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Pembrolizumab in advanced recurrent endometrial cancer: A cost-effectiveness analysis

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HIGHLIGHTS

- Treatment options for recurrent endometrial cancer are limited.
- Pembrolizumab is an effective treatment option for patients who fail first line therapy.
- In our model, pembrolizumab is cost-effective relative to bevacizumab and pegylated liposomal doxorubicin.

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ABSTRACT

Objective. To determine the cost-effectiveness of pembrolizumab in patients with recurrent endometrial cancer that have failed first-line chemotherapy.

Methods. We created a model to evaluate the cost-effectiveness of pembrolizumab compared to pegylated liposomal doxorubicin (PLD) or bevacizumab for the treatment of women with recurrent endometrial cancer who have failed carboplatin and paclitaxel. Microsatellite instability-high (MSI-H) and non-microsatellite instability-high (non-MSI-H) tumors were evaluated. We included 4400 patients in the model; 800 patients were assumed to have MSI-H tumors. Drug costs were calculated using 2016–2017 wholesale acquisition costs, and cost of Grade III-IV toxicities was estimated from clinical experience. Effectiveness was calculated as 2-year overall survival (OS). We calculated incremental cost-effectiveness ratios (ICERs) to determine the cost per 2-year survivor. Univariate sensitivity analyses were performed. The willingness to pay threshold was $100,000 per year of OS.

Results. The cost of therapy with PLD and bevacizumab were $33.2 million (M) and $167.9 M, respectively. The cost of pembrolizumab therapy was $318.3 M for non-MSI-H patients compared to $57.9 M for MSI-H patients. For non-MSI-H patients, bevacizumab was cost-effective relative to PLD with an ICER of $153,028, while pembrolizumab was not cost-effective relative to bevacizumab with an ICER of $341,830. For MSI-H patients, pembrolizumab was cost-effective compared to PLD with an ICER of $147,249, while bevacizumab was subjected to extended dominance. Sensitivity analysis revealed that for non-MSI-H patients, one cycle of pembrolizumab would need to cost $7253 or less to be cost-effective.

Conclusions. For patients with MSI-H recurrent endometrial cancers who have failed first-line chemotherapy, pembrolizumab is cost-effective relative to other single agent drugs. To be cost-effective in non-MSI-H patients, the cost of pembrolizumab should decrease substantially.

1. Introduction

With over 60,000 new cases annually, endometrial cancer is the most common gynecologic cancer in the United States [1]. While the majority of patients present with early stage disease and are cured with surgery alone, effective treatment options for those who recur are limited [2]. Combination paclitaxel and carboplatin is an effective treatment at the time of first recurrence and is better tolerated than triplet therapy with doxorubicin, cisplatin, and paclitaxel [3]. Unfortunately, the prognosis for patients who fail this therapy is poor. Several single agent therapies have also shown activity in recurrent endometrial cancer. Pegylated liposomal doxorubicin (PLD) and bevacizumab demonstrate some of the best response rates [4,5]. Additional chemotherapeutic agents that have shown activity in heavily treated recurrent endometrial cancer include doxorubicin, topotecan, paclitaxel,

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docetaxel, and cisplatin; unfortunately, response rates are uniformly low and median overall survival (OS) is measured in months [6–10].

Drugs targeting immune checkpoints such as the programmed death 1 (PD-1) receptor have showed promise in a variety of cancer types including non-small cell lung cancers, melanoma, renal cell carcinoma, and endometrial cancer [11–14]. In a recent phase II trial, the PD-1 blocking monoclonal antibody, pembrolizumab, demonstrated robust antitumor activity in mismatch repair deficient tumors regardless of tumor origin [15]. PD-1 inhibitors prevent the receptors from binding to programmed death ligand 1 (PDL-1) and impair the tumor's ability to evade T cell-mediated programmed cell death. The objective of our study was to determine the cost-effectiveness of pembrolizumab in patients with recurrent endometrial cancer that have failed first-line chemotherapy.

2. Methods

2.1. Model

Of the 60,000 yearly cases of endometrial cancer, approximately 15% will recur, and over half of those patients will fail first line chemotherapy [1,2]. We estimated that our target population included approximately 4400 patients. To compare cost-effectiveness of pembrolizumab with two other single agent therapies, pegylated liposomal doxorubicin (PLD) and bevacizumab, two separate cost-effectiveness models were created: microsatellite instability high (MSI-H) endometrial cancers, and non-microsatelitte instability high (non-MSI-H) endometrial cancers. All patients received 6 cycles of paclitaxel and carboplatin for first recurrence. For the PLD arm, the median number of cycles was 3 cycles and for the bevacizumab arm, the median number of cycles was 5 cycles [4,5]. Although the median cycles of pembrolizumab used in the Le trial was not published, we estimated 8 cycles in the model [15].

