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ORIGINAL RESEARCH

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Combining lenvatinib and pembrolizumab for the management of endometrial carcinosarcoma: a retrospective case series

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Abstract

Uterine cancer is a prevalent gynecological malignancy globally. Endometrial carcinosarcomas constitute a rare and aggressive subtype of uterine malignancy. In recent years, immunotherapy has emerged as a treatment option after the failure of platinum-based chemotherapy. This case series explores the use of pembrolizumab and lenvatinib in treating endometrial carcinosarcoma. This retrospective case series was conducted at a single tertiary care center in northern New Jersey, United States, and included patients seen between 2019 and 2023 who had confirmed uterine carcinosarcoma treated with pembrolizumab and lenavatinib. Patient demographics, oncologic characteristics, and details of immunotherapy were extracted from electronic medical records (Epic). Statistical analysis included survival analysis for progression-free survival (PFS) and overall survival (OS). A total of eight patients with endometrial carcinosarcoma, microsatellite stable, were treated with pembrolizumab plus lenvatinib and included in the case series. All patients received cytoreductive surgery and chemotherapy with carboplatin plus paclitaxel. The median follow-up duration with the oncologist was 5.6 months (IQR (Interquartile range): 3.5, 9.0). OS ranged from 0.4 to 19.3 months. One patient was excluded from the OS analysis due to a loss of follow-up. The median PFS was 3.6 months (IQR: 1.8, 4.4). This case series provides valuable insight into applying pembrolizumab and lenvatinib as a second-line treatment for endometrial carcinosarcoma after the failure of platinum-based chemotherapy. The observed improvements in PFS and OS, coupled with manageable side effects, highlight the potential efficacy of this treatment.

Keywords

Lenvatinib; Pembrolizumab; Endometrial carcinosarcoma; Immunotherapy

1. Introduction

Uterine cancer, primarily attributed to endometrial cancer, stands as the second most prevalent gynecological cancer worldwide, with an annual incidence of approximately 1 to 2% among women in the United States [1, 2]. The incidence and mortality of endometrial cancer have been increasing over the past four decades [3, 4]. The prognosis of endometrial cancer depends on staging, grade, histology and various subtypes. Poor outcomes are often associated with late stages, higher grades and specific histologies such as serous and clear cell [5–7]. Endometrial carcinosarcomas, also known as malignant mixed Müllerian tumors, constitute a rare and aggressive subtype of uterine malignancy, accounting for roughly 5% of all uterine cancers. Despite their relatively low frequency, they disproportionately contribute to a greater proportion of mortality in uterine malignancies [7]. These tumors are poorly differentiated and characterized by distinct malignant epithelial and mesenchymal components [8]. Their recurrence and metastasis patterns closely resemble that of carcinoma rather than sarcoma. Notably, carcinosarcomas generally manifest poorer outcomes compared to other subtypes such as endometrioid, clear cell, and serous carcinomas [9].

The management of endometrial carcinosarcomas involves a comprehensive approach encompassing surgical procedures for staging, systemic therapy and radiation therapy [10]. In regards to systemic therapy, the current standard aligns with the treatment paradigm for non-endometrioid high-grade endometrial carcinosarcoma [4, 11]. Chemotherapy utilizing paclitaxel and carboplatin is recommended [4, 12]. However, despite timely and adjuvant multimodal therapy, more than half of endometrial carcinosarcoma cases experience recurrence within the first 2 years [13]. In recent years, immunotherapy has emerged as the standard treatment modality after the failure of platinum-based chemotherapy and might be introduced earlier in regimens for de novo metastatic patients. However, patients

who underwent adjuvant therapy for endometrial carcinosarcoma still receive first-line therapy of carboplatin and paclitaxel without immunotherapy [4, 7, 10, 14].

For endometrial cancers, molecular analysis has unveiled various clinically significant molecular subgroups with distinct clinical prognoses, such as microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient (dMMR) and p53 abnormality. Pembrolizumab, a selective humanized immunoglobulin G4 (IgG4) kappa monoclonal antibody that inhibits the programmed death ligand 1 (PD-L1) receptor, is approved alongside lenvatinib, an oral multikinase inhibitor, for metastatic non-MSI-H/dMMR advanced endometrial cancer after prior treatments have failed [15, 16]. However, its application in endometrial carcinosarcoma remains an emerging domain awaiting further study. Our study aimed to present a case series on the treatment efficacy of pembrolizumab and lenvatinib after the failure of first-line carboplatin and paclitaxel chemotherapy in patients with uterine carcinosarcoma.

