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ORIGINAL RESEARCH

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Pembrolizumab monotherapy in heavily treated recurrent cervical cancer patients: case series report

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Abstract

This study aimed to evaluate the effectiveness of pembrolizumab among patients with recurrent cervical cancer. We retrospectively reviewed the medical records of patients diagnosed with recurrent cervical cancer and treated with pembrolizumab. Fixed does of pembrolizumab 200 mg was administered intravenously every three weeks. The primary endpoint was the objective response rate. In total, 14 patients were included in this study. Median number of pembrolizumab cycles was five (range, 1–28). The objective response rate was 28.6%, with one complete response and three partial responses. The treatment was generally well tolerated. None of the patients experienced treatment discontinuation or treatment-related death due to adverse events. Pembrolizumab monotherapy showed modest antitumor activity against recurrent cervical cancer. Pembrolizumab monotherapy is an alternative treatment option for patients with recurrent cervical cancer.

Keywords

Recurrent cervical cancer; Pembrolizumab; Immunotherapy; Immune checkpoint inhibitor

1. Introduction

Cervical cancer is one of the most common cancers worldwide [1]. In 2020, more than 600,000 women were newly diagnosed, and about 340,000 deaths were recorded [2]. In Korea, nearly 3000 new cases and 749 deaths are expected by 2022 [3]. Surgery with or without concurrent chemoradiation (CCRT) is the initial treatment for newly diagnosed cervical cancer [4]. Chemotherapy is currently the treatment of choice for recurrent or metastatic cervical cancer [5]. However, treatment options remain limited for patients who experience tumor progression after chemotherapy.

Immune checkpoint inhibitors have been studied as alternative therapies in cancer treatment, and programmed death protein-1 (PD-1) is one of the most commonly studied immune checkpoint proteins. Pembrolizumab, a monoclonal antibody targeting the PD-1 pathway, has shown promising results in recurrent and metastatic cervical cancer [6, 7]. Based on these results, in 2018, pembrolizumab was approved by the US Food and Drug Administration for patients with recurrent or metastatic cervical cancer. This study aimed to evaluate the effectiveness of pembrolizumab among patients with recurrent cervical cancer.

2. Materials and methods

We retrospectively reviewed the clinicopathological records of patients with recurrent cervical cancer who were treated with pembrolizumab between December 2018 and December 2022 at St. Vincent Hospital, Catholic University of Korea.

The inclusion criteria were as follows: (1) histologically confirmed adenocarcinoma, adenosquamous carcinoma, or squamous cell carcinoma; (2) tumor progression or recurrence after the use of platinum-based combination chemotherapy; and (3) administration of pembrolizumab for at least one treatment cycle. Fixed does of pembrolizumab 200 mg was administered intravenously every three weeks until disease progression.

Programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) 22C3 pharmDx assay was used to analyze tumor PD-L1 expression to determine the combined positive score (CPS). CPS was defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the number of all viable tumor cells, and multiplied by 100 [8]. CPS $\geq$1 was defined as positive PD-L1. Baseline imaging studies were performed before the administration of the first cycle of pembrolizumab.

Magnetic resonance imaging (MRI) and/or computerized tomography (CT) were performed after every 2–3 cycles of pembrolizumab. Treatment response was analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [9]. After 1–2 weeks of each cycle, the patient visited the outpatient clinic, and the adverse effects were recorded. Any possible adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [10].

The primary endpoint was the objective response rate

(ORR). Secondary endpoints were progression-free survival (PFS) and overall survival (OS). ORR was defined as the percentage of patients who have a complete response (CR) or partial response (PR). PFS was defined as the time from the initiation of pembrolizumab treatment to tumor progression and, if not, to the date of the last follow-up. OS was defined as the time from the start of pembrolizumab treatment to death and, if not, to the date of the last follow-up. Both PFS and OS were assessed using RECIST version 1.1.

3. Results

Fourteen patients were included in this study. The clinicopathological characteristics of patients are presented in Table 1.

The patient's initial stage varied from stage IB1 to IVB. Six patients were initially treated with concurrent chemoradiotherapy, and six were initially treated with radical hysterectomy. Two patients were initially treated with chemotherapy. All patients received at least one line of platinum-based combination chemotherapy with or without bevacizumab. Eleven patients (78.6%) were PD-L1 positive, and three patients (21.4%) were PD-L1 negative. Ten (71.4%) and four (28.6%) patients had squamous cell carcinoma and adenocarcinoma histologies, respectively.

The median follow-up time was 10 (range, 1–34) months. Thirteen of the 14 patients (92.9%) discontinued pembrolizumab treatment. Among the 13 patients, only one had CR. The median number of pembrolizumab cycles was five (range, 1–28). The treatment was generally well tolerated. None of the patients experienced treatment discontinuation or treatment-related death due to adverse events. Five patients received different chemotherapy regimens after discontinuing pembrolizumab.

The patients' responses to pembrolizumab are presented in Table 2. In the total population, one patient (7.1%) achieved CR, and three (21.4%) achieved PR. Three patients (21.4%) had stable disease (SD), and seven (50.0%) experienced disease progression. The ORR was 28.6%.

The characteristics of the four patients who responded to pembrolizumab are presented in Table 3. One patient achieved and maintained CR until the data cutoff date was reached. The remaining three patients initially had PR but eventually had disease progression.

Eleven of the 14 patients (78.6%) experienced disease progression, and 8 of the 14 patients (57.1%) had died at the time of data cutoff. The median PFS was 4 (95% confidence interval (CI) 1.5–6.5) months, and the median OS was 16 (95% CI 8.9–23.1) months (Fig. 1A–B).

4. Discussion

In Korea, the use of pembrolizumab is approved only if first-line chemotherapy fails. All patients in this study received at least one line of platinum-based combination chemotherapy with or without bevacizumab. Pembrolizumab is only approved as a single-agent treatment and not combined with other agents. Consequently, pembrolizumab has been attempted as a last option for heavily pretreated patients who lack alternative treatment options.

This study showed the efficacy of pembrolizumab monotherapy in patients who underwent substantial treatment for recurrent cervical cancer. The ORR was 28.6%, which was comparable to that reported in previous studies. Two clinical trials (KEYNOTE028 and KEYNOTE158) showed ORRs of 17% and 12%, respectively [6, 7]. A multicenter retrospective study showed a 19% ORR [11].

The efficacy of pembrolizumab monotherapy for recurrent cervical cancer was comparable to that of other chemotherapies. In previous clinical studies, cisplatin or carboplatin plus paclitaxel with or without bevacizumab showed the best response in recurrent or metastatic cervical cancer [12–15]. However, if these regimens fail, there are limited options for chemotherapy. Topotecan, ifosfamide, and gemcitabine were tested as single-agent chemotherapies [16–18], with ORRs of 19%, 14%, and 8%, respectively. These agents were also tested in combination with cisplatin in a phase 3 setting. Cisplatin plus topotecan achieved an ORR of 27% and was significantly better than cisplatin alone [19]. Cisplatin plus ifosfamide achieved an ORR of 31%, while cisplatin plus gemcitabine achieved an ORR of 22% [12, 20].

Although it is difficult to compare our results directly with those from well-designed clinical trials, this study showed similar antitumor activity of pembrolizumab in patients with recurrent cervical cancer.

Cisplatin or carboplatin plus paclitaxel chemotherapy with or without bevacizumab is considered the first-line therapy for recurrent cervical cancer [4]. These regimens achieved an ORR of 36% without bevacizumab, whereas an ORR of 48% was observed when bevacizumab was combined [5]. These rates are higher than that of pembrolizumab [6, 7]. However, compared to other conventional agents, such as topotecan, ifosfamide, and gemcitabine, which are administered in the second-line setting, the results of this study are reassuring. Moreover, pembrolizumab should be considered a second-line agent for recurrent cervical cancer, and for patients who are heavily treated with cytotoxic agents and lack alternative treatment options.

Results of KEYNOTE826 study showed modest antitumor activity of adding pembrolizumab to platinum-based combination chemotherapy as first-line therapy for recurrent cervical cancer [21]. Based on these results, pembrolizumab can be considered not only in the second-line setting, but also in the first-line therapy for recurrent cervical cancer.

This study has some limitations. It was a retrospective study with a relatively short follow-up period. Moreover, the number of patients enrolled may have been insufficient. Nevertheless, this study showed that pembrolizumab monotherapy is useful in patients with recurrent cervical cancer.

5. Conclusions

In conclusion, pembrolizumab monotherapy showed modest antitumor activity against recurrent cervical cancer in real-world practice. Pembrolizumab monotherapy is an alternative treatment option for patients with recurrent cervical cancer.

TABLE 1. Clinico-pathological characteristics of patients (n = 14).

Characteristic	Total (n = 14, %)
Age, years	
Median, range	50 (25–67)
Initial FIGO stage	
I	4 (28.6)
II	2 (14.3)
III	7 (50.0)
IV	1 (7.2)
Histology	
Squamous cell carcinoma	10 (71.4)
Adenocarcinoma	4 (28.6)
PD-L1 expression	
≤1	3 (21.4)
>1	11 (78.6)
Previous radiation therapy	13 (92.8)
Number of previous lines of chemotherapy	
1	7 (50.0)
2	5 (35.7)
3	1 (7.2)
≥4	1 (7.2)
Number of pembrolizumab cycles	
Median, range	5 (1–28)
Follow-up time (months)	
Median, range	10 (1–34)

FIGO: International Federation of Gynecology and Obstetrics; PD-L1: programmed death-ligand 1.

TABLE 2. Tumor responses to pembrolizumab (n = 14).

	Total (n = 14, %)
Best overall response	
CR	1 (7.2)
PR	3 (21.4)
SD	3 (21.4)
PD	7 (50.0)
Objective response rate	4 (28.6)
Disease control rate	7 (50.0)

CR: complete response; PR: partial response; SD: stable disease; PD: programmed death.

TABLE 3. Clinico-pathological characteristics of patients who respond to pembrolizumab (n = 4).

Patient no.	Histolog	Initial stage	PD-L1 expression	Number of pembrolizumab cycles	Best response	Final response	PFS, months	Ongoing treatment	Death
1	ACC	IB	positive	5	CR	CR	34	No	No
2	SCC	IIIC	positive	9	PR	PD	6	No	No
3	SCC	IIIC	positive	12	PR	PD	8	No	Yes
4	SCC	IIIC	positive	28	PR	PD	20	No	Yes

PD-L1: programmed death-ligand 1; PFS: progression-free survival; ACC: adenocarcinoma; SCC: squamous cell carcinoma; CR: complete response; PR: partial response; PD: programmed death.

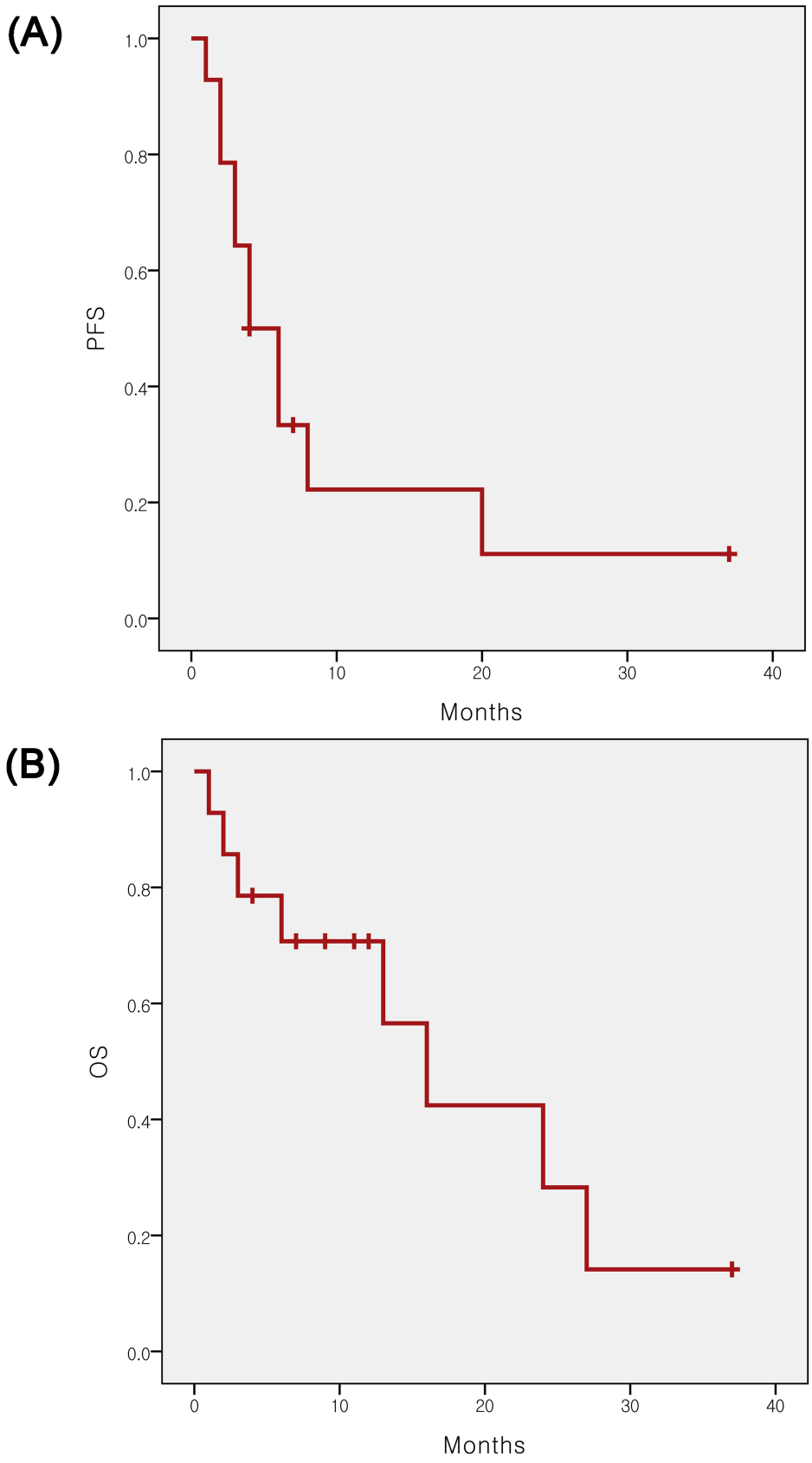

FIGURE 1. Survival outcomes (n = 14). (A) progression-free survival, (B) overall survival. PFS: progression-free survival; OS: overall survival.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author.

AUTHOR CONTRIBUTIONS

SIK—done the design of study and manuscript preparation; YG, JHY and DCP—done the reference collection. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the Institutional Review Board of the Catholic University of Korea (VC23RASI0040). The requirement for informed consent was waived owing to the retrospective nature of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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