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Case series

Combination lenvatinib plus pembrolizumab in the treatment of ovarian clear cell carcinoma: A case series

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A B S T R A C T

Effective second-line treatment options for patients with recurrent ovarian clear cell carcinoma (OCCC) are limited. This case series sought to report tumor characteristics and oncologic outcomes in a small group of patients treated with combination lenvatinib and pembrolizumab.

A retrospective analysis of patients with ovarian clear cell carcinoma treated with combination lenvatinib and pembrolizumab at a single institution was performed. Patient and tumor characteristics were collected including demographics and germline/somatic testing. Clinical outcomes were also evaluated and reported.

Three patients with recurrent OCCC were included in the study. The median age of patients was 48 years old. All patients had platinum-resistant disease and had received 1–3 prior lines of therapy. The overall response rate was 100% (3/3). Progression-free survival ranged from 10 months to not-yet-reached. One patient remains on treatment, while the other two died of disease with overall survival of 14 and 27 months.

Combination lenvatinib-pembrolizumab demonstrated favorable clinical response in these patients with platinum-resistant, recurrent, ovarian clear cell carcinoma.

1. Introduction

The treatment of ovarian clear cell carcinoma (OCCC) presents several challenges for clinicians. While historically included in many large epithelial ovarian cancer clinical trials, they compose only a small fraction of enrolled patients, with clinical decision-making for these patients often limited to small sub-group analyses or retrospective studies. It is well-established that the clinical-pathologic behavior of OCCC is distinct from its more commonly diagnosed high-grade serous carcinoma counterpart. While ovarian clear cell carcinoma is more likely to present at an earlier stage, it is often resistant to standard platinum-based therapy and in advanced stage disease is associated with a poorer prognosis (Sugiyama et al., 2000).

In addition, OCCC tumors utilize distinct molecular pathways. While *TP53* mutations are relatively ubiquitous in the HGSOC population, they are infrequent in OCCC. Conversely, approximately 40–50% of OCCC tumors harbor *ARID1A* and/or *PIK3CA* mutation (Wiegand et al., 2010).

In patients with recurrent, platinum-resistant OCCC, there is a paucity of effective second-line therapies with response rates to traditional cytotoxic therapy reported as low as 1% (Crotzer et al., 2007). The lack of effective treatments in this setting as well as the increasing availability of molecular data has shifted interest towards molecularly-targeted therapy. While there are currently no FDA-approved targeted agents for OCCC, targeted agents are often employed in the presence of actionable mutations (Oda et al., 2018). However, in the absence of known targetable mutations, data-driven, effective treatment options are extremely limited, and response rates are low.

In this setting, off-label treatments are sometimes employed in our practice, such as combination therapy with lenvatinib, a multi kinase inhibitor with strong anti-angiogenic effects, and pembrolizumab, a monoclonal antibody that blocks programmed death-1 (PD-1) receptor. The rationale for utilizing this combination in OCCC patients is based on data from both endometrial and renal cell carcinoma populations.

In patients with advanced endometrial cancer, the single-arm KEYNOTE-146/Study-111 included five evaluable patients with clear cell adenocarcinoma histology. Among these patients, the response rate was 80% (2 complete, 2 partial, 1 stable disease). A durable response was noted with a duration of response ranged from 6.3 to 19.5+ months (Makker et al., 2020). Subsequent phase 3 data evaluating lenvatinib plus pembrolizumab for the treatment of recurrent mismatch repair proficient endometrial cancer was published in Keynote-775/Study-309 and demonstrated improved progression-free and overall survival

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compared to standard cytotoxic therapy (Colombo, 2021).

Although clear cell renal cell carcinoma (RCC) and OCCC can have distinct genomic alterations, important genomic similarities have been demonstrated in driver mutations such as the PI3K and SWI-SNF pathways (Ji et al., 2018). In patients with RCCC, the combination of lenvatinib plus pembrolizumab has demonstrated encouraging antitumor activity in both the first-line and recurrent settings (Motzer, 2021; Lee et al., 2021).

To our knowledge, there is limited to no data regarding the use of this combination regimen in patients with OCCC. Here we report the outcomes of patients with OCCC treated with combination lenvatinib and pembrolizumab.

2. Methods

A retrospective review was conducted at a single institution. This review was approved by the institutional review board (IRB#2020C0176). All patients with OCCC treated with a combination of lenvatinib and pembrolizumab were included in the analysis. No patients were excluded. Patient demographic data was collected as well as tumor characteristics and germline/somatic genetic testing when available. Clinical outcomes such as response rate, progression free survival, and overall survival were calculated and reported descriptively given the small number of patients included.

3. Results

Patients with platinum-resistant (defined as progression <6 months from receiving platinum-based therapy) recurrent clear cell ovarian cancer treated with a combination of lenvatinib and pembrolizumab between September 2019 to December 2021 were identified through chart review. A total of three patients met inclusion criteria. Patients included had an ECOG performance status of 0–1 and had received 1–3 prior lines of therapy. One patient received prior immunotherapy (combination ipilimumab/nivolumab). The two patients who had not received immunotherapy prior each had only one prior line of standard systemic chemotherapy. The overall response rate was 100% (3/3) with a PFS ranging from 10 months to not yet reached (Table 1).

No germline pathogenic variants were identified in any patient. All patients had MSI-stable tumors with low tumor mutational burden. Table 2 provides germline and somatic testing information for each patient.

