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Lenvatinib plus Pembrolizumab Combination Therapy for Advanced or Recurrent Endometrial Cancer: A Single-Center, Retrospective Analysis

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A multi-kinase inhibitor, lenvatinib, plus an immune checkpoint inhibitor, pembrolizumab, became a viable therapeutic option for advanced or recurrent endometrial cancer in Japan by the end of 2021. The Japanese population has a relatively unique genetic background. Hence, the safety profile and effectiveness of lenvatinib plus pembrolizumab may differ between the Japanese and other populations. This single-center, retrospective study aimed to evaluate the treatment efficacy of lenvatinib plus pembrolizumab and the safety profile of the associated adverse events. The clinical records of 15 patients, who received lenvatinib plus pembrolizumab for advanced or recurrent endometrial cancer at the Tohoku University Hospital, were reviewed. Best overall response and disease control rates were 40.0% and 73.3%, respectively. Treatment was discontinued owing to disease progression and adverse events in six patients, respectively. As of the end of July 2023, treatment was ongoing in the remaining three patients. The median treatment and progression-free survival durations were 118 and 258 days, respectively. Relative dose intensity of lenvatinib was not positively associated with progression-free survival, neither during the first 4 weeks after treatment initiation nor during the entire treatment period. All patients experienced one or more adverse events, the most common of which were hypothyroidism (90%) and hypertension (83.3%). Among the 15 patients, 13 required lenvatinib dose reduction owing to adverse events. One patient developed grade 4 interstitial pneumonia requiring intensive care. Our results validate the short-term efficacy of lenvatinib plus pembrolizumab, and indicate that dose optimization of lenvatinib could be individualized without impairing efficacy.

Keywords: combination therapy; endometrial cancer; lenvatinib; pembrolizumab; relative dose intensity
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Introduction

Endometrial cancer (EC) is the most frequently observed gynecological malignancy in Japan. The number of patients with EC in Japan is increasing annually, and 17,880 cases were reported in a nationwide surveillance in 2019 (National Cancer Center Japan 2023). More than half of the patients were diagnosed with stage IA diseases, many of which were curable by either surgery or surgery combined with adjuvant therapy (Shigeta et al. 2017; Yoshino et al. 2022; Hasegawa-Minato et al. 2023). On the other hand, systemic chemotherapy is the standard therapeutic strategy for patients with advanced or recurrent EC that can neither be controlled with surgery nor radiotherapy. Doxorubicin and cisplatin (AP) combination therapy is the first-line treatment for such patients (Thigpen et al. 2004; Randall et al. 2006). While the Gynecologic Oncology Group 177 trial demonstrated that paclitaxel plus AP (TAP) improved overall survival (OS) compared to that with AP alone, TAP has not been considered as a standard chemotherapy option

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for every patient because of its neurotoxic effects (Fleming et al. 2004). Paclitaxel and carboplatin (TC) combination therapy and AP are widely used as a front-line therapy for advanced or recurrent EC in Japan (Hoskins et al. 2001; Nomura et al. 2011). A direct comparison between AP and TC is yet to be performed; however, the non-inferiority of TC to TAP has been demonstrated in clinical trials (Miller et al. 2020).

Patients with advanced or recurrent EC commonly develop chemoresistance, regardless of the regimen. The absence of effective therapeutic options has resulted in a poor prognosis for these patients. Notably, in Japan, the 5-year OS of stage IV patients with EC is approximately ≤ 30%, without improvement (Nagase et al. 2021; Yoshino et al. 2022).

However, the situation is changing after the approval of pembrolizumab, an immune checkpoint inhibitor (ICI). The phase II KEYNOTE-158 Study reported the clinical benefits of pembrolizumab in patients with non-colorectal solid cancers, including EC with mismatch repair (MMR) deficiency (Marabelle et al. 2020; O'Malley et al. 2022). Notably, approximately 17% of the tumors in patients with EC were MMR deficient, which was the highest among the 12 different tumor types (Le et al. 2017). Subsequently, the Study 309/KEYNOTE-775 trial reported the advantage the lenvatinib (a multi-kinase inhibitor) plus pembrolizumab combination therapy on OS over that of conventional second-line chemotherapies in patients with advanced or recurrent EC, regardless of MMR status (Makker et al. 2022). Based on these results, lenvatinib plus pembrolizumab was made available to patients with advanced or recurrent EC, under public health insurance coverage in Japan in December 2021.

While the prognosis of patients with advanced or recurrent EC is expected to be improved with lenvatinib plus pembrolizumab, clinicians need to appropriately manage the associated adverse events (AEs), which differ from those of conventional cytotoxic anticancer agents. Severe immune-related AEs often require immediate primary and intensive care provided by multi-disciplinary teams. Clinicians need to distinguish between immune- and lenvatinib-related AEs, as some AEs, such as liver dysfunction, proteinuria, and diarrhea, are commonly induced by both lenvatinib and pembrolizumab.