2.2. Clinical estimates

Based on published data, approximately 17–28% of endometrial cancers are MSI-H [15–18]. We conservatively selected 17% for our model input. OS at two years was estimated based on previously published data. For MSI-H patients treated with pembrolizumab, 2-year OS is 64% [15]. In Ott's study, 2-year OS for non-MSI-H patients is estimated to be 50% [14]. No difference in OS based on MSI status was assumed for the PLD and bevacizumab groups. Two-year OS for PLD and bevacizumab are 20% and 40% respectively [4,5] (Table 1).

2.3. Cost estimates

Drug costs per cycle were obtained from the University of Alabama at Birmingham hospital pharmacy using 2016 and 2017 wholesale acquisition costs (Table 1). To incorporate toxicity costs, the most commonly reported Grade III-IV toxicity for each agent was included in the model and related costs were estimated based on clinical experience. For PLD, the incidence of palmar-plantar-erythrodysesthesia is 23% and related costs were estimated to be $250 [19]. For bevacizumab, hypertension occurs with 8% of cases and related costs were estimated to be $500 [5,20]. Of those treated with pembrolizumab, approximately 5% experience anemia with an estimated cost of $1000 [14] (Table 2).

Table 1
Drug costs and two year survival based on MSI status.

Treatment (1 cycle)	Cost	MSI-High	Non-MSI-High
Pembrolizumab	$9026	64%	50%
Bevacizumab	$7585	40%	40%
Pegylated liposomal doxorubicin	$2509	20%	20%

Table 2
Drug toxicities.

Drug	Grade III–IV toxicity	Probability	Cost of toxicity treatment
Pembrolizumab	Anemia	5%	$1000
Bevicizumab	Hypertension	8%	$500
PLD	Palmar-plantar erythrodysesthesia	23%	$250

2.4. Cost-effectiveness analysis

Cost was defined as the total cost per treatment arm, and effectiveness as number of two-year survivors. We selected this definition of effectiveness since median OS had not been reached in the previously mentioned phase II trial [15]. We calculated incremental cost-effectiveness ratios (ICERs) to compare the cost per 2-year survivor for patients who received pembrolizumab compared to PLD and bevacizumab. We assumed a standard willingness-to–pay (WTP) threshold of $100,000 per life year, or $200,000 per 2 years of OS. In order to account for uncertainty in our model, we performed univariate sensitivity analyses on number of cycles given, effectiveness, and cost of pembrolizumab. Threshold values were determined from sensitivity analyses, which mark where a change in model input would result in a different outcome. All calculations were performed using TreeAge Pro Healthcare software (Williamston, MA).

3. Results

In the MSI-H cohort, the cost of pembrolizumab was $57.9 million (M), and yielded 507 two-year-survivors. Comparatively, PLD cost $6 M and resulted in 158 survivors, while bevacizumab cost $30.5 M and produced 317 survivors. The ICER for pembrolizumab compared to PLD was $147,249, which fell below our predetermined willingness-to-pay threshold of $200,000 per 2-year survivor. Bevacizumab fell subject to extended dominance as there was both a more costly/more effective treatment, and a less costly/less effective treatment (Table 3).

In the non-MSI-H cohort, the cost of pembrolizumab therapy was $318.3 M (with 1804 2-year survivors) compared to $137.4 M for bevacizumab (1443 survivors) and $27.2 M for PLD (722 survivors). Compared to PLD, the ICER of pembrolizumab was $341,830 per 2-year survivor and the ICER for bevacizumab was $153,028 (Table 4).

Univariate sensitivity analyses were performed to determine the effect of varying number of cycles, effectiveness, and cost of pembrolizumab. Eight cycles of pembrolizumab were used in the baseline model. This was varied from 4 to 16 cycles in the sensitivity analysis. With increasing cycles, both the total cost of treatment and ICER for pembrolizumab increases. The ICER for pembrolizumab remains below $200,000 per 2-year survivor for 10 cycles of treatment or less. Varying the efficacy of pembrolizumab from 20% to 80% in MSI-H tumors affects total number of survivors and the ICER. The ICER remains below $200,000 per 2-year survivor as long as efficacy is 57% or greater, which is the reported 2 year overall survival for non-colorectal cancers in Le's study [15]. Varying the cost of pembrolizumab has profound impacts on both the total cost of treatment and the ICER. For the non-MSI-

Table 3
Baseline model results for MSI-High patients.

Treatment	Total cost (million)	Two-year survivors	ICER
Pembrolizumab	$57.9	507	$147,249
Bevacizumab	$30.5	317	Dominated
PLD	$6.0	158	NA

Table 4
Baseline model results for non-MSI-High patients.

Treatment	Total cost (million)	Two-year survivors	ICER
Pembrolizumab	$318.3	1804	$341,830
Bevacizumab	$137.4	1443	$153,028
PLD	$27.2	722	NA

H cohort, decreasing the cost of one cycle of pembrolizumab to $7253 or less would drop the ICER to below $200,000, making it cost-effective.

4. Discussion

Recent data has shown that some patients with recurrent endometrial cancer will have a robust response to the PD-L1 inhibitor, pembrolizumab [14]. This response appears to be stronger when cancers display mismatch repair deficiency [15]. While these results are promising, pembrolizumab, like many novel immunotherapeutic agents, is expensive. We demonstrated that in our model, relative to single agent PLD and bevacizumab, pembrolizumab is cost-effective for MSI-H recurrent endometrial cancers with an ICER of $147,249 per 2-year survivor. Pembrolizumab remained cost-effective up to 10 cycles of treatment and as long as efficacy was greater than 57%. Pembrolizumab was not cost-effective in non-MSI-H patients. In order to be cost-effective in non-MSI-H patients, the cost of pembrolizumab would need to decrease to $7253 or less. Bevacizumab was cost-effective relative to pembrolizumab and PLD in our baseline model with an ICER of $153,028. Although the cost-effectiveness of pembrolizumab has been examined in other cancer types, the cost-effectiveness of this treatment for endometrial cancer has not been studied [21–25].

Despite using published literature and conservative cost estimates, the authors acknowledge several limitations. While most ICERs are calculated for life year saved or quality adjusted life year saved, to appropriately compare our selected therapies, we calculated ICERs for 2-year survivors. We selected this definition of effectiveness as median OS has not been reached in the Le phase II trial of pembrolizumab. The lack of survival data in published literature precluded us from comparing pembrolizumab to other commonly used therapies like the combination of doxorubicin and cisplatin. Additionally, incorporating the cost of drug toxicities into a cost-effective model is challenging. We did not account for all possible drug toxicities in the model. Le's study examined mismatch repair deficient tumor's but did not specifically determined MSI status. Data would suggest a high degree of concordance of mismatch repair deficiency and microsatellite instability high status in endometrial cancers, and these terms are used interchangeably in our study [26,27]. We acknowledge there is an absence of definitive data investigating the specific response rate of non-MSI-H endometrial cancers treated with pembrolizumab. In the KEYNOTE study referenced, the majority of cancers that were tested were non-MSI-H (18/19 patients). Five additional patients were not tested [14]. In the absence of more conclusive data, we assumed that the OS for non-MSI-H patients to be similar to the OS observed in Ott's study due to the fact that the vast majority of these patients were non-MSI-H.

Additionally, the median number of cycles of pembrolizumab administered in the phase II trial was not published. To account for this, we performed a univariate sensitivity analysis for number of cycles of pembrolizumab. Some patients in this trial were receiving pembrolizumab at two week intervals for up to two years, which would greatly exceed the median number of cycles used in our model. If the survival seen in patients treated with pembrolizumab requires a prolonged duration of treatment, the cost of the drug would need to decrease dramatically.

The cost of cancer care in the United States was estimated to be $125 billion dollars in 2010, and projected to climb to nearly $160 billion dollars by 2020 [28]. Innovations in novel targeted therapies offer exciting possibilities for the future of cancer care, but the majority of these drugs carry substantial costs. Only in rare circumstances where the survival benefit is large, like in the case of pembrolizumab with MSI-H recurrent endometrial cancers are these agents cost-effective. The cost of drugs is an increasingly important consideration as the cost of health care continues to climb. Continued innovation is necessary for development of novel cancer therapies, but making these therapies feasibly affordable is paramount as well.

Author contributions

Formulation of research question: Straughn, Dilley, Smith.
Literature review: Dilley, Smith, Barrington.
Model design and selection of inputs: Dilley, Smith, Barrington.
Clinical cost estimates and project oversight: Straughn.
Manuscript drafting: Barrington.
Critical revision: Straughn, Dilley, Barrington.

Conflict of interest report

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