Real-World Experience with Pembrolizumab Treatment in Patients with Heavily Treated Recurrent Gynecologic Malignancies

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Purpose: We evaluated the efficacy and safety of pembrolizumab in patients with recurrent gynecologic cancers in real-world practice.

Materials and Methods: We conducted a retrospective, single-institution study of patients with recurrent gynecologic malignancies treated with pembrolizumab. The primary endpoints were the objective response rate (ORR) and safety.

Results: Thirty-one patients treated with pembrolizumab were included. The primary disease sites were the uterine cervix (n=18), ovaries (n=8), and uterine corpus (n=5). Fifteen of the 31 patients (48%) had an Eastern Cooperative Oncology Group performance status of ≥2. The median number of prior chemotherapy lines was 2 (range, 1–6), and 14 of 31 patients (45%) had received ≥ 3 prior lines of chemotherapy. The overall ORR was 22.6%: specifically, 22.3% (4 of 18 patients), 12.5% (1 of 8 patients), and 40% (2 of 5 patients) for cervical, ovarian, and endometrial cancers, respectively. During a median follow-up of 4.7 months (range, 0.2–35.3), the median time to response was 1.9 months (range, 1.4–5.7). The median duration of response was not reached (range, 8.8-not reached). The median progression-free survival was 2.5 months (95% confidence interval, 1.7-not reached). Adverse events occurred in 20 patients (64.5%), and only 3 (9.7%) were grade ≥3. There was one case of suspicious treatment-related mortality, apart from which most adverse events were manageable.

Conclusion: In real-world practice, pembrolizumab was feasible and effective in heavily treated recurrent gynecologic cancer patients with poor performance status who may not be eligible for enrollment in clinical trials.

Key Words: Gynecologic neoplasms, pembrolizumab, recurrence

INTRODUCTION

Gynecologic malignancies, including ovarian cancer, endometrial cancer, and cervical cancer, are major causes of death due to cancer among women worldwide.[1] Ovarian cancer is typically diagnosed at an advanced stage. In about 70–80% of patients with advanced ovarian cancer, cytoreductive surgery with platinum-based chemotherapy often leads to complete remission; however, most patients experience recurrence and eventually develop chemoresistance.[2] While early-stage endometrial or cervical cancer can be cured, by local therapy, such as surgery or radiotherapy with concurrent or sequential chemotherapy,[3] advanced or recurrent tumors, for which only first- or second-line systemic therapy has been established, are incurable. Therefore, there is an urgent need for more effective

anticancer therapeutic strategies for advanced or recurrent gynecologic cancers.

Immunotherapy has long been studied as a promising anticancer treatment strategy. Immune checkpoint inhibitors (ICIs), including programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitors, such as pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab, and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors, such as ipilimumab, work by blocking the pathways that downregulate the activity of T lymphocytes. In recent years, various ICIs have been found to provide improvements in overall survival (OS) for various advanced cancers,[4-6] including recurrent gynecologic cancers.[7,8]

Virus-associated malignancies are considered attractive targets for immunotherapy because viral proteins are strong immune stimulants.[9] From this perspective, cervical cancer may be a good candidate for immunotherapy because cervical cancer is associated with persistent human papillomavirus infection, which accounts for as much as 86% of the global incidence of cervical cancer.[10] In addition, approximately 50% of ovarian cancer patients exhibit homologous recombination deficiency in the DNA repair system,[11] which could potentiate immunogenicity for anticancer immunotherapy.[12] About 22−33% of endometrial cancers are also known to involve mismatch repair deficiency (MMRd) or high microsatellite instability (MSI-H),[13] which has been confirmed to be a predictive marker of ICI effectiveness.[13,14] In clinical settings, a combination of pembrolizumab and lenvatinib has been approved in advanced endometrial cancer by the Food and Drug Administration (FDA) based on a promising response rate of 40%.[7] Pembrolizumab has also been approved by the FDA for the management of advanced cervical cancer, with demonstrated anticancer activity.[8] Furthermore, in recurrent ovarian cancer, nivolumab[15] and pembrolizumab[16] have shown anticancer activity as a monotherapy or in combination with bevacizumab[17] or poly ADP ribose polymerase inhibitors[18] in several clinical trials.

As described, gynecologic cancers are good candidates for anticancer immunotherapy; therefore, more clinical studies using immunotherapy are warranted in the field of gynecologic cancer. Currently, real-world data regarding ICIs in gynecologic cancers are limited.[19] In the present study, we retrospectively evaluated the efficacy and safety of pembrolizumab among patients with recurrent gynecologic cancers in real-world practice.

MATERIALS AND METHODS

Study population
We performed a retrospective study of patients with recurrent or refractory gynecologic malignancies who were treated with pembrolizumab at CHA Bundang Medical Center between February 2016 and March 2020. In Korea, pembrolizumab can be prescribed to patients with any type of solid tumor that ex-

hibits MSI-H and/or MMRd, recurrent cervical cancer, and recurrent ovarian cancer expressing PD-L1.

The inclusion criteria were as follows: 1) pathologic diagnosis of a gynecologic malignancy, including the uterine cervix, ovaries, or uterine corpus; 2) tumor progression during or after one or more lines of standard treatment, irrespective of Eastern Cooperative Oncology Group (ECOG) performance status, and 3) at least one cycle of treatment with pembrolizumab. The patients received 200 mg of pembrolizumab as 30-minute intravenous infusions every 3 weeks until disease progression, unacceptable toxicities, or patient withdrawal. The present study was approved by our Institutional Review Board (CHA IRB 2018-09-019).

Evaluation of efficacy and safety
Abdomino-pelvic and/or chest computed tomography (CT) scans were performed every 9 weeks. In addition, pelvic magnetic resonance imaging, whole body bone scans, or positron emission tomography CT scans were performed if indicated. If clinical symptoms deteriorated, imaging studies were performed immediately. Tumor responses were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[20] The primary efficacy endpoint was the objective response rate (ORR) and safety. Safety was assessed by reviewing medical records, including review of systems, physical examination findings, and blood tests prior to each treatment cycle. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Secondary end points included the duration of response, defined as the time from response to tumor progression or death, whichever occurred first; progression-free survival (PFS), defined as the time from start of pembrolizumab to tumor progression or death, whichever occurred first; and OS, defined as the time from the start of treatment to death from any cause. The efficacy and safety profile analyses included all patients who received at least one cycle of pembrolizumab.

Determination of PD-L1 expression
Tumor PD-L1 expression was evaluated using the PD-L1 IHC 22C3 antibody (Dako, Santa Clara, CA, USA) to determine the tumor proportion score (TPS), defined as the percentage of viable tumor cells with staining at any intensity, or using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) to determine the combined positive score (CPS), defined as the ratio of the number of PD-L1 positive cells (tumor cells, lymphocytes, and macrophages) to the total number of viable tumor cells multiplied by 100. PD-L1 positivity was defined as a TPS ≥1% or CPS ≥1.

Statistical analysis
Efficacy and safety profile analyses included all patients who received at least one cycle of pembrolizumab. ORR point esti-

mates were accompanied by 95% confidence intervals (CIs) using the Clopper-Pearson exact method based on a binomial distribution. Patients without response data were considered as non-responders. The duration of response, PFS, and OS were estimated using the Kaplan-Meier method. All statistical calculations were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Analysis items with p values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics
Thirty-one patients treated with pembrolizumab were included. The primary disease sites were the uterine cervix (n=18), ovary (n=8), and uterine corpus (n=5). The median age at diagnosis was 53.0 years (range, 30–79); 48.4% (15/31) of patients had an ECOG performance status of 2 or 3; and 77.5% (24/31) had stage III or IV disease at the initial diagnosis. The median number of prior chemotherapy lines, including neoadjuvant chemotherapy, was 2 (range, 1–6). As of March 31, 2020, the date of data cutoff, the median follow-up time was 4.7 months (range, 0.2–35.3). Twenty-one patients (72.4%) had discontinued pembrolizumab, most commonly due to disease progression (41.9%, n=13) (Fig. 1). The median number of pembrolizumab cycles was 6 (range, 1–30). The baseline characteristics are listed in Table 1.

Efficacy
The overall ORR was 22.6% (95% CI: 10.0–41.1), with a complete response in 2 patients (6.5%) and a partial response in 5 patients (16.1%). According to tumor types, the ORRs were 22.3% (4 of 18 patients) for cervical cancer, 12.5% (1 of 8 pa-
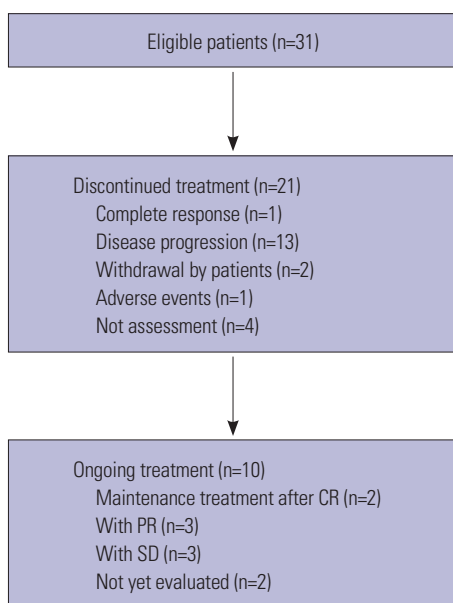
tients) for ovarian cancer, and 40% (2 of 5 patients) for endometrial cancer (Table 2). The median duration of response was not reached (range, 8.8-not reached). The disease control rate was 38.7% (95% CI: 21.8–57.8), including 7 responders and 5 patients with stable disease (Table 2). A clinical summary of the seven responders is provided in Supplementary Table 1 (only

Table 1. Clinicopathologic Characteristics of the Patients (n=31)

Characteristics	n (%)
Median age (range), yr	53.0 (30–79)
ECOG performance status	
0	4 (12.9)
1	12 (38.7)
2	6 (19.4)
3	9 (29.0)
FIGO stage at diagnosis	
I	2 (6.5)
II	5 (16.1)
III	18 (58.1)
IV	6 (19.4)
PD-L1 expression status*	
≥1	23 (74.2)
<1	2 (6.5)
Not tested	6 (19.4)
Histology	
Uterine cervix	18 (58.1)
Squamous cell carcinoma	12 (66.7)
Adenocarcinoma	4 (22.2)
Adenosquamous cell carcinoma	2 (11.1)
Ovary	8 (24.1)
High-grade serous carcinoma	6 (75.0)
Endometrioid adenocarcinoma	1 (12.5)
Clear cell carcinoma	1 (12.5)
Uterine corpus	5 (16.1)
High-grade serous carcinoma	1 (20.0)
Carcinosarcoma	1 (20.0)
Neuroendocrine carcinoma	1 (20.0)
Leiomyosarcoma	1 (20.0)
Dedifferentiated carcinoma	1 (20.0)
Target lesion size, median (range), mm	119.0 (9.0–405.0)
Time from diagnosis to pembrolizumab therapy (yr)	
≤1	6 (19.4)
>1	25 (80.6)
Prior lines of chemotherapy	
1	7 (22.6)
2	10 (32.3)
3	3 (9.7)
4	8 (25.8)
≥5	3 (9.7)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PD-L1, programmed death-ligand 1.
*Determined using the tumor proportion score or the combined positive score.

Eligible patients (n=31)

↓

Discontinued treatment (n=21)
Complete response (n=1)
Disease progression (n=13)
Withdrawal by patients (n=2)
Adverse events (n=1)
Not assessment (n=4)

↓

Ongoing treatment (n=10)
Maintenance treatment after CR (n=2)
With PR (n=3)
With SD (n=3)
Not yet evaluated (n=2)

Fig. 1. Patient distribution according to treatment response outcomes.

Table 2. Antitumor Activities of Pembrolizumab Assessed by RECIST v1.1 (n=31)

Antitumor activity	Total (n=31)	Cervix (n=18)	Ovary (n=8)	Uterus (n=5)
Best overall response				
CR	2 (6.5)	1 (5.6)	0	1 (20.0)
PR	5 (16.1)	3 (16.7)	1 (12.5)	1 (20.0)
SD	5 (16.1)	3 (16.7)	2 (25.0)	0
PD	13 (41.9)	8 (44.4)	2 (25.0)	3 (60.0)
Could not be assessed	6 (19.4)	3 (16.7)	3 (37.5)	0
ORR	22.6			
DCR	38.7			
Time to response, median	1.9 (1.4–5.7)			
Duration of response, median	NR (8.8–NR)			
Estimated number of patients with duration of response (n=7)				
>6 months	5			
>12 months	4			
>18 months	2			

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate, DCR, disease control rate; NR, not reached. Data are presented as n (%).
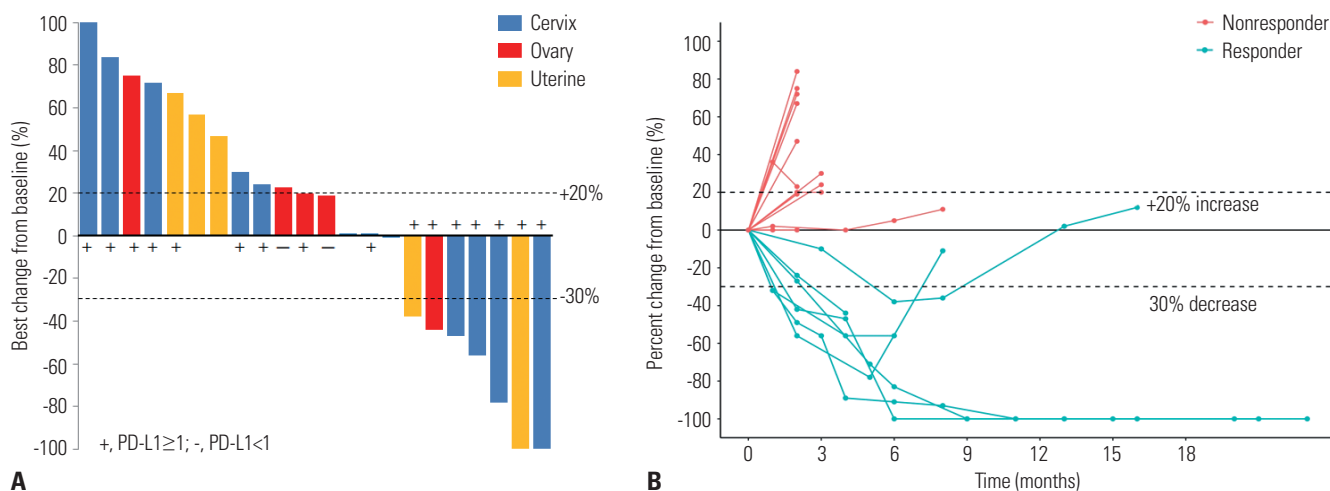
Fig. 2. Antitumor activity of pembrolizumab. (A) Waterfall plot showing the distribution of best percentage changes in the sum of target lesion size from baseline according to RECIST version 1.1 (n=22). (B) Kinetics of changes in tumor burden over time with pembrolizumab treatment.

online).

The best percentage change in the target lesion from baseline and changes in tumor burden over time for the 22 patients who underwent one or more evaluable post-baseline imaging assessments are shown in Fig. 2. At the time of data cutoff, 19 (61.3%) patients in the total population had experienced disease progression or death. The median PFS was 2.5 months (95% CI: 1.7-not reached), and the estimated PFS rate at 6 months was 41.2%. 14 (45.2%) patients died. The median OS was 14.3 months (95% CI: 3.7–not reached). The OS rates estimated at 6 and 12 months were 63.7% and 50.9%, respectively (Supplementary Fig. 1, only online). One (Cx010) of the seven responders had died as of the data cutoff date (Supplementary Table 1, only online).

Adverse events

AEs occurred in 20 patients (64.5%), and only 3 (9.7%) had grade ≥3 AEs (Table 3). The most common AEs of any grade were hypothyroidism (12.9%), anemia (12.9%), and fatigue (9.7%). There was one case (Cx001) of suspected treatment-related mortality. Patient Cx001 began to receive pembrolizumab with an indwelling Foley catheter, having undergone percutaneous nephrostomy in the left kidney and colostomy with an ECOG performance status of 2. Twenty days after initial pembrolizumab, interstitial pulmonary infiltrates, implying combined interstitial lung disease and pulmonary edema, occurred abruptly, and the patient died of respiratory failure the next day (Supplementary Fig. 2, only online). There were no other treatment-related fatal AEs. Most AEs were manageable.

DISCUSSION

To the best of our knowledge, this is one of the first real-world studies of gynecologic cancers with pembrolizumab. We demonstrated that pembrolizumab therapy is a feasible option for heavily treated gynecologic cancer patients with poor performance status in real-world practice. Notably, pembrolizumab therapy was effective in patients with poor performance status that would be excluded from well-designed clinical trials.

The overall ORR among our 18 cervical cancer patients was 22% (4/18), which is comparable to the rate of 4–26% reported in previous studies as shown in Table 4.[8,21-23] The ORRs for ovarian cancer (13%) and endometrial cancer (40%) in the present study were also similar to previously reported data: 10–33% for ovarian cancer[15,16,24,25] and 13–57% for endometrial cancer[14,24,26] as shown in Table 4. Prospective clinical trials and real-world experience studies differ on a couple of points. First, in prospective studies, only patients with good performance status (ECOG ≤1) are enrolled. However, in this study, approximately half of the patients (15/31) showed poor general condition (ECOG ≥2). Second, in prospective studies, a lower proportion of patients (31–38%) receive three or more lines of chemotherapy.[8,21] However, in the present study, 45% of the patients had already received three or more lines of chemotherapy. Moreover, one prospective study only enrolled patients harboring MSI-H or MMRd, which are generally accepted predictive biomarkers.[14] Therefore, it is difficult to directly compare our results with those of prospective trials. Despite the worse patient conditions and later line of therapy in our study, the comparable outcomes were notable as real-world data. Overall outcomes, including excellent responders (Ut002, Cx006, and Ov004) with poor performance status who received pembrolizumab (Supplementary Table 1, only online), suggest that ICIs might be effective among heavily treated patients in late stages of gynecological cancer.

Regarding AEs, the patients in this study were less likely to have frequent and severe AEs than patients enrolled in clinical trials, attributable to their worse performance status. However, AEs might have been underestimated in this study because not all grades of AEs could be monitored, particularly, if they were of lower grades in retrospective studies. Although there was one case of suspected treatment-related mortality, AEs were mostly manageable. This suggests that patients with advanced gynecologic cancer should not be excluded from ICI therapy simply because of poor performance status. Nevertheless, since the patient who died had several comorbidities, including an indwelling Foley catheter, percutaneous nephrostomy, and colostomy, we should exercise caution in administering ICI therapy to patients with comorbidities.

The discovery of predictive biomarkers is an urgent need for ICI therapy. MMRd/MSI-H, tumor mutational burden, PD-L1 expression, and tumor-infiltrating lymphocytes have recently been studied as potential biomarkers of ICI therapy. In particular, MMRd/MSI-H has been confirmed to be a predictive biomarker for favorable responses to pembrolizumab, leading to FDA agnostic approval for pembrolizumab therapy in any

Table 3. Adverse Events in the Treated Patients (n=31)

Adverse events	Any grade	Grade 3/4/5
Any adverse event	20 (64.5)	
Hypothyroidism	4 (12.9)	0
Anemia	4 (12.9)	0
Fatigue	3 (9.7)	0
Renal insufficiency	2 (6.5)	1 (3.2)
Rash	1 (3.2)	0
Thrombocytopenia	1 (3.2)	1 (3.2)
Anorexia	1 (3.2)	0
Abdominal pain	1 (3.2)	0
Diarrhea	1 (3.2)	0
AST/ALT elevation	1 (3.2)	0
Interstitial lung disease combined with pulmonary edema	1 (3.2)	1 (3.2)

ALT, aspartate aminotransferase; ALP, alkaline phosphatase.
Data are presented as n (%).

Table 4. Summary of the Literature on Immune Checkpoint Inhibitor Monotherapy in Recurrent Gynecologic Cancers

Site	Phase	Drug	N	Rate of PD-L1 expression[†]	ORR	A/E >gr3	Study, reference	Year
Cervix	IB	Pembrolizumab 10 mg/kg q2w	24	100%	17%	5 (21%)	Keynote028[21]	2017
	II	Pembrolizumab 200 mg q3w	98	84%	12%	12 (12%)	Keynote158[8]	2019
	I/II	Nivolumab 240 mg q2w	19	63%	26%	4 (21%)	Checkmate358[22]	2019
	II	Nivolumab 3 mg/kg q2w	25	77%	4%	6 (24%)	NRG-GY002[23]	2020
Ovary	II	Nivolumab 1 or 3 mg/kg q2w	20	80%	15%	8 (40%)	[15]	2015
	IB	Pembrolizumab 10 mg/kg q2w	26	100%	12%	1 (4%)	Keynote028[16]	2019
	IB	Avelumab 10 mg/kg q2w	125	61%	10%	9 (7%)	JAVELIN[25]	2019
	II	Pembrolizumab 200 mg q3w	15	N/A*	33%	N/A	Keynote158[24]	2020
Endometrium	IB	Pembrolizumab 10 mg/kg q2w	24	100%	13%	4 (17%)	Keynote028[26]	2017
	II	Pembrolizumab 10 mg/kg q2w	15	N/A*	53%	N/A	[14]	2017
	II	Pembrolizumab 200 mg q3w	49	N/A*	57%	N/A	Keynote158[24]	2020

ORR, objective response rate; A/E, adverse event; N/A, non-available.
*All tumors showed either high microsatellite instability or mismatch repair deficiency, [†]Rate of ≥1 PD-L1 expression assessed using the combined positive score.

type of solid tumor, including gynecologic cancers. In the present study, we analyzed predictive factors for responses. No clinicopathologic factors, including tumor type, age, ECOG performance status, number of prior lines of chemotherapy, and PD-L1 status, predicted response (data not shown). This is probably because of the small number of patients and heterogeneous tumor group.

The limitations of this study include its retrospective design, small sample size, heterogeneous tumor types, and short follow-up period. Also, we did not perform a response evaluation based on immune RECIST or immune-related RECIST to assess the immune response. This could be regarded as a limitation of the retrospective study. Therefore, it is essential to prospectively collect clinical data of patients who receive ICI therapy according to each type of gynecological cancer from multiple centers.

Collectively, in real-world practice, pembrolizumab was feasible and effective in heavily treated recurrent gynecologic cancer patients with poor performance status who may not be eligible for enrollment in clinical trials. Further studies are warranted to discover predictive biomarkers for ICIs in gynecologic cancer.

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AUTHOR CONTRIBUTIONS

Conceptualization: Min Chul Choi, Yong Wha Moon, and Won Duk Joo. Data curation: all authors. Formal analysis: Min Chul Choi. Funding acquisition: Yong Wha Moon. Investigation: Min Chul Choi and Yong Wha Moon. Methodology: Min Chul Choi. Project administration: Min Chul Choi and Yong Wha Moon. Resources: Min Chul Choi. Software: Min Chul Choi. Supervision: Min Chul Choi, Yong Wha Moon, and Won Duk Joo. Validation: Min Chul Choi, Yong Wha Moon, and Won Duk Joo. Visualization: Min Chul Choi. Writing—original draft: Min Chul Choi and Yong Wha Moon. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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