Genetic polymorphisms are associated with drug metabolism (Belle and Singh 2008). The Japanese population, with its oceanic island ethnicity, has a relatively unique genetic background compared with that of other countries or regions. Hence, the safety profile and effectiveness of lenvatinib plus pembrolizumab may differ between the Japanese and other populations, as indicated in a subpopulation analysis in the Study 309/KEYNOTE-775 trial that enrolled Japanese patients (Makker et al. 2022; Yonemori et al. 2022). The safety and effectiveness of lenvatinib plus pembrolizumab in the Japanese population must be verified using real-world data. Therefore, in this study, we retrospectively assessed the short-term treatment outcomes and profiles of AEs at our institute. Furthermore, we narratively reviewed an informative case series of some AEs.

Methods

Study design, setting, and participants

Patients diagnosed with advanced or recurrent EC and initiated on lenvatinib plus pembrolizumab at the Tohoku University Hospital, by the end of December 2022, were eligible to participate in this single-center, retrospective study. Patients with endometrial carcinosarcoma were also eligible for this study because carcinosarcoma is currently considered an aggressive subtype of EC and is treated with similar strategies (Yamagami et al. 2020). The standard dose of lenvatinib was 20 mg per day orally and that of pembrolizumab was 200 mg per body intravenously every 3 weeks.

Ethical considerations

This study was approved by the Institutional Review Board of the Tohoku University School of Medicine (approval number: 2023-1-045), and conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived owing to the retrospective nature of the study.

Methodological considerations

Patient information included age, height, and body weight at the time of lenvatinib plus pembrolizumab induction, International Federation of Gynecology and Obstetrics (FIGO) 2008 stage, treatment duration, post-induction progression-free survival (PFS), number of prior chemotherapy regimens, and hematologic and non-hematologic AEs of any grade recorded during the treatment period. MMR status in tumors was collected as well. In this study, MMR was assessed by either mismatch repair analysis or comprehensive genomic analysis. Estimated body surface area was calculated using the DuBois formula. Tumor response was evaluated in accordance with the immune response evaluation criteria in solid tumors (Seymour et al. 2017). Relative dose intensity (RDI) for lenvatinib was calculated by dividing the delivered dose intensity (DDI) with the standard dose intensity (SDI). The DDI was determined by multiplying the number of days of treatment by the corresponding daily-delivered dose. The SDI was determined by multiplying the number of days of treatment with the standard dose of lenvatinib (20 mg/body).

Statistical analysis

Survival assessment was performed using the Kaplan–Meier method. The Mann–Whitney U test was used for the comparison of PFS between two groups. Two-sided P values < 0.05 was considered significant. All statistical analyses were performed using the GraphPad Prism 8.4.3 (GraphPad Software, Boston, MA, USA).

Results

Patient characteristics

Fifteen patients were enrolled in this study. Patient characteristics are summarized in Table 1. The detailed clinical background is also summarized in Table 2. The median age was 66 years. Fourteen patients were diagnosed with recurrent EC who underwent hysterectomy at their primary surgery. The remaining one patient was diagnosed with advanced EC, whose primary disease was unresectable. One of the nine patients examined was MMR deficient. The number of previous chemotherapy regimens ranged from one to three. Eight patients with recurrent EC received lenvatinib plus pembrolizumab as first-line treatment after the recurrence.

Therapeutic outcomes

Fig. 1 summarizes the treatment duration of the 15 patients with sequential results of the tumor response evaluation and lenvatinib dose. The median follow-up period was 340 days (range: 140-510). The median treatment period with lenvatinib plus pembrolizumab, and the median PFS after lenvatinib plus pembrolizumab induction were 118 (35-510) and 258 (53-510) days, respectively. Fig. 2 illustrates the Kaplan–Meier curve for PFS. Regarding the association between clinical parameters shown in Table 1 and PFS, nine patients who had been treated with one previous chemotherapy regimen tended to exhibit longer PFS than the other six patients treated with two or three previous chemotherapy regimens, although no statistical differences were observed ($P = 0.4374$, Fig. 3).

Lenvatinib plus pembrolizumab was discontinued owing to disease progression and AEs in six patients, respectively. Of the six patients who discontinued treatment because of AEs, two experienced disease progression at day 112 (Patient #8 in Fig. 1) and 9 (Patient #6 in Fig. 1) from the day of treatment discontinuation, respectively, whereas four patients had no disease progression on follow-up, as of July 2023. The treatment was ongoing in the remaining three patients, as of the end of July 2023. Among these, one patient (Patient #1 in Fig. 1) had mismatch repair-deficient tumor. She discontinued lenvatinib because of grade 2 hypertension and was being treated with pembrolizumab monotherapy, with no disease progression.