2. Method

This retrospective case series took place at Englewood Hospital and Medical Center, a single tertiary care facility in New Jersey, USA, spanning from 2019 to 2023. The research focused on women diagnosed with uterine carcinosarcomas who received treatment combining pembrolizumab and lenvatinib. Eligible participants were those with a confirmed diagnosis of uterine carcinosarcoma determined by final surgical pathology and who underwent the specified combined therapy.

The patient data were extracted from the electronic medical record system (Epic) and encompassed information such as age, race, body mass index (BMI) and existing medical conditions. Oncological attributes retrieved included the cancer stage at initial diagnosis and at the commencement of immunotherapy, primary cancer treatments administered, initial surgical interventions, previous treatment regimens, PD-L1 status (positive or negative), and MMR status (proficient or deficient). Positive PD-L1 status was defined as the presence of membranous staining in at least 1% of viable tumor cells. Immunotherapy-related variables comprised initiation and conclusion dates, cycle counts, reasons for treatment cessation, the necessity of steroid administration during immunotherapy, dates of disease progression or recurrence, last follow-up with the oncologist, current clinical status and mortality dates.

In the statistical analysis, continuous variables were represented using medians and interquartile ranges due to the non-normal distribution of the data. Categorical factors and ordinal variables were described using frequencies and percentages. The primary outcomes assessed were progression-free survival (PFS) and overall survival (OS). PFS was defined as the duration from the initiation of immunotherapy to the occurrence of disease progression, while OS was defined as the time from the start of immunotherapy to the date of death. Since the study is a case series, a specific cutoff for significance was not determined.

3. Result

Eight patients diagnosed with endometrial carcinosarcoma underwent treatment with pembrolizumab plus lenvatinib and were included in the case series. The median age of these patients was 68 (interquartile range (IQR): 66, 71), with a median BMI of 29.5 (IQR: 23, 33). Among them, five (62.5%) were white, one (12.5%) was black, one (12.5%) was Asian, and one (12.5%) identified as another race. All eight patients were diagnosed at either stage III or IV at the initiation of immunotherapy. Cytoreductive surgery was performed in all eight patients before chemotherapy. Initially, all patients received carboplatin plus paclitaxel, with six patients (75%) completing six cycles. Additionally, six (75%) patients had received one prior line of treatment, and three patients (37.5%) underwent adjuvant chemoradiation. Recurrence was observed in seven patients (87.5%) before the start of immunotherapy. One patient opted to begin immunotherapy after completing two cycles of chemotherapy due to hospitalization for sepsis. All patients were MMR proficient, and six (75%) were PD-L1 negative (Table 1).

All eight patients were administered the standard dose of pembrolizumab (200 mg). Among them, five patients (62.5%) received the standard dose of lenvatinib (20 mg), while three patients (37.5%) received a reduced dose (10 mg). The decision to start patients on a reduced dosage was based on individual baseline characteristics and tolerance of side effects. This decision, recommended by the oncologist, was made after thorough discussions with the patients. Additionally, one patient (12.5%) received steroids during immunotherapy. Treatment was discontinued by three patients (37.5%) within the first three cycles; two patients discontinued due to disease progression, and one ceased treatment based on the preference of the patient and their family to pursue palliative care. Lastly, one patient was lost to follow-up after 3.6 months (Table 2).

The median oncology follow-up duration was 5.6 months (IQR: 3.5, 9.0). OS ranged from 0.4 to 19.3 months, with a median of 6.3 months (IQR: 3.7, 9.4). The follow-up time is shorter than OS because patients cease follow-ups with oncologists. However, the time of death was still able to be obtained from the Epic system. One patient was excluded from the OS analysis due to loss of follow-up. The median PFS was 3.6 months (IQR: 1.8, 4.4). No patients discontinued treatment due to treatment-related toxicity and currently, none of the patients are on active treatment (Table 2).