4. Discussion

This small case series demonstrated a favorable response to combination therapy with lenvatinib plus pembrolizumab in patients with recurrent, platinum-resistant OCCC. While this study is limited by a very small sample size, the response rate in all three patients compares favorably with the historically quoted response rates of 1–33% for patients with platinum-resistant, recurrent disease (Crotzer et al., 2007; Esposito, 2014; Gien et al., 2022). Due to the nature of this small case series, this study is certainly limited by potential for significant selection bias as it is likely patients in relatively good health with an appropriate functional status were selected to undergo treatment with a regimen associated with potential for significant toxicity. Additionally, because this study included only those patients treated with immunotherapy combination, a comparison group of other patients with clear cell ovarian cancer treated during the same time frame is not available for reference.

Limited data support the biologic rationale for targeting angiogenesis/VEGF pathways in patients with OCCC. It has been demonstrated that VEGF is strongly expressed in a vast majority of OCCC and expression has been inversely correlated with prognosis (Mabuchi et al., 2010). There is also limited retrospective data to suggest PFS benefit for patients with advanced OCCC with the addition of bevacizumab in the first-line setting (Tate et al., 2021). Targeting this pathway alone may be insufficient, as seen in the phase 2 trial (GOG 254) evaluating sunitinib (combined VEGF/PDGF tyrosine kinase inhibitor) in the treatment of recurrent/persistent OCCC, which demonstrated a response rate of only 6.7% with a median PFS of 2.7 months and a median OS of 12.8 months (Chan et al., 2018).

Similarly, the use of pembrolizumab monotherapy in patients with recurrent, platinum-resistant epithelial ovarian cancer has not demonstrated significant clinical benefit in the overall population. A recent analysis by Gordhandas et al. demonstrated that a majority of OCCC are copy number low and would not be expected to respond to checkpoint inhibitors (Gordhandas et al., 2022). A subgroup analysis of patients treated with single-agent pembrolizumab with OCCC, however, did demonstrate an overall response rate of 15.8% (95% CI 3.4–39.6%), which compares favorably to historic controls (Matulonis, 2019). Furthermore, NRG-GY003 evaluated nivolumab +/- ipilimumab with a majority of responses noted in patients with OCCC (Zamarin et al., 2020). Combination anti-PD-L1 therapy with avelumab plus pegylated liposomal doxorubicin did not demonstrate clinical benefit over PLD monotherapy in the overall population or OCCC subgroup (Pujade-Lauraine et al., 2021).

More recent data from a trial combining pembrolizumab with epacadostat (NRG GY016) demonstrated ORR 21% in OCCC population (Gien et al., 2022). Using pembrolizumab in combination with Lenvatinib or epacadostat may be important for effectiveness of IO in this population. Extrapolating from the clinical evidence from the endometrial literature it is reasonable to consider the combination of an antivascular therapy to pembrolizumab may improve responses in OCCC (Makker et al., 2020).

When considering lenvatinib/pembrolizumab in this patient

Table 2
Germline and somatic tumor testing.

Patient	Germline	Somatic Testing				
		MSI	TMB (Muts/Mb)	LOH	PDL1	Somatic gene mutations
1	Negative	Stable	0	3.30%	<1%	*ARID1A, PPP2R1A*
2	Negative	Stable	3.7	NA	<1%	*TP53, NCOR1, MCL1*
3	Negative	Stable	4	<16%	NA	*PIK3CA, ARID1A, TERT*

MSI = microsatellite instability; TMB = tumor mutational burden; LOH = loss of heterozygosity; NA = not performed

Table 1
Patient demographics and clinical outcomes.

Patient	Histology	Race	Previous lines of therapy	Previous radiation	Response rate	PFS (months)	OS (months)
1	OCCC	White	1	No	PR	25*	25*
2	OCCC	Black	1	No	PR	10	13
3	OCCC	White	3	Yes	PR	18	26

OCCC = ovarian clear cell carcinoma; PR = partial response; SD = stable disease; *remains on treatment ongoing response

population, it is important to weigh the side effect profile and potential for significant toxicity, particularly when the use of this regimen is palliative in nature. Only one patient in the current case series experienced a grade 3 or greater adverse event (rectovaginal fistula) and none of the patients discontinued therapy due to toxicity. However, it is reasonable to assume, that in a larger population, rates of grade 3 or greater adverse events would likely approach those reported in larger studies of other disease sites with grade 3 or greater AE rates as high as 89% (Makker et al., 2020).

As tumor genetic information becomes more commonplace, there are increasing opportunities for targeting potential drivers in rare tumors. Guided by data from histologic clear cell counterparts in both endometrial and renal cell carcinoma as well as initial clinical activity among patients with OCCC presented here, the authors feel that there is rationale to support the use of the regimen of lenvatinib plus pembrolizumab in these patients with extremely limited effective treatment options available.

5. Conclusion

Lenvatinib plus pembrolizumab appears to have favorable clinical activity among patients with OCCC with responses noted among all three patients included and durable responses achieved. In a patient population with very limited treatment options available, this combination warrants further investigation in this patient population.

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None of the authors have a significant conflict of interest related to the current study.

CRediT authorship contribution statement

Corinne A. Calo: Conceptualization, Methodology, Formal analysis, Writing – original draft, Supervision, Data curation. **Monica D. Levine:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Supervision, Data curation. **Morgan Brown:** Data curation. **David M. O'Malley:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Supervision. **Floor J. Backes:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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