Sequential tumor regression analysis of the 15 patients is summarized in Fig. 4. One and five patients exhibited complete and partial responses, respectively, to lenvatinib plus pembrolizumab. Four patients experienced disease

Table 1. Patient characteristics.

Parameters	Median (Range)
Age (years)	66 (37-78)
BMI (kg/m^2)	20 (16.4-34.5)
Body surface area (m^2)	1.52 (1.178-2.02)
Parameters	**No. of patients (%)**
Stage (FIGO2008)	
I	5 (33.3)
II	0 (0)
III	4 (26.6)
IV	6 (40)
Histology	
Endometrioid carcinoma (Grade1/2)	2 (13.3)
Endometrioid carcinoma (Grade3)	4 (26.6)
Serous carcinoma	6 (40)
Mixed cell carcinoma	2 (13.3)
Carcinosarcoma	1 (6.6)
MMR status	
pMMR	8 (53.3)
dMMR	1 (6.6)
Not inspected	6 (40)
Previous chemotherapy regimen	
1	9 (60)
2	4 (26.6)
3	2 (13.3)

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair; pMMR, mismatch repair-proficient; dMMR, mismatch repair-deficient.

Table 2. Summary of the clinical information of the 15 patients enrolled.

Patient number*	BMI (kg/m^2)	Stage (FIGO2008)	Histology	MMR status	Primary surgery	Treatment-free interval before lenvatinib and pembrolizumab introduction	No. of previous chemotherapy lines	Disease localization at the time of lenvatinib plus pembrolizumab introduciton
1	16.4	IB	Endometrioid carcinoma (Grade3)	dMMR	Yes	263	1	brain, lung
2	25.4	IIIC1	Endometrioid carcinoma (Grade1)	pMMR	Yes	403	1	lung
3	33.5	IB	Endometrioid carcinoma (Grade3)	Not inspected	Yes	869	1	lung
4	34.5	IVB	Endometrioid carcinoma (Grade1)	pMMR	Yes	23	2	lung, peritoneum, lymph node
5	18.6	IIIB	Serous carcinoma	pMMR	Yes	108	1	vagina
6	18.6	IB	Carcinosarcoma	Not inspected	Yes	392	2	lung, lymph node
7	19.9	IVB	Serous carcinoma	pMMR	Yes	0	3	bone, lymph node
8	18.5	IVB	Serous carcinoma	pMMR	No	0	1	uterus, ovary, bone, lymph node
9	20.2	IIIC1	Serous carcinoma	pMMR	Yes	129	2	lymph node
10	19.5	IB	Serous carcinoma	pMMR	Yes	945	2	lung
11	31	IVB	Endometrioid carcinoma (Grade3)	Not inspected	Yes	0	1	vagina, lymph node
12	17.1	IVB	Endometrioid carcinoma (Grade3)	Not inspected	Yes	0	1	lymph node
13	29.9	IVB	Mixed cell carcinoma	Not inspected	Yes	182	3	peritoneum, lymph node
14	20	IIIC2	Mixed cell carcinoma	pMMR	Yes	135	1	lymph node
15	23	IA	Serous carcinoma	Not inspected	Yes	1,635	1	peritoneum

*Patient number corresponds to information in Fig. 1.

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair; pMMR, mismatch repair-proficient; dMMR, mismatch repair-deficient.

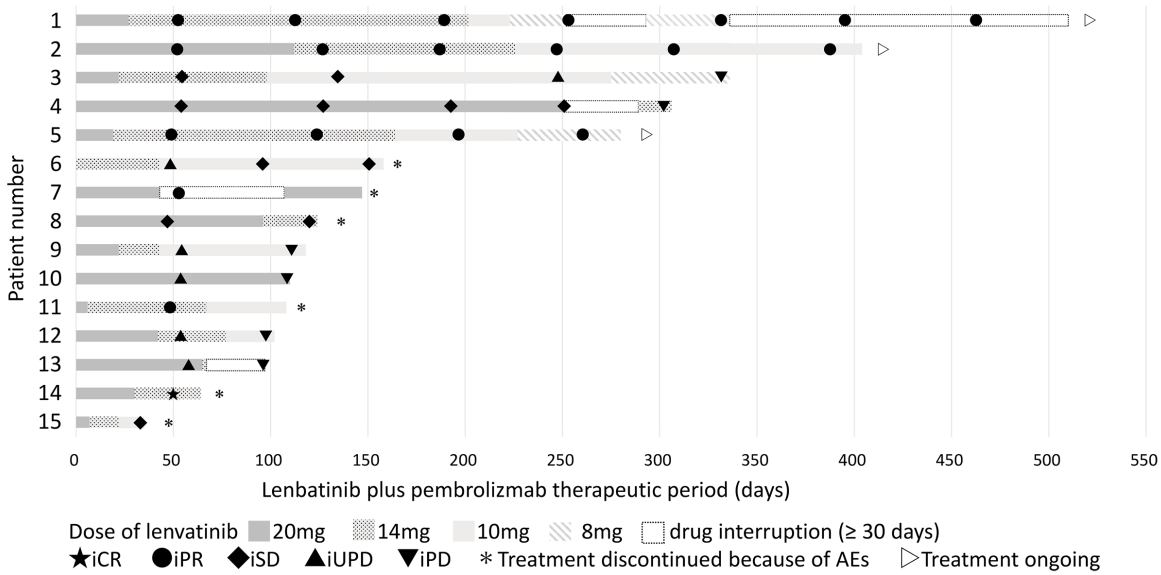

Fig. 1. Patient treatment course.
A summary of the treatment duration of the 15 enrolled patients based on the sequential results of the tumor response evaluation and lenvatinib dose. Tumor response was evaluated in accordance with the immune response evaluation criteria for solid tumors. Drug interruptions ≥ 30 days are indicated in unshaded/white boxes. iCR, immune complete response; iPR, immune partial response; iSD, immune stable disease; iUPD, immune unconfirmed progressive disease; iPD, immune progressive disease; AE, adverse event.

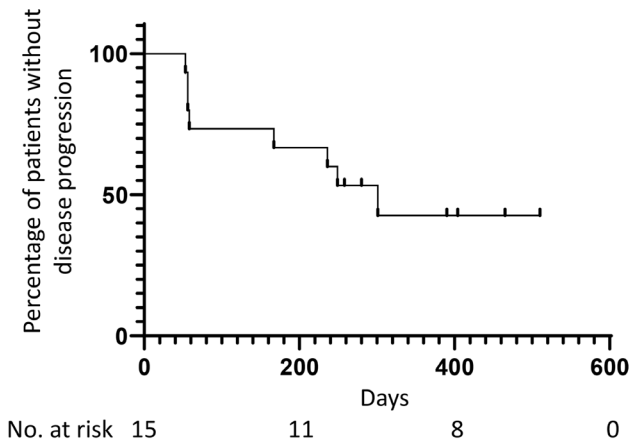

Fig. 2. Progression-free survival.
Progression-free survival curve as determined by the Kaplan–Meier method.

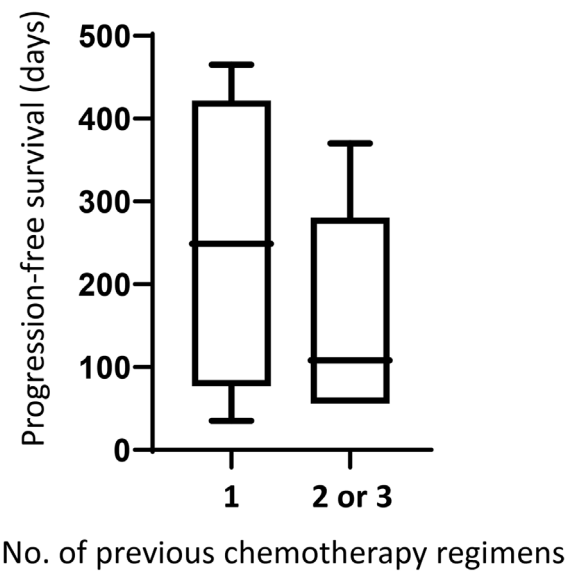

Fig. 3. Progression-free survival based on prior therapy.
Progression-free survival was compared between the patients treated with one previous chemotherapy regimen and those treated with two or three previous regimens. The number of the previous chemotherapy regimens corresponds to that summarized at the bottom of Table 1. The Mann–Whitney U test was applied for the statistical comparison.

progression without temporary cancer regression. Overall response and disease control rates in the 15 patients were 40.0% and 73.3%, respectively.

Relative dose intensity for lenvatinib

As regards lenvatinib administration, all 15 patients required AE-related treatment interruptions. Of these, 13 patients required lenvatinib dose reduction. Lenvatinib dose transition is presented in Fig. 1. Of the 15 patients, the primary administration dose of lenvatinib was set at 14 mg/day for one patient, at the physician's discretion, and at 20 mg/day for the others. Furthermore, we assessed the relationship between the RDI and PFS in all patients. As depicted in Fig. 5, the RDI of neither the first 4 weeks nor the entire treatment period was positively associated with PFS.