4. Discussion

Our study revealed that patients treated with surgery and first-line systematic treatment of carboplatin plus paclitaxel had a PFS of 3.6 months and an OS of 6.3 months. Due to the rarity of endometrial carcinosarcomas, evidence on current standards of care is limited and primarily derived from retrospective or non-randomized studies [17]. The gold standard for treating non-metastatic cancer is the complete resection of the disease with negative surgical margins. In cases of advanced disease (Stage III, IV), the preferred regimen remains systemic chemotherapy with carboplatin and paclitaxel [12]. All our patients received standard care, involving

TABLE 1. Basic characteristics of study population.

Characteristics	n (%)
Age at diagnose (yr)	66.5 (64.8–68.8)
BMI	29.5 (23.3–33.4)
Race	
White	5 (62.5)
Black	1 (12.5)
Asian	1 (12.5)
Other	1 (12.5)
Comorbidities	
Hypertension	3 (37.5)
Hyperlipidemia	1 (12.5)
Diabetes	2 (25.0)
Gastroesophageal reflux disease	2 (25.0)
Breast cancer history	2 (25.0)
Heart failure	1 (12.5)
Venous thromboembolism	1 (12.5)
Stage at diagnosis	
I	3 (37.5)
II	1 (12.5)
III	3 (37.5)
IV	1 (12.5)
Stage when starting immunotherapy	
III	3 (37.5)
IV	5 (62.5)
MMR proficient	8 (100.0)
PL-D1 status	
Positive	2 (25.0)
Negative	6 (75.0)
Prior cancer treatment	
Surgery + Chemotherapy	5 (62.5)
Surgery + Chemotherapy + Radiotherapy	3 (37.5)
Prior lines of treatment	
1	5 (62.5)
2	1 (12.5)
3	1 (12.5)
4	1 (12.5)

Categorical variables were presented as n (%), and continuous variables were presented as median (interquartile range).
BMI: body mass index; MMR: mismatch repair; PL-D1: programmed death ligand 1.

TABLE 2. Treatment outcomes.

Variables	n (%)
Cycles of immunotherapy	
1	1 (12.5)
3	2 (25.0)
5	1 (12.5)
7	1 (12.5)
8	1 (12.5)
12	1 (12.5)
15	1 (12.5)
Lenvatinib starting dose	
10 mg	3 (37.5)
20 mg	5 (62.5)
Steroid during immunotherapy	1 (12.5)
Oncology follow up time	5.6 (3.5, 9.0)
Progression-free survival	3.6 (1.8, 4.4)
Overall survival	6.3 (3.7, 9.4)
Reason for stopping immunotherapy	
Progression	7 (87.5)
Declination	1 (12.5)
Current status	
Alive with Disease	2 (25.0)
Deceased	5 (62.5)
Loss of Follow-up	1 (12.5)
Currently on immunotherapy	0

Categorical variables were presented as n (%), and continuous variables were presented as median (IQR).

surgery and chemotherapy with carboplatin and paclitaxel. Pembrolizumab combined with lenvatinib is the recommended therapy for non-MSI-H/dMMR advanced endometrial carcinoma [10]. Our study indicated that this regimen might serve as a potential second-line treatment for endometrial carcinosarcomas.

Before the introduction of immunotherapy, there was no consensus on second-line therapy and the PFS after recurrence was only 1.8 months. The typical second-line regimen often involved rechallenge with platinum-based chemotherapy, including agents such as pegylated liposomal doxorubicin, ifosfamide with paclitaxel, gemcitabine or topotecan [4]. In our study, the implementation of pembrolizumab plus lenvatinib demonstrated an improved PFS of 3.6 months, making it a more favorable option for second-line therapy following the failure of platinum-based chemotherapy.

