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A Markov model to evaluate cost-effectiveness of antiangiogenesis therapy using bevacizumab in advanced cervical cancer

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HIGHLIGHTS

- The cost of incorporating bevacizumab for treatment of cervical cancer is driven by drug costs not management of bevacizumab-induced complications.
- The availability of less expensive biosimilars is predicted to result in dramatic reductions in the incremental cost-effectiveness ratio.

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ABSTRACT

Objective. To evaluate the cost-effectiveness of bevacizumab in recurrent/persistent and metastatic cervical cancer using recently reported updated survival and toxicology data.

Methods. A Markov decision tree based on the Gynecologic Oncology Group 240 randomized trial was created. The 2013 MediCare Services Drug Payment Table and Physician Fee Schedule provided costs. In the 5-year model subjects transitioned through the following states: response, progression, minor complications, severe complications, and death. Patients experiencing a health utility per month according to treatment effectiveness were calculated. Because cervical cancer survival is measured in months rather than years, results were reported in both quality adjusted cervical cancer life months and years (QALmonth, QALY), adjusted from a baseline of having advanced cervical cancer during a month.

Results. The estimated total cost of therapy with bevacizumab is approximately 13.2 times that for chemotherapy alone, adding $73,791 per 3.5 months (0.29 year) of life gained, resulting in an incremental cost-effectiveness ratio (ICER) of $21.083 per month of added life. The ICER increased to $5775 per month of added life and $24,597/QALmonth ($295,164/QALY) due to the smaller difference in QALmonths. With 75% bevacizumab cost reduction, the ICER is $6737/QALmonth ($80,844/QALY), which translates to $23,580 for the 3.5 month (0.29 year) gain in OS.

Conclusions. Increased costs are primarily related to the cost of drug and not the management of bevacizumab-induced complications. Cost reductions in bevacizumab result in dramatic declines in the ICER, suggesting that cost reconciliation in advanced cervical cancer may be possible through the availability of biosimilars, and/or less expensive, equally efficacious anti-angiogenesis agents.

1. Introduction

Women with recurrent and metastatic cervical cancer have a poor prognosis and comprise a population for whom effective therapy has remained an unmet clinical need. In 2009, Gynecologic Oncology Group (GOG) protocol 204 established cisplatin in combination with paclitaxel as the standard chemotherapy regimen [1]. Although response rates (RR) of up to 36% can be achieved in platinum-naïve patients, they are not durable, with early progression, rapid deterioration of quality of life (QoL), and death within 7 to 12 months being the rule. Furthermore, due to acquired drug resistance associated with prior platinum exposure during cisplatin-based chemoradiation for locally advanced disease, re-treatment with platinum-based therapy at recurrence is less effective [2].

Tumor-associated angiogenesis is a phenotypic driver of cervical carcinogenesis and can be inhibited by targeting the vascular

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endothelial growth factor (VEGF) pathway with the humanized monoclonal antibody bevacizumab [2]. Anti-VEGF therapy was studied in the phase III randomized trial, GOG protocol 240 [3]. Following a data freeze during December 2012, the Data Safety Monitoring Board (DSMB) of the National Cancer Institute (NCI) reported in early 2013 that there was a statistically significant improvement in the primary endpoint, overall survival (OS) (17 versus 13.3 months; hazard ratio (HR) of death 0.71 (98% CI, 0.54–0.95; 1-sided p = 0.004), as well as progression-free survival (PFS) (8.2 versus 5.9 months; HR of progression 0.67 (95% CI, 0.54–0.82); 2-sided p = 0.002), and RR (48% versus 36%; relative probability of response 1.35; (95% CI, 1.08–1.68; 2-sided p = 0.008), without any significant deterioration in QoL with bevacizumab use [3]. On August 14, 2014, the United States (U.S.) Food and Drug Administration (FDA) approved expanding the label of bevacizumab to include cervical cancer [5]. The FDA cited a median of a 3.9 month improvement in OS (16.8 months with chemotherapy plus bevacizumab vs 12.9 months with chemotherapy alone) by invoking data from the time of the December 2013 data freeze that had not yet reached the NCI when the DSMB declared the study positive [5]. When the pre-specified 346 deaths had occurred in late 2014, a protocol-specified final OS analysis demonstrating continued separation of the survival curves (median of 16.8 months vs 13.3 months; HR 0.765 (95% CI: 0.62, 0.95; p = 0.0068) was presented along with a toxicity update. Major treatment-related toxicities of chemotherapy plus bevacizumab included grade 2 or higher fistula (8.6%), grade 3 or higher thromboembolism (8.2%) and manageable hypertension (25%) [6].

New technologies reflect their development costs and have been cited for increasing the cost of healthcare. Recently, Phippen et al. developed a preliminary cost-effectiveness decision model using data from the GOG 240 trial and reported that with an incremental cost-effectiveness ratio (ICER) of $155 K/quality adjusted life year (QALY), the addition of bevacizumab to standard chemotherapy approaches common cost-effectiveness standards [7]. However, the static nature of this model is problematic and results in an oversimplification. Specifically, it does not account for transitioning of patients between different states as they did on the GOG 240 study. Furthermore, their model did not incorporate the updated data such as the increased OS improvement of 3.9 months and fistula rate of 8.6% obtained from the protocol-specified final analysis [5,6]. Using the more accurate survival and toxicology data and a sophisticated model that allows for transitions between states to reflect what occurred on study (and in the real world), we sought to study the cost of bevacizumab in advanced cervical cancer according to payment models relevant to the U.S.

2. Methods

A Markov decision tree using the TreeAge Pro program (TreeAge 2013) was created to perform a cost-effectiveness analysis of chemotherapy versus chemotherapy plus bevacizumab for treatment of recurrent/persistent or metastatic cervical cancer using the data from the GOG 240 study [3,8,9]. Costs were obtained from the Center for MediCare Services Drug Payment Table and Physician Fee Schedule. Only 2013 direct costs were used; billed charges and indirect costs were not included (Table 1).

The model was designed from the perspective of the patient and the health service payer, with a homogeneous population of untreated patients with advanced cervical cancer. Our time horizon was 60 months (5 years).

In the Markov model, five possible health states exist: respond, progress, limited complications, severe complications, and die (Fig. 1). A patient is modeled as being in one state during a month, and may transition to a different state with some probability in the next month. Patients who respond to treatment (stable or reduced disease) may remain in response or experience complications or progress in the next cycle. Those who progress are removed from participation and may possibly receive salvage/palliative therapy but ultimately die (Fig. S1). Limited complications include hypertension, treated pharmacologically. Because no patients in GOG 240 were taken off study for treatment-induced hypertension, those who develop limited complications in our model recover and may continue to respond or progress. Severe complications are represented by thromboembolism and fistula. Patients with severe complications end their participation and receive pharmacologic and/or surgical management of their complication. Finally, we assume for a patient will go to the 'die' state only following progression and therefore we did not factor in death from other causes. Importantly, the number of treatment-related deaths in the chemotherapy and chemotherapy plus bevacizumab arms in GOG study 240 were equal.

A patient starts in the respond state, then each month either stays in the same state or moves to a new one. Each month the cost of treatment is incurred and a health utility level is experienced. After 60 months, the total cost is calculated and the total months lived as well as the equivalent quality adjusted months are added up. The results are the expected costs and months, averaged over all patients.

To ensure validity of our Markov model, several assumptions were made (Table Online). Patients who respond cannot directly go to the death state without first passing through the progression state. Because

Table 1
Cost for cancer therapy and management of complications.

Health states	CHEMORx only	CHEMORx + bevacizumab
Cancer therapy[a]	$524	$7540
Treatment of hypertension[b]	$285	$285
Weighted thromboembolism[c]	$4261 × 4/6	$4261 × 18/37
Weighted fistula[d]	$16,000/3 × 2/6	$16,000/3 × 19/37

	Total cost per 28-day cycle	Cost breakdown	Total cost per 28-day cycle	Cost breakdown
Respond	$524		$7540	
Progress	$262		$262	
Limited complications[e]	$809	ChemoRx + treatable hypertension	$7825	ChemoRx plus bevacizumab + treatable hypertension
Severe complications	$4157	Weighted thromboembolism + weighted fistula/expected number of cycles	$4331	Weighted thromboembolism + weighted fistula/expected number of cycles
Die	$0	–	$0	–

Note: in the GOG 240 population, approximately 1 of every 3 patients who developed GI-vaginal fistula underwent fecal diversion via colostomy.
[a] Cost of chemotherapy alone or chemotherapy plus bevacizumab.
[b] Cost of anti-hypertensive medication.
[c] Cost of hospitalization, imaging studies, and anti-coagulation; weighted estimation based on analysis of adverse events from the primary manuscript.
[d] Cost of imaging studies, colostomy and 3 days of hospitalization; weighted estimation based on analysis of adverse events from the primary manuscript.
[e] For limited complications the patient remains on therapy with chemotherapy alone or chemotherapy plus bevacizumab. Therefore the costs listed for limited complications include both the cost of managing hypertension plus the cost of cancer therapy.