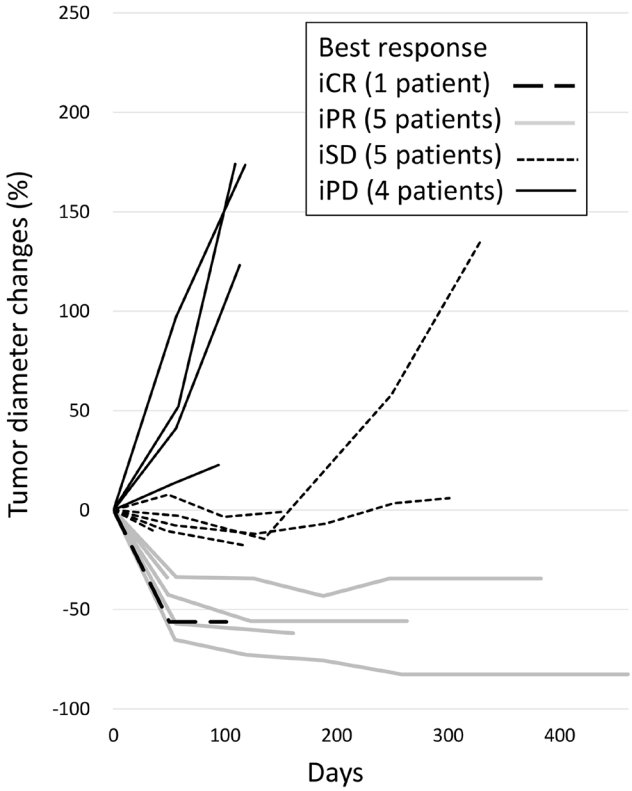

Fig. 4. Tumor diameter changes.
Sequential changes in tumor diameter observed in the 15 enrolled patients after initiating lenvatinib plus pembrolizumab combination therapy. Tumor response was evaluated in accordance with the immune response evaluation criteria for solid tumors (iRECIST). The y-axis exhibits the percent change in the sum of the diameters of the target lesions, defined by iRECIST from baseline. The percentage change was not 100% in a patient who experienced iCR because the target lesion included lymph node metastasis. iCR, immune complete response; iPR, immune partial response; iSD, immune stable disease; iPD, immune progressive disease.

Summary of AEs

The AEs observed during the study period are summarized in Table 3. All patients experienced at least one AE, the most frequent of which hypothyroidism (93.3%) and hypertension (80%). When limited to grade 3 or 4 AEs, hypertension was the most common (40%), followed by liver dysfunction, proteinuria, fatigue, and appetite loss. The AEs associated with dose reduction were as follows: hypertension (n = 4), liver dysfunction (n = 3), thrombocytopenia (n = 3), hand-foot syndrome (n = 3), diarrhea (n = 3), proteinuria (n = 2), fatigue (n = 2), weight loss (n = 2), and anorexia (n = 2). The AEs associated with treatment discontinuation in six patients are summarized in Table 4. In patient #8, the treatment was discontinued because of grade 1 interstitial pneumonia, taking her general condition into account.

Report of two cases with serious AEs

Herein, we describe two cases of severe immune-related AEs. The first patient, a woman in her 50s, had stage IVB advanced EC (Patient #11 in Fig. 1). Lenvatinib plus pembrolizumab was initiated as second-line chemotherapy, and the response was partial. She visited our hospital on the 108th day after lenvatinib plus pembrolizumab initiation, with a complaint of persistent dyspnea in the last 7 days. Computed tomography revealed diffuse ground-glass opacities in both lungs (Fig. 6). Grade 4 interstitial pneumonia (IP) was diagnosed. Lenvatinib or pembrolizumab were suspected of causing the pneumonia. The patient received intensive respiratory management, non-invasive positive pressure ventilation, and steroid pulse therapy in the intensive care unit for 10 days. She recovered and was discharged after 37 days of hospital stay. Considering the risk of IP recurrence, the combination therapy was discontinued after a consensus between the patient and clinicians. Follow-up at the end of July 2023, approximately 10 months post-discontinuation of lenvatinib plus pembrolizumab, revealed no progression of residual dis-