Previous studies have indicated the median PFS of subsequent therapy is 1.8 months, whereas, in our study, the PFS of lenvatinib plus pembrolizumab as the later line of therapy was extended to 3.6 months [17]. In a prior case series involving patients with advanced or recurrent uterine carcinosarcoma treated with lenvatinib plus pembrolizumab, the median PFS and OS were reported as 2.6 months and 2.8 months, respectively [18]. In our study, we demonstrated a

better outcome with PFS and OS of 3.6 and 6.3. Notably, in this earlier case series, patients received surgery and chemotherapy similar to our study. However, they applied pembrolizumab plus lenvatinib after two lines of prior treatment, whereas in our study, five out of eight (62.5%) patients underwent pembrolizumab plus lenvatinib as their second-line treatment. This suggested that introducing pembrolizumab plus lenvatinib earlier in the treatment course could be a viable option in the current therapeutic approach. However, the extension of survival could potentially be attributed to the earlier administration of the treatment regimen, rather than a genuine increase in patient survival. Further studies with larger sample sizes and control groups are necessary to ascertain whether there is a significant difference in survival when introducing pembrolizumab plus lenvatinib as a second-line treatment compared to other available treatment options.

On the other hand, the NRG-GY018 trial has suggested that first-line chemotherapy plus pembrolizumab followed by pembrolizumab maintenance could improve oncologic outcomes regardless of the MMR status or histologic findings [19]. This trial implies that pembrolizumab could be a key component of the regimen and might help explain the better outcome observed in our study, which applied immunotherapy in the earlier line of treatment. Another phase 3 trial has demonstrated that the combination of lenvatinib and pembrolizumab leads to significantly longer PFS and OS compared to chemotherapy [14]. However, this trial did not include patients with the carcinosarcoma histologic subtype. Further research is warranted to explore the potential benefits of combining chemotherapy and immunotherapy in patients with endometrial carcinosarcomas.

In the KEYNOTE-775 trial, 65% of patients with advanced endometrial carcinoma experienced side effects necessitating dose reductions and 33% required discontinuation of both pembrolizumab and lenvatinib due to severe side effects [20]. In contrast, in our study manageable side effects were observed, none of the participants required a dose reduction or discontinuation due to side effects; treatment cessation primarily resulted from disease progression. The relatively high rate of treatment discontinuation noted in both previous case series and our study within a few cycles underscores the challenge of treating endometrial carcinosarcoma [18]. Further study is needed to optimize dosing to improve the efficacy of the regimen and also to assess potential side effects accordingly.

The limitation of this case series lies in the small number of patients studied, although the number was higher than those included in previous case series. Further investigations with larger cohorts and extended follow-up periods are essential to more comprehensively explore the potential benefits of pembrolizumab and lenvatinib in treating endometrial carcinosarcoma, specifically as a second line treatment. Identifying molecular markers beyond PD-L1 and MMR status that can predict the response to immunotherapy is also a crucial avenue for future research. Additionally, our study, along with previous case series, revealed that most patients were PD-L1 negative, raising questions about the efficacy of pembrolizumab in this specific population [18]. This suggests the need to explore other immunotherapeutic strategies for improved outcomes.

5. Conclusions

In conclusion, this case series provides valuable insights into the use of pembrolizumab and lenvatinib in endometrial carcinosarcoma. The data suggests that pembrolizumab and lenvatinib may be a promising second-line treatment for endometrial carcinosarcoma, given the observed improvements in both PFS and OS. However, further studies with larger sizes are warranted to delve deeper into treatment efficacy and explore potential combinations and dose adjustments with pembrolizumab and lenvatinib in the management of endometrial carcinosarcoma.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YHC, SI, HA and MJ—conceived the presented idea. HA and AF—developed the research protocol and obtained IRB approval. YHC and SI—collected the data and completed the analysis. YHC, SI, LF, HA and NR—wrote the manuscript. AF, NR and MJ—supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The case series is conducted according to the principles expressed in the Declaration of Helsinki. It was reviewed and approved by our Institutional Review Board (IRB, Title: Combining lenvatinib and pembrolizumab for the management of endometrial carcinosarcoma: a retrospective case series; Number: E-24-957). Informed consent was waived by the IRB due to the retrospective nature of the study.

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CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest to disclose. We affirm that this research was conducted in an

unbiased manner, and any findings or conclusions presented in the paper are based solely on the merits of the research itself. There are no financial, personal or professional relationships or circumstances that could potentially influence the objectivity or integrity of the research reported in this paper.

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