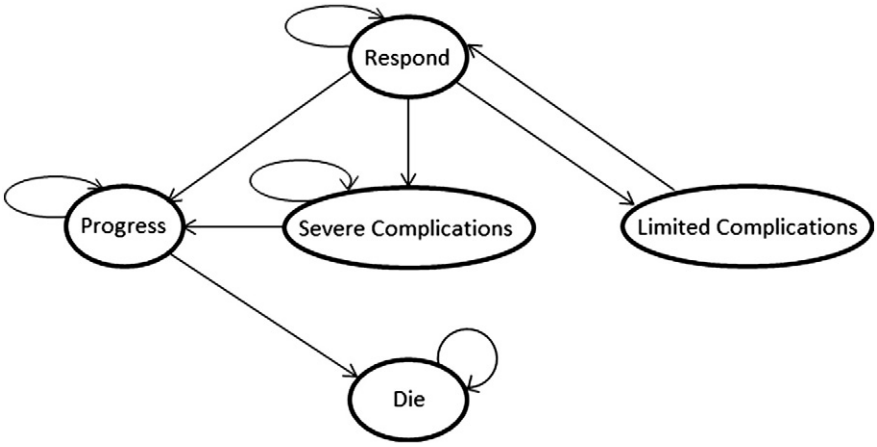

Fig. 1. Markov diagram for women with advanced cervical cancer treated on Gynecologic Oncology Group protocol 240. Circular arrows indicate that patients can stay in that state with some probability for more than one cycle. Our model has the feature that a patient can stay in any of the 5 states for more than 1 cycle. 'Die' (or death) is an absorbing state, which means that once a patient enters that state she will never leave that state. As time passes, most of the patients will go to the 'die' state.

the protocol-specified treatment occurred at 21-day intervals in GOG 240, we rounded up and made the length of a cycle in the Markov model one month. Based on GOG 240, the mean number of cycles for patients receiving chemotherapy alone is 6, and for those receiving chemotherapy plus bevacizumab the mean number of cycles is 7. Therefore, the costs associated with managing complications included medication for blood pressure control (grade 2 or higher hypertension occurred in 25% treated with bevacizumab versus 1.8% receiving chemotherapy alone), imaging and anti-coagulation for thromboembolism (grade 3 or higher thromboembolism occurred in 8.2% receiving bevacizumab versus 1.8% treated with chemotherapy alone), and colostomy for some patients with fistula (grade 2 or higher fistula occurred in 8.6% treated with bevacizumab versus 1% receiving chemotherapy alone [6]). The incidence of febrile neutropenia and treatment-related deaths did not differ between the chemotherapy alone and chemotherapy plus bevacizumab cohorts in GOG 240.

Based on the 1-month/cycle of therapy methodology, using the data reported in GOG 240, the transition probabilities were obtained (Table 2). Because the costs are incurred monthly and the median survival difference is just 3.9 months, we did not discount the costs to the net present value. Discounting would be appropriate for costs occurring over many years.

2.1. Health utilities

In the Markov model, the patient experiences a health "reward" or "utility" in each month, representing the effectiveness of the treatment that depends on the health state during that month. The patient's overall effectiveness is the sum of these utilities over all months. Based on the judgment of treating physicians and the patients' pain assessment reports, the utilities were assumed for each state (Table 3). Without loss of generality, the reward for the respond state was rescaled to be 1. Receiving a reward of '1' indicates that the patient lived one month in the health state of responding to treatment for advanced cervical cancer. When the patient moves to a worse health state, the life quality is adjusted downward for that month. If the patient receives a limited complication in the month, her health utility is 0.75, compared to the baseline of 1, which is being in the respond state.

The health utilities are similar to those used in the Markov analysis by Refaat et al. to examine the use of bevacizumab for breast cancer treatment [10]. One important difference is that Refaat et al. assigned 0.25 for complications and we divided complications into severe (0.5 utility) and limited (0.75 utility). The sum of the utilities over all months can be seen as a type of quality adjusted cervical cancer life month (QALmonth) measure, compared to the baseline of 1/month for those in the respond state. A corresponding measure can be expressed in years, with 1 QALmonth = 1/12 Quality adjusted cervical cancer life year (QALY).

The baseline health utility of 1 could be rescaled to reflect the health level of having advanced cervical cancer compared to being in perfect health. For example, Montero et al. used a baseline health utility of 0.715 for patients with metastatic breast cancer, then adjusted from that for various changes in health state, building upon Lloyd et al. [11,12].

3. Results

3.1. Estimating cost

Based on the cost of treatment and medications to treat complications, the data involving cost/month were generated (Table 1). Once

Table 2
Transition probabilities of going to new health state given that a patient was in a prior health state at the end of the previous month (i.e., cycle).

	From i to j	Respond	Limited complications	Progress	Severe complications	Die
Chemo only	Respond	0.8671	0.0024	0.1270	0.0035	0
	Limited complications	1[a]	0[a]	0	0	0
	Progress	0	0	0.8623	0	0.1377
	Severe complications	0	0	0	0.1[a]	0.9[a]
	Die	0	0	0	0	1
Chemo + bevacizumab	Respond	0.8720	0.0273	0.0823	0.0184	0
	Limited complications	1[a]	0[a]	0	0	0
	Progress	0	0	0.8771	0	0.1229
	Severe complications	0	0	0	0.1[a]	0.9[a]
	Die	0	0	0	0	1

Note that the probabilities in a row must sum to 1, since 100% of the patients will either: 1) move from that health state to a new health state, or 2) remain in the same health state.
[a] Probability is assumed by authors based on judgment of treating physicians.

Table 3
Health utilities assignments.

Health states	Respond	Progress	Limited complications	Severe complications	Die
Utility per month in state	1	0.5	0.75	0.5	0

again this assumes, due to anticipated treatment delays, that each cycle is set to last for 1 month.

3.2. Markov modeling

The cost-effectiveness model was developed using response, progression, and survival data from GOG 240 and the incidence of bevacizumab-specific complications as reported in the primary publication [3] along with the updated data [5,6]. Specifically, the response, progression, and non-fistula toxicity were obtained from the primary publication [3] as these did not change upon regulatory review and final protocol-specified analysis. The corrected survival and true fistula rates were obtained from the updated data [5,6]. Assignment of health utilities and probability estimation of time spent in one or another health state led to the construction of the Markov Decision Tree (Fig. S1).

3.3. Measuring internal validity of the Markov model

To describe the gains in survival time in expected life months, the Markov model was simplified by having each treatment cycle (and health status state) occur at 28-day intervals. We checked the validity of our model by comparing with the primary manuscript, which reported an OS difference of 3.7 months favoring the arms that administered chemotherapy plus bevacizumab (17 versus 13.3 months), as well as the updated median of 3.9 months in the FDA approval [5]. In our Markov model, the expected life months until death were calculated to be 15 months for chemotherapy alone and 18.5 months for chemotherapy plus bevacizumab, a difference of a mean of 3.5 months. Similarly, the difference in PFS also favors the patients receiving bevacizumab with 7.7 months for the chemotherapy alone cohort and 10.4 months for those who received chemotherapy plus bevacizumab, a difference of 2.7 months. In both analyses, and consistent with the findings of the original paper, treatment with chemotherapy plus bevacizumab yields higher expected life months.

3.4. Expected cost and cost effectiveness

The estimated total cost of therapy with bevacizumab is approximately 13.2 times that for chemotherapy alone. For each patient, the estimated total cost of chemotherapy alone is $6053 and that of chemotherapy plus bevacizumab is $79,844. In terms of the OS advantage described by the Markov model, an average gain of 3.5 life months will cost an extra $73,791. Fig. 2 depicts a tradeoff between life months gained and increased cost of therapy incorporating bevacizumab. The ICER is $21,083/month ($252,9964/year). If the payer is able or willing to pay $21,083 for one more additional life month ($252,996 for one more additional life year) before death, then chemotherapy plus bevacizumab should be administered.

Because treatment with chemotherapy plus bevacizumab leads to an increase in bevacizumab-specific complications, to better analyze cost-effectiveness, the impact of the decrease in QoL from complications was modeled by QALmonth. For example, as specified in the model, the severe complication state yields a utility of 0.5 per cycle, compared with a 1 for a person in the respond state. The expected QALmonth for the chemotherapy plus bevacizumab cohort is higher than that for the chemotherapy alone cohort. When the QALmonth measure is used, the difference goes down to 3.0 QALmonth (14.3–11.3 QALmonth or 0.25 QALY). The ICER increases to $24,597/QALmonth ($73,731/3 months or $73,731/(3/12) = $295,164/QALY) due to the smaller difference in QALmonths (see dashed line in Fig. 3). For these patients, an increase of an average of 3.5 months alive (living in the different possible states (respond, progress, limited complications, or severe complications) is modeled as equivalent to 3.0 months in the respond state. A sensitivity analysis of remaining in the severe complication state for an additional month appears in Fig. S2.

3.5. Projected impact of decreasing the cost of bevacizumab

If the cost of bevacizumab were to decrease substantially, both the total cost of the chemotherapy plus bevacizumab treatment and the ICER will be reduced without change in efficacy (Fig. 3). With a 50% reduction in the cost of bevacizumab, the ICER is $12,691/QALmonth ($152,292/QALY). This translates to $38,072 for the 3.5 month (or 0.29 year) gain in OS. With a reduction to only 25% of current cost, the ICER is $6737/QALmonth ($80,844/QALY). This translates to $23,580 for the 3.5 month (or 0.29 year) gain in OS.

4. Discussion

One of the major challenges facing healthcare worldwide is the incremental cost-effectiveness and the threshold for using or rejecting specific drugs. Bevacizumab is one of the most expensive drugs currently available. In many countries with national health services, its use has been restricted based on cost-effectiveness studies that suggest that the drug is not cost-effective.

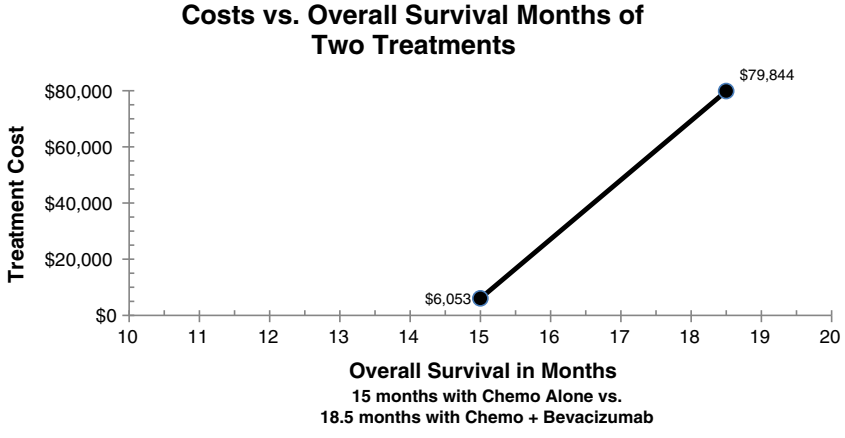

Fig. 2. Cost effectiveness analysis of chemotherapy with and without bevacizumab in life months until death.

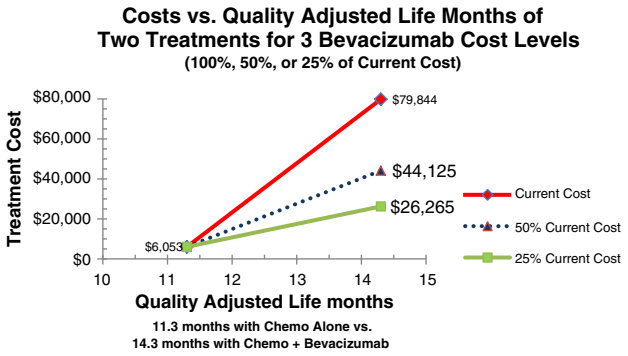

Fig. 3. Cost-effectiveness of chemotherapy with and without bevacizumab for QALmonths and with projected reduction in cost of bevacizumab.

Cost-effectiveness studies on integrating bevacizumab in the management of US FDA-approved indications have been performed previously and include metastatic and recurrent colorectal cancer, primary untreated non-small cell lung cancer, and renal cell carcinoma [13–20]. For example, Shiroiwa et al. reported a maximum ICER of $145,000 per life year for colorectal cancer [16], while Chien et al. reported a maximum ICER of over $300,000 for patients with non-small cell lung cancer for whom bevacizumab was added to chemotherapy [18]. Although in their economic evaluation of new targeted therapies Benedict et al. did not report the ICER for bevacizumab in the treatment of metastatic renal cell carcinoma, the investigators concluded that sunitinib is a cost-effective alternative to befacizuamb with savings of $67,798 per patient treated in the United States [20].

Although approved for recurrent glioblastoma, cost-effectiveness studies for this indication are lacking [22–25]. Additionally, cost-effectiveness of bevacizumab in metastatic breast cancer has been evaluated [10–12,21], with marginal cost effectiveness of $232,720.72 reported by Refaat et al. [10]. Although not approved in age-related macular degeneration, bevacizumab is considered an acceptable alternative to ranibizumab based on a randomized trial [26].

In four phase III randomized studies in newly diagnosed, platinum sensitive, and platinum resistant ovarian cancer, the arms administering chemotherapy and bevacizumab all met their primary endpoints with significant improvements in PFS [27–30]. Bevacizumab has not been approved in the U.S. for frontline ovarian cancer therapy, although the FDA has approved use in patients with platinum-resistant recurrent disease. Cohn et al. evaluated GOG 218, which studied bevacizumab in frontline therapy and concluded that the addition of bevacizumab to standard chemotherapy was not cost-effective with an ICER of $401,088 per progression-free life year saved for the bevacizumab throughout arm (primary plus maintenance therapy) [31]. The ICER fell below $100,000 per progression-free life year saved when the cost of bevacizumab was reduced to 25% of baseline. In another cost-effectiveness analysis, Chan et al. reported that for the high risk subset from the ICON 7 study that experienced an OS benefit, the incremental cost of bevacizumab was $170,000 [31,32].

The dominant theme to emerge from cost-effectiveness studies is that with the exception of the non-lethal condition of age-related macular degeneration for which very small dosages of drug are required, bevacizumab will not be cost-effective in the management of solid tumor malignancies due to the current high cost of the drug, relatively limited impact on duration of survival, and healthcare expenditures required to manage anti-VEGF-specific toxicology [10–12,15,16,18,20,31–33].

The growing use of bevacizumab can be demonstrated by sales data. In 2013, with global sales of $6.7 billion, bevacizumab ranked 9th in terms of revenue generated among the top 50 pharmaceutical agents [34]. Looking back, sales for bevacizumab grew by 9% between 2011 and 2012 to reach $6.3 billion in 2012 compared to $5.8 billion in 2011 [35]. The increase was attributable to increased usage in established indications (colorectal and lung cancer), along with E.U. approval to treat platinum-sensitive ovarian cancer which was granted in 2012. In the U.S. market sales of bevacizumab increased from $2.6 billion in 2011 to $2.7 billion in 2012 while in Western Europe sales increased from $1.6 billion in 2011 and $1.7 billion in 2012 [35]. Sales in other international markets were boosted by the CEMAI region (Central and Eastern Europe, Middle East, Africa, and the Indian Subcontinent), Latin America, and the APAC regions (Australia, China, and Japan). Based on growing sales, health care payers have implicitly indicated a relatively high willingness to pay per QALY gained.

For our analysis we chose a monthly Markov cycle because that time period corresponds with the time span in which a patient could transition to a new health state. Furthermore, because survival for patients with advanced cervical cancer is measured in months rather than years, we feel that our choice of reporting results in QALmonth is appropriate, adjusted from a baseline of living a month responding to treatment for advanced cervical cancer. We found that the cost of therapy resulting from the incorporation of bevacizumab was nearly 13.2 times that of chemotherapy alone and when taking into account complications, the ICER is $24,597/QALmonth (or $295,164/QALY) or a mean of $73,791 extra for a single patient over the course of the treatment, over the cost of chemotherapy alone.

Investigators bringing bevacizumab to cervical cancer are not in a position to determine whether $73,791 cost per patient treated is cost-effective therapy. Similarly, those studying cost of care are unable to assign a price to a gain in 3.9 months of a woman's life. This is for society to determine. But what must be emphasized is that, with the exception of imatinib in chronic myelogenous leukemia, significant breakthroughs in oncology are currently not expected to impact survival beyond several months [36]. As a result, the ICERs associated with novel therapies may appear unacceptably high. The benefit conferred by bevacizumab to women with advanced cervical cancer is noteworthy as these cancers do not appear to be as chemosensitive as other solid tumors (eg., ovarian cancer, etc.). In addition, the population with recurrent/metastatic disease is unique as the majority have been previously irradiated which leads to diminished bone marrow reserves and an increased risk for fistula formation. The FDA's August 14, 2014 decision to approve bevacizumab for advanced cervical cancer [4] constitutes a regulatory milestone allowing the study of potentially more efficacious treatments for cervical cancer to move forward.

The current study was limited by creation of a cost-effectiveness model from a singular data set, as GOG study 240 is the only randomized controlled clinical trial evaluating bevacizumab with chemotherapy in advanced cervical cancer [3]. Subsequently, this model does not incorporate all possible clinical outcomes. However, with recent FDA approval of this agent in advanced cervical cancer, the authors hope to repeat an analysis based on real world experience. Additionally, regarding potential costs of bevacizumab-related complications such as hypertension, fistula, thromboembolism or hemorrhage, there is limited information for which these costs were derived. These limitations may be addressed with further studies. Our model does not incorporate the societal impact of lost of productivity. Nor is this study from a patient perspective therefore, cost beyond therapeutic cost are not included. Finally, reimbursements and costs differ according to country and time making this analysis most relevant to 2013 and the United States.

While awaiting reform of the U.S. healthcare system and cost reconciliation, it appears that many cancer patients in need of oncologically effective but cost-*ineffective* therapies will be treated using the old arsenal of cytotoxic agents, an armamentarium of oncologic dead ends. When considering the relatively young median age at diagnosis of women with advanced cervical cancer, the number of life-years lost to family and to society are unacceptable. The societal and clinical dilemma can be reconciled from the vantage point of seeing things in the long-term. Specifically, with significant reductions in drug cost, the ICERs become more acceptable. This may be realized through the introduction of generics into the market.

Biosimilars have been available on the European market since 2006, and the next wave of biopharmaceuticals that will lose patent protection include more complicated products such as monoclonal antibodies [37]. On June 27, 2013, the European Medicine Agency's Committee for Medicinal Products for Human Use recommended approval for two biosimilar infliximab products to be marketed in the European Union, making them the first biosimilar antibodies made available to patients in a highly regulated market [38].

According to GMR Data (an independent business information research company recognized for market and financial accuracy), the financial peak of bevacizumab has been forecasted for 2018, before it loses its patent exclusivity in the U.S. in 2019 and in the E.U. in 2022 [39]. Bevacizumab is considered to be an especially challenging product to establish biosimilarity. The Generics and Biosimilars Initiative estimates that there are 15 biosimilars of bevacizumab in development [40]. It is possible that through the availability of effective biosimilars, cost-effective prolongation of life in advanced cervical cancer may be feasible. The hypothetical 75% reduction in cost of bevacizumab examined in this study is based on realistic expectations given significantly reduced costs of generic antiretroviral therapy [S1} and the biosimilar of imatinib made in India [S2, S3].

Unlike clinical trials in ovarian cancer in which incorporation of bevacizumab has been unable to improve OS, the GOG 240 study in advanced cervical cancer has convincingly demonstrated a significant improvement in OS when bevacizumab is combined with chemotherapy, resulting in US FDA approval and a change in practice. Although our cost-effectiveness analysis confirms that the use of bevacizumab incurs high expense mostly due to the cost of the drug as opposed to the management of bevacizumab-specific toxicity, we acknowledge that this will unlikely dissuade clinicians from considering bevacizumab for appropriate patients in this clinical setting. However, we feel that it is important to frame the regulatory approval and resulting drug availability against the backdrop of the current healthcare climate which remains problematic. From a methodologic standpoint, conclusions derived from Markov modeling are typically not persuasive enough by themselves to substantially influence medical or policy decisions, but the data we have reported is hypothesis-generating. Ultimately, these results will need to be supported by real world data that can capture many other aspects of cost, particularly toxicity management, that our model is unable to allow for (eg., increased costs incurred through physician and nursing visits, loss of work, etc.). Moving forward, conclusions drawn from extension of cost-effectiveness assessments to other countries where cervical cancer is an even more frequent cause of morbidity and mortality will become even more compelling from the policy maker's vantage point.

Conflict of interest statements

LE Minion, J Bai, LR Keller, GK Forde, and JK Chan report no conflicts of interest.

RN Eskander reports that he serves on the Genentech Speaker's Bureau for bevacizumab in cervical and ovarian cancer.

KS Tewari and BJ Monk report that their institutions have received research funding from Genentech and both have served as consultants and on advisory boards for Genentech/Roche.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.02.027.

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