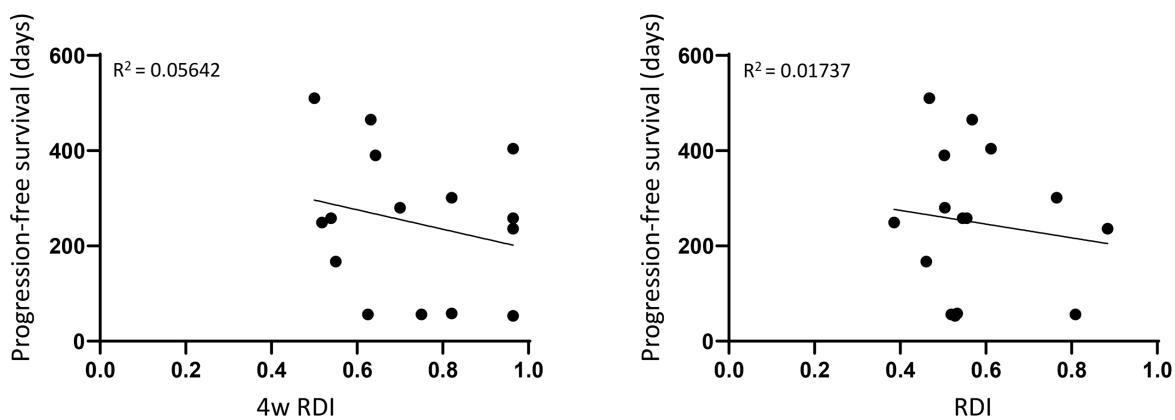

Fig. 5. Progression-free survival and relative dose intensity.
Correlation between progression-free survival (PFS) and relative dose intensity (RDI) of lenvatinib in the first 4 weeks after lenvatinib plus pembrolizumab or RDI of lenvatinib during the entire treatment period is demonstrated using scatter plots. R, correlation coefficient; 4w RDI, RDI in the first 4 weeks after lenvatinib plus pembrolizumab induction.

Table 3. Summary of adverse events.

Adverse effects	No. of patients (%)	
	All grades	Grade 3/4
Hypothyroidism	14 (93.3)	0 (0)
Hypertension	12 (80.0)	6 (40.0)
Thrombocytopenia	10 (66.6)	2 (13.3)
Liver dysfunction	9 (60.0)	4 (26.6)
Fatigue	8 (53.2)	4 (26.6)
Loss of appetite, anorexia	6 (40.0)	4 (26.6)
Fever	6 (40.0)	0 (0)
Hand-foot syndrome	6 (40.0)	2 (13.3)
Proteinuria	5 (33.3)	4 (26.6)
Renal impairment	4 (26.6)	0 (0)
Diarrhea	4 (26.6)	0 (0)
Electrolyte imbalance	3 (20.0)	2 (13.3)
Skin symptoms, other than hand-foot syndrome	3 (20.0)	0 (0)
Interstitial pneumonia	2 (13.3)	1 (6.6)
Thromboembolism	2 (13.3)	0 (0)
Hypoadrenocorticism	1 (6.6)	1 (6.6)
Ataxia	1 (6.6)	1 (6.6)

Table 4. Adverse events associated with treatment discontinuation.

Patient number*	Adverse events associated with treatment discontinuation
6	Loss of appetite (Grade 3), fatigue (Grade 3)
7	Hand-foot syndrome (Grade 3), erythema multiforme major (Grade 2)
8	Interstitial pneumonia (Grade 1)
11	Interstitial pneumonia (Grade 4)
14	Liver dysfunction (Grade 4)
15	Fatigue (Grade 3), ataxia (Grade 3)

*Patient number corresponds to information in Fig. 1.

ease.

The second patient, a woman in her 60s, had recurrent EC (Patient #2 in Fig. 1). Levothyroxine sodium hydrate was administered following a diagnosis of grade 2 hypothyroidism during the third cycle of pembrolizumab. On the 247th day after lenvatinib plus pembrolizumab initiation, blood analysis revealed severe hypocortisolism, accompanied by decreased adrenocorticotropic hormone levels (Fig. 7). A detailed medical interview revealed that she had been experiencing grade 3 anorexia and grade 3 fatigue in the last 2 weeks before the hospital visit. Following as diagnosis of grade 3 secondary hypocortisolism, adrenocorticotropic hormone replacement therapy was initiated, and the patient's symptoms resolved immediately. Treatment with lenvatinib plus pembrolizumab was resumed without dose reduction.

Discussion

This retrospective study assessed the clinical outcomes of 15 patients diagnosed with advanced or recurrent EC and treated with lenvatinib plus pembrolizumab. Although this was a small-scale study with a relatively short observational period, the observed response rate and PFS indicated the benefits of lenvatinib plus pembrolizumab for advanced or recurrent EC in the Japanese population. Although the Study 309/KEYNOTE-775 did not include patients with endometrial carcinosarcoma, carcinosarcoma is now considered as an aggressive subtype of EC and clinically treated in the same manner as EC. A retrospective study reported the response rate to lenvatinib plus pembrolizumab, which was similar to that in the Study 309/KEYNOTE-775 trial, among patients with carcinosarcoma (How et al. 2021). Although further study is warranted, it is considered feasible to apply lenvatinib plus pembrolizumab for patients with endometrial carcinosarcoma.

