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Pembrolizumab and lenvatinib in recurrent ovarian clear cell carcinoma resistant to chemotherapy

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ABSTRACT

Background: Treatment of ovarian clear cell carcinoma (CCC) poses many challenges. Effective treatment options for recurrent and metastatic disease remain limited.
Case: A 70-year-old woman with recurrent metastatic ovarian CCC experienced durable response to the combination of pembrolizumab, a PD-1 targeting monoclonal antibody and lenvatinib, an oral multikinase inhibitor, after failing standard and experimental treatments. She experienced a 40.1% reduction of target lesions over 26 weeks of therapy. CA-125 trends confirmed serial CT scan findings of shrinking disease burden. She experienced overall mild side effects from the drug combination, and lenvatinib dosage was decreased from 20 to 10 mg/day over her 10 cycles.
Conclusion: The combination of pembrolizumab and lenvatinib may represent a new treatment option for chemotherapy-resistant ovarian CCC.

1. Introduction

Ovarian clear cell carcinoma (CCC) is a rare histologic subtype of epithelial ovarian carcinoma, and accounts for 5–25% of all epithelial ovarian carcinoma cases, depending on geographic location (Banerjee and Kaye, 2013). Despite having clinical, histopathological, and genetic characteristics that differ from high grade serous ovarian carcinoma (HGSC), the most common subtype of ovarian cancer, the treatment pathways have remained the same, mostly due to a paucity of clinical data specific for ovarian CCC (Stewart et al., 2023). Standard treatment involves aggressive cytoreductive surgery followed by systemic platinum-based chemotherapy. Ovarian CCC is characterized by a biologically aggressive behavior and resistance to most standard treatments. Accordingly, many patients experience a disease recurrence, even with early-stage disease, and prognosis is usually poor. The discovery and clinical testing of novel therapeutic strategies, especially for recurrent and metastatic disease, is of the utmost importance.

Ovarian CCC is known to have a distinct molecular genetic profile compared to HGSC. While HGSC is characterized by high rates of germline BRCA1/2 and somatic TP53 mutations, CCC has a much lower frequency of BRCA1 and BRCA2 mutations and is observed to often have wild-type TP53 (Sugino et al., 2019). However, ovarian CCC is associated with ARID1A and PIK3CA mutations, reported in 40–57% and 33% of cases, respectively (Tan et al., 2011; Mutations, 2023). As loss of ARID1A function has been associated with increased microsatellite instability and tumor mutational burden, targeting immune checkpoint blockade represents a promising potential treatment strategy for ovarian CCC (Shen et al., 2018). Furthermore, there is early clinical evidence that ovarian CCC may respond more favorably to anti-PD-L1 agents than HGSC (Stewart et al., 2023; Matulonis et al., 2019). As it is thought that ovarian CCC progression is due in part to VEGF-mediated angiogenesis, targeting angiogenesis is another potential treatment pathway (Stewart et al., 2023).

The combination of pembrolizumab, a monoclonal antibody targeting programmed death receptor-1 (PD-1), with lenvatinib, an oral multikinase inhibitor that targets vascular endothelial growth factor receptors, has been evaluated in a number of gynecologic malignancies and is currently FDA-approved for use in advanced, microsatellite stable, mismatch-repair proficient (pMMR), endometrial carcinoma (Makker et al., 2022). Given current understanding of the genetic profile and pathogenesis of many ovarian CCC, the use of this drug combination has potential merit.

We present a patient with recurrent CCC of the ovary with ARID1A/PIK3CA mutation who previously failed multiple lines of standard and

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experimental therapies. Treatment with pembrolizumab and lenvatinib, approved on a compassionate basis, elicited an impressive and durable disease response.

2. Case

The patient is a 70-year-old woman, germline BRCA wild-type, who was initially diagnosed with stage IIIB clear cell ovarian cancer in February 2020. After laparotomy with optimal tumor cytoreduction, adjuvant treatment was initiated with 6 cycles of paclitaxel/carboplatin. A CT scan after adjuvant treatment (7/7/2020) demonstrated no evidence of disease (NED). She was then initiated on poly-ADP-ribose polymerase (PARP) inhibitor therapy, with a total daily dose of olaparib of 600 mg (9/2020). However, due to bone marrow toxicity, the olaparib dose was dose reduced to 500 mg and later 400 mg, and was eventually discontinued in 11/2020 due to hyponatremia. During her follow up, a CT scan (4/5/2021) demonstrated multifocal retroperitoneal recurrent disease with multiple enlarged lymph nodes involving the left iliac chain and a nodule in the chest. The patient was then seen at our institution for a second opinion, and subsequently transferred her care. She then received treatment with 6 cycles of weekly paclitaxel (80 mg day 1, 8, and 15 q28 days) (5/5/21–10/13/21). A PET CT after the 6 cycles of paclitaxel (10/25/21) demonstrated a mixed response, with improvement in thoracic lymphadenopathy but with the addition of several hypermetabolic retroperitoneal and pelvic lymph nodes when compared with prior scans. The patient underwent planned removal of a benign pituitary adenoma on 12/13/21; subsequently, 3 further cycles of taxol with avastin 10 mg/kg were administered (2/11/22–4/21/22). After a subsequent PET/CT scan (4/27/22) demonstrated mixed changes in metastatic nodal disease with several small new nodal lesions, this treatment was discontinued.

During her course, the patient underwent next generation sequencing of her tumor as well as germline genetic testing. She was found to be germline BRCA1/2 negative. Her tumoral testing yielded LOH less than 16%, microsatellite stable, tumor mutational burden (TMB) 1 mut/Mb, and mutations in ARID1A (R1335), PIK3CA (G118D), and PPP2R1A (P179R). Immunohistochemical studies yielded HER2 overexpression (score 3 +).

At this point, the patient was enrolled in NRG-GY014 (Tazemetostat in Clear Cell ovarian cancer harboring ARID1A mutations); her treatment started on 5/24/22. A baseline CT scan was performed on 5/13/22, which demonstrated mild disease progression compared to her 4/2022 scan. There was noted to be interval progression in her lymphadenopathy as well as increase in a left anterior pelvis implant, now 4.4 cm. Unfortunately, a CT scan (7/13/22) performed after 3 cycles of trial drug demonstrated progression of her metastatic disease, with an interval increase in her retroperitoneal lymphadenopathy, and increased size of her left anterior pelvic soft tissue implant, now measuring 6.2 cm (prior 4.4 cm). She was removed from the trial on 7/18/22.

She was then offered, on a compassionate basis, the combination of lenvatinib/pembrolizumab; pembrolizumab 200 mg q3 weeks was initiated on 8/15/22, and lenvatinib initiated 9/8/22 at a dose of 20 g/day. Her CT scan from 7/13/22 was used as a baseline (Fig. 1A.) Lenvatinib was decreased to 14 mg with cycle 3 (9/30/22) due to fatigue. A CT scan from 11/8/22, 3 months (4 cycles) after started lenvatinib/pembrolizumab noted interval decrease in recurrent pelvic tumor from 6.2 cm to 4.8 cm without new lesions (Fig. 1B). She continued therapy with a dose of Lenvatinib of 14 mg. She experienced some side effects such as nausea and diarrhea. Her subsequent CT scan (2/13/23), 6 months after initiating lenvatinib/pembrolizumab, demonstrated further decrease in the size of her recurrent clear cell carcinoma with the left anterior pelvis index lesion then measuring 3.7 (prior 4.8 cm) (Fig. 1C). Given her continued response but difficult side effects of nausea and diarrhea, her dose of lenvatinib was decreased to 10 mg starting with cycle 10, with the hope of increasing the tolerability of the combined regimen. She continues on combination treatment with pembrolizumab 200 mg every 3 weeks with lenvatinib 10 mg daily. The patient's disease course with treatments is illustrated in Fig. 2 and Fig. 3.

3. Discussion

Ovarian CCC is an aggressive and difficult to treat gynecologic malignancy; we present a case of a patient with recurrent treatment-resistant ovarian CCC with ARID1A/PIK3CA mutation who had a partial and durable response to treatment with pembrolizumab and lenvatinib over 7 months of treatment.

ARID1A mutations are the most frequently observed genetic alterations in ovarian CCC, estimated to occur in 40–57% of tumors (Tan et al., 2011). It is known that mutations in ARID1A contribute to a loss of function in a vital tumor suppressor pathway. These alterations increase reliance on cell cycle checkpoints during DNA replication, and are associated with response to immune checkpoint blockade therapy (Stewart et al., 2023). This has borne out in preclinical studies, as anti-PD-L1 antibody has shown effectivity in mouse models of ARID1A-deficient tumors (Shen et al., 2018). Unfortunately, efficacy of immune checkpoint blockade has yet to be shown in clinical studies of epithelial ovarian cancer, however ovarian CCC patients enrolled in early phase trials of nivolumab (anti-PD-1), avelumab (anti-PD-L1), and ipilimumab/nivolumab (anti-CTLA4/anti-PD-1) were more likely to respond to treatment than their HGSC counterparts (Stewart et al., 2023; Matulonis et al., 2019; Zamarin et al., 2020; Disis et al., 2019).

While bevacizumab, the first VEGF targeted agent approved for use in ovarian cancer, did not demonstrate significant benefit for ovarian CCC patients in the ICON7 clinical trial, the study was underpowered for this histologic subtype (Oza et al., 2017). Other early multi-target tyrosine kinase inhibitors that block key components of angiogenesis, nintedanib and sunitinib, have not shown clear benefit in single-agent clinical trials of ovarian CCC, however these drugs, in combination

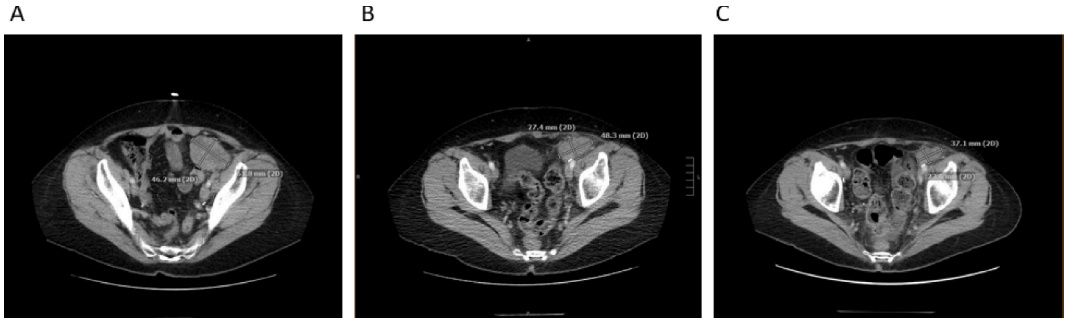

Fig. 1. CT scans demonstrating activity of pembrolizumab/Lenvatinib in clear cell carcinoma. Representative pelvic soft tissue implant. A. Baseline measurement of left anterior pelvic soft tissue implant, 6.2 cm, B. Regression of index lesion after 12 weeks of pembrolizumab/Lenvatinib therapy, 4.8 cm; stable disease (overall 22.6% reduction in target lesion), C. Further regression of index lesion after 26 weeks of pembrolizumab/Lenvatinib, 3.7 cm; partial response (overall 40.3% reduction in target lesion).

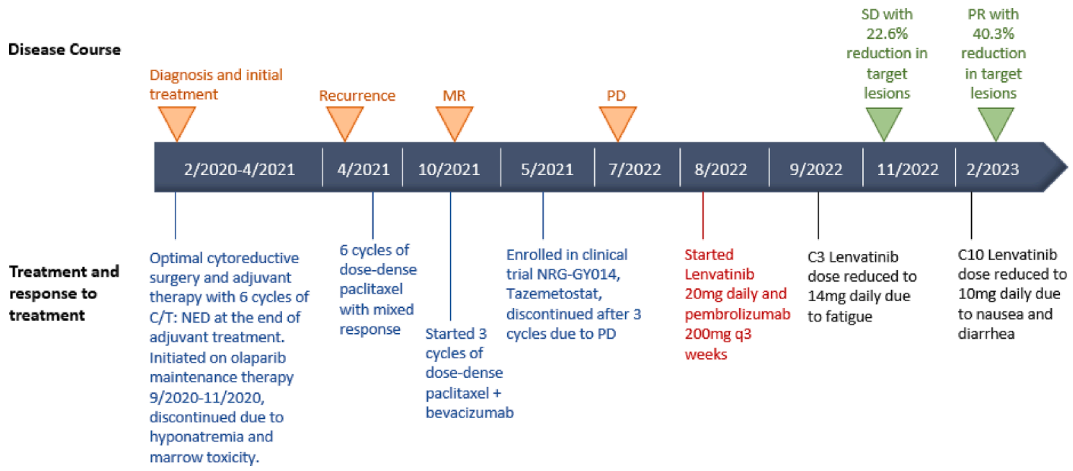

Fig. 2. Timeline of patient's disease course with treatment: (C/T, carboplatin/paclitaxel: PD, progression of disease; MR, mixed response; SD, stable disease; PR, partial response; NED, no evidence of disease.

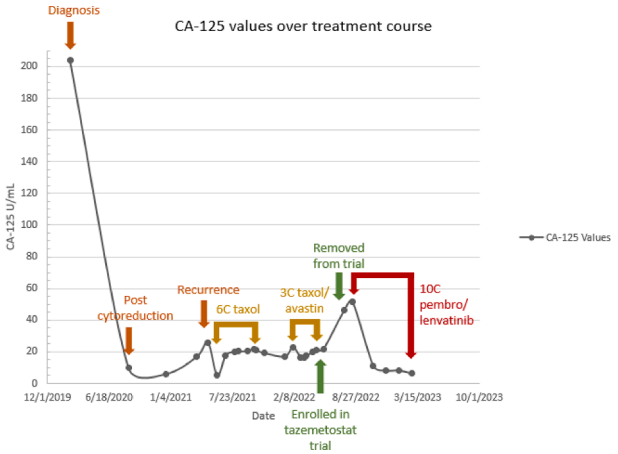

Fig. 3. Graphical representation of patient's CA-125 values alongside disease and treatment course.

with other agents, require further research (Chan et al., 2018; Glasspool et al., 2020). Little clinical research has been published on lenvatinib in ovarian CCC. One Phase I study evaluated the combination of lenvatinib and weekly paclitaxel in patients with recurrent ovarian cancer; they enrolled 2 patients with ovarian CCC (out of N = 26). The patients with recurrent ovarian CCC experienced clinical benefit (Backes et al., 2021).

It is interesting to consider our patient's tumor's genetic landscape in the context of her robust response to pembrolizumab combined with lenvatinib. On sