost-effective use of bevacizumab to date in the treatment of gynecologic malignancies. It is encouraging that only a modest reduction in the cost of bevacizumab makes the addition of bevacizumab to cytotoxic chemotherapy cost-effective. Our model also shows that the addition of bevacizumab at 7.5 mg/kg to cisplatin and paclitaxel is cost-effective without discounting the cost of bevacizumab. Although this dose-reduced model assumed equal efficacy of the lower dose bevacizumab strategy, results from bevacizumab use in two phase III ovarian cancer trials support this assumption [12,13]. The importance of OS is not debatable, and advanced, recurrent, or persistent cervical cancer is the first gynecologic malignancy treated with bevacizumab to yield significantly improved OS [3]. This provides unprecedented impetus to find a cost-effective strategy for bevacizumab use in this setting, which may include prospective assessment of a lower dose regimen.

The value of any cost-effectiveness analysis hinges upon societal acceptance of and policy adherence to the willingness-to-pay threshold. In our analysis, we propose a willingness-to-pay threshold of US\$100K above which any ICER is cost prohibitive. Currently, choosing the willingness-to-pay threshold is somewhat arbitrary in the United States where access to drugs and interventions are expected by patients and families regardless of the costs, and there is no single payer system; however, in England, the National Institute for Health Care Excellence (NICE) rigorously analyzes the cost-effectiveness of new healthcare interventions and frequently sets the willingness-to-pay threshold at approximately £30,000 (approximately US\$50K) [14]. The NICE-determined threshold is often reflected in healthcare benefit availability such that the populous is only offered interventions that are cost-effective according to the NICE evaluation. A willingness-to-pay threshold of US\$50K has been used in previous cost-effectiveness analyses, thought to have been derived from the cost of dialysis; however, this threshold does not reflect inflation and there is uncertainty about its origins [15]. Questions remain for all healthcare economists about the validity of any single threshold, which inferentially assumes the opinion of the populous on the value of life, while recognizing the difficulty of making policy decisions under single payer systems when a definitive threshold is not identified [15]. One published strategy to determine the willingness-to-pay threshold is to equate the threshold to per capita gross domestic product (GDP): highly cost-effective interventions fall below the per capita GDP, cost-effective interventions are below three times the GDP, and cost-prohibitive interventions are greater

than three times the GDP [7,16]. In the United States, this would correlate with a maximum willingness-to-pay threshold of nearly US\$155K based on the 2012 per capita GDP of \$51,689 [17]. Tethering the willingness-to-pay threshold in the United States to an economic index like the per capita GDP allows patients and policy makers to appreciate the value derivation of acceptable interventions. The ability of society to increase productivity thereby increasing per capita GDP could incentivize the population should they determine the willingness-to-pay threshold is unfairly low. Using this proposed strategy, the use of bevacizumab in recurrent cervical cancer with an ICER/QALY of \$155K would meet criteria to be considered cost-effective.

The strengths and limitations of our analysis arise primarily from the fact that our results reflect the conditions in the GOG 240 clinical trial only. Cost-effectiveness analyses rely on the accuracy of the measured effect or benefit as well as an accurate reflection of the costs. As costs were not obtained prospectively, estimates and assumptions were necessary, and are inherent in cost-effectiveness models. Populating a model with survival and toxicity data exclusively from a clinical trial that has a finite endpoint could over/under-represent the true benefit of the experimental intervention resulting in an inaccurate ICER [18]. This uncertainty, though, is corrected through robust sensitivity analysis that varies the costs through a wide range of possibilities to prove the reliability of the model. Varying the costs in our model, aside from bevacizumab costs, did little to affect the base case results, showing the strength of our model's predictions. Additionally, the rigorous inclusion and exclusion criteria governing most clinical trials means that the observed results may not be generalizable to the greater population [18]. Interventions that were cost-effective based on clinical trial results are frequently prescribed to “trial-unworthy” patients resulting in higher toxicity rates and decreased cost-effectiveness, barring a concomitant increase in efficacy.

Another challenge of cost-effectiveness modeling is objectively assessing an intervention's impact on patient quality of life (QOL). Our findings are reported as an ICER/QALY, where QALY would imply that QOL assessments and survival are linked to patient assigned utility scores. Since GOG 240 did not include utility scores in the QOL assessment, we used survival as a surrogate for utility score (a utility score of 1 equals a year of life in perfect health). This assumption allowed reporting of a QALY; however, it is recognized that no one receiving chemotherapy is living in perfect health, which suggests that if actual utility scores were available our calculated ICER/QALY could be slightly different. Because the GOG 240 study demonstrated no significant difference in QOL between the two arms, the benefit of bevacizumab therapy remains unquestioned and our overall conclusions are substantiated.

Cancer of the cervix is a significant cause of cancer-related death globally. Estimates from the International Agency for Research on Cancer (IARC) published in 2013 suggest that 265,653 women died from cervical cancer in 2012 making it the fourth leading cause of cancer-related mortality worldwide [19]. The incidence of new cervical cancer diagnoses around the globe in 2012 was projected at 527,624 cases, few of which were contributed by wealthy nations [19]. The socioeconomic disparity in cervical cancer burden is not just a foreign problem. Within the United States, epidemiological research demonstrates that cervical cancer mortality rates are highest among the least educated patients without insurance [20]. Being uninformed and uninsured decreases the likelihood of receiving

routine cervical cytology cancer screening tests that are attributed with an 80% reduction in the incidence of invasive cervical cancer [21]. The socioeconomic link with cervix cancer domestically and abroad suggests the poor and uninsured will make up the vast majority of patients with recurrent, persistent, or advanced disease. As a result, the patients most in need of a bevacizumab-containing chemotherapy regimen will not be able to afford the cost, even within the United States, further demonstrating the need to prove treatments are cost-effective.

The addition of bevacizumab to standard chemotherapy offers a significant overall survival advantage for patients with recurrent, persistent, or advanced cancer of the cervix. While some may argue that the ICER of \$155K remains cost-prohibitive based on traditional willingness-to-pay thresholds, our study illustrates that the use of bevacizumab in recurrent cervical cancer is the most cost-effective use of this expensive treatment in gynecologic cancers to date. Furthermore, if we adjust our economic expectations of affordability to a GDP-driven willingness-to-pay approach, or if a reduced bevacizumab dosage of 7.5 mg/kg were to be found equally effective, this treatment would meet traditional cost-effectiveness criteria. With the cost of healthcare rising, and the likelihood that more stringent affordability criteria will be applied to new treatments before acceptance into practice, our findings are encouraging and support further exploration of the use of bevacizumab in cervix cancer.

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Highlights

- Bevacizumab plus paclitaxel and cisplatin in advanced, recurrent or persistent cervix cancer has an ICER/QALY of \$155K.
- Bevacizumab use in this setting is more cost-effective than in any other gynecologic malignancy to date.
- Marginally discounting the cost of bevacizumab by >37.5% results in an ICER/QALY of \$100K.

Fig. 1.

Depiction of the model showing the chemotherapy (chemo) arm expanded and chemo + bevacizumab (Bev) arm collapsed for simplicity as it has an identical appearance to the chemo arm. HTN, hypertension; TE, thromboembolism; GI, gastrointestinal; GU, genitourinary.

Fig. 2.

Sensitivity analysis graph showing the common willingness-to-pay threshold for incremental cost-effectiveness of \$100K and the increasing cost-effectiveness of chemo + bevacizumab as the chemotherapy cost of the regimen decreases from 100%. Chemo + bevacizumab becomes cost-effective when the cost of chemotherapy for this regimen is discounted 37.5%.

Table 1

Survival, adverse events, and salvage bevacizumab values used in model.

Input parameter	Chemo	Chemo + Bev
Survival^a		
Overall survival	13.3 months	17 months
Toxicity^a		
Genitourinary fistula	0.5%	2.7%
Gastrointestinal fistula	0%	3.2%
Hypertension	1.8%	24.5%
Thromboembolism	1.4%	8.2%
Salvage bevacizumab^a		
Single agent or in combination	6.7%	3.5%

Chemo, paclitaxel + cisplatin; Bev, bevacizumab.

^aTewari et al. N Engl J Med 2014;370:734–43.

Table 2

Model costs.

Expenses	CPT/J Code	Chemo	Chemo + Bev	Salvage Bev
Chemotherapy				
Intravenous medication therapy	96365	\$75.53	\$75.53	\$75.53
Chemotherapy administration	96413	\$143.24	\$143.24	\$143.24
Intravenous hydration	96361	\$15.31	\$15.31	\$15.31
Benadryl injection	J1200	\$0.78	\$0.78	
Ranitidine hydrochloride injection	J2780	\$1.64	\$1.64	
Dexamethasone injection	J1100	\$1.90	\$1.90	
Zofran injection	J2405	\$2.43	\$2.43	
Cisplatin injection ^a	J9060	\$18.57	\$18.57	
Paclitaxel injection ^a	J9265	\$51.91	\$51.91	
Bevacizumab injection (15 mg/kg) ^b	J9035		\$6,673.91	\$6,673.91
Laboratory fees (complete blood count, chemistries, urinalysis)		\$52.58	\$56.93	\$15.04
Physician visit	99214	\$76.55	\$76.55	\$76.55
Cost per cycle		\$440.44	\$7,118.70	\$6,999.58
Number of cycles		6	7	6
Cost per regimen		\$2,642.64	\$49,830.90	\$41,997.48
Toxicity	ICD-9		Cost	
Genitourinary fistula	619.8		\$10,770	
Gastrointestinal fistula	569.81		\$28,999	
Fistula composite ^c			\$19,885	
Hypertension	401.1		\$2,081	
Thromboembolism	415.1		\$6,218	

Chemo, paclitaxel + cisplatin; Bev, bevacizumab.

^a Assumes a body surface area of 1.76 m².^b Assumes a body weight of 70 kg.^c Calculated from half the sum of genitourinary and gastrointestinal fistula costs.

Table 3

Model-generated results.

Model strategy	Regimen	C	IC	E	IE	ICER
Decision analysis	Chemo	\$5,687.76		1.11		
	Chemo + Bev	\$53,783.66	\$48,095.90	1.42	0.31	\$155,148.10

C, cost; IC, incremental cost; E, effectiveness in years; IE, incremental effectiveness in years; ICER, incremental cost-effectiveness ratio; Chemo, paclitaxel + cisplatin; Bev, bevacizumab.