Maintaining a high RDI is considered important for improving patient prognosis in the treatment of liver cancer with lenvatinib monotherapy (Kirino et al. 2020). Several studies have reported the association between RDI of multikinase inhibitor monotherapy, including lenvatinib, and cancer treatment prognosis (Kawashima et al. 2011; Hirano et al. 2015; Nakano et al. 2019). In contrast, the results of

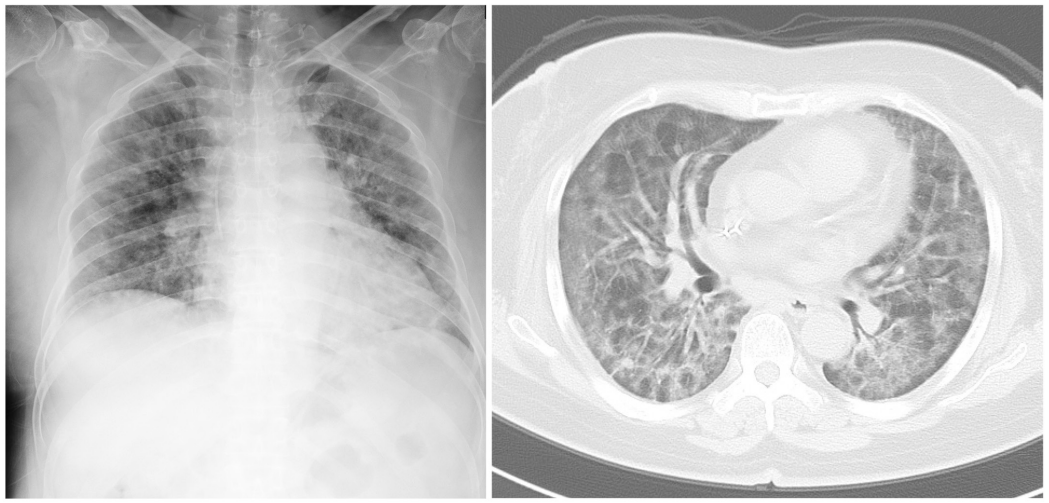

Fig. 6. Clinical images of the patient with interstitial pneumonia.
Chest radiography and computed tomography images obtained at the time of admission (Patient #11 in Fig. 1).

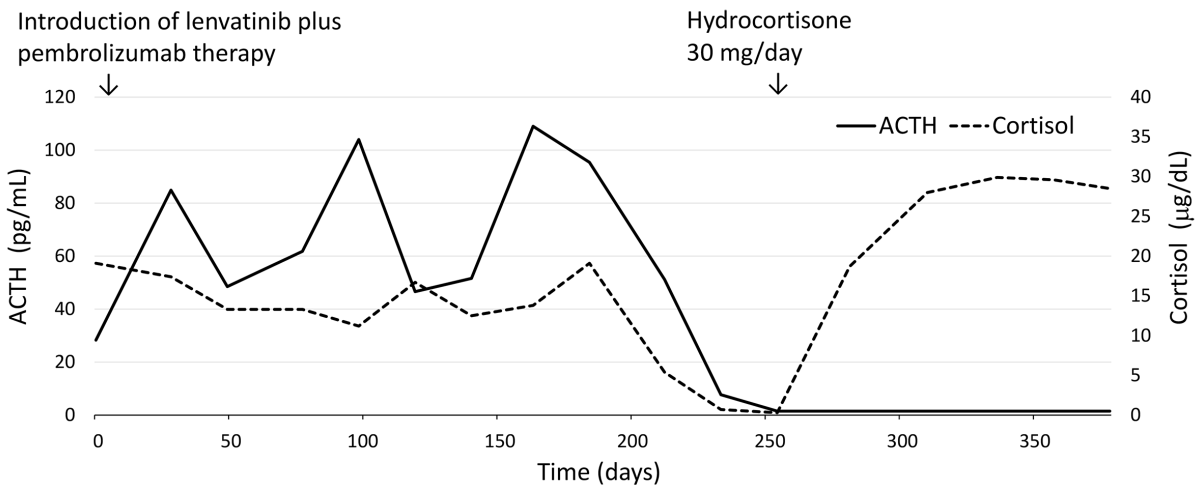

Fig. 7. Adrenocorticotropic hormone and cortisol changes in serum.
Consecutive changes in serum adrenocorticotropic hormone (ACTH) and cortisol levels are summarized (Patient #2 in Fig. 1). The reference ranges of ACTH and cortisol in our institution were 7.2-63.3 pg/mL and 4.5-21.1 μg/dL, respectively.

our study did not indicate an association between lenvatinib RDI and PFS. Switching of cancer cells from "immune desert" to inflamed tumors is a suggested mechanism of action of lenvatinib (Kimura et al. 2018; Kato et al. 2019). This indicates that the mechanisms of action of lenvatinib plus pembrolizumab in the treatment of EC differ from those of lenvatinib monotherapy. Furthermore, a phase III clinical trial that examined the clinical benefits of pazopanib (a multi-kinase inhibitor), reported that the East Asian population required more frequent dose modifications owing to certain AEs than other populations (du Bois et al. 2014). This implies the unique pharmacogenetics of multi-kinase inhibitors in the East Asian population. Altogether, it is possible that the dose of lenvatinib, in combination with pembrolizumab, can be optimized according to patient characteristics without impairing curability. At the same time, it should be noted that large-scale multicenter studies are needed to clarify the dose optimization of lenvatinib in combination with pembrolizumab, in the treatment of EC in this population.

In a sub-analysis of the Study 309/KEYNOTE-775 trial, the hazard ratio was significantly lower in the lenvatinib plus pembrolizumab arm than that in the chemotherapy arm, among patients with a single prior chemotherapy regimen. However, no statistically significant difference between patients with two or more prior chemotherapy regimens were reported (Makker et al. 2022). Although no statistically significant difference was observed in our study, the results illustrated in Fig. 3 are consistent with those of the aforementioned trial. Although not in combination with lenvatinib, KEYNOTE-158 Study reported higher overall response rate to pembrolizumab monotherapy among

patients who had received less than two lines of prior therapy than those who received two or more lines of prior therapy, which supports earlier introduction of pembrolizumab (O'Malley et al. 2022). Altogether, we consider it possible that lenvatinib plus pembrolizumab may be more beneficial if introduced immediately after the failure of the first-line chemotherapy, similar to that of pembrolizumab monotherapy.

Aggressive histologic subtypes, such as serous, clear, or carcinosarcoma, have a risk of recurrence (Cirisano et al. 2000; Sakuragi et al. 2000; Maggino et al. 2015). Less-aggressive, estrogen-related EC, such as Grades 1 or 2 are commonly observed in patients aged 40-50 years, whereas aggressive histologic EC is more frequent in patients aged ≥ 60 years (Brinton et al. 2013; Shigeta et al. 2017). This suggests that lenvatinib plus pembrolizumab therapy is more frequently applied to older patients who may have pre-existing comorbidities, are less tolerable to AEs, and are at a higher risk of treatment-related morbidity than younger patients. Notably, only two of the 15 patients in our study presented with low-risk histologic subtypes. Furthermore, the median age of the patients was 66 years, in contrast to the fact that the incidence rate per 100,000 individuals is the highest among Japanese women aged-55-59 years (National Cancer Center Japan 2023). Considering the several severe AEs observed in our study, tolerability of lenvatinib plus pembrolizumab should be carefully determined according to age, performance status, and pre-existing comorbidities. From this perspective, comprehensive geriatric assessment (CGA) might help clinicians to assess tolerability in a multifaceted approach (Owusu and Berger 2014). CGA has been developed to quantify the status of older patients from multiple aspects such as activity of daily living, nutrition, and cognitive and social function. An objective evaluation with CGA in combination with other clinical information might be an informative indicator for the administration of lenvatinib plus pembrolizumab to older patients.

Appropriate management of AEs during lenvatinib plus pembrolizumab treatment is crucial for safe and effective cancer treatment. As some AEs were less likely discovered with blood analysis data, clinicians should comprehensively and periodically assess the condition of patients through detailed medical interviews, physical examination, as well as routine laboratory data analysis. Furthermore, patient education is important for the early detection of severe AEs. In particular, ICIs are not widely used in patients with gynecologic malignancies. Clinicians should be familiar with the management of immune-related AEs (irAEs) and patients should be provided with sufficient information regarding irAEs.

In addition, we encountered several cases of successful disease control without disease progression for a certain period after the discontinuation of lenvatinib plus pembrolizumab. Although treatment discontinuation should be carefully decided according to the severity of AEs, our experience indicates the merit of the proactive lenvatinib plus pembrolizumab induction in the treatment of recurrent or advanced EC.

The AE profile in this study was similar to that in the Study 309/KEYNOTE-775 trial (Yonemori et al. 2022). However, the frequency of hypothyroidism was higher in our study (93.3%) than that in the Study 309/KEYNOTE-775 trial (57.4%) (Makker et al. 2022). Our data, in conjunction with the sub-analytic results of the Study 309/KEYNOTE-775 focusing on Japanese participants (Yonemori et al. 2022), indicate that the Japanese population may likely develop hypothyroidism with lenvatinib plus pembrolizumab administration.

Our study's small scale—comprising only 15 patients—and the short observational period were its limitations. Therefore, large-scale, multicenter, longitudinal studies are needed to further validate the effectiveness of lenvatinib plus pembrolizumab administration in Japanese patients with advanced or recurrent EC.

In conclusion, we have demonstrated the short-term efficacy and AE profile of lenvatinib plus pembrolizumab in Japanese patients with advanced or recurrent EC. Future studies should address dose optimization for the appropriate management of AEs, in association with RDI, and the underlying pharmacogenetics in the Japanese population.

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Conflict of Interest

The authors declare no conflict of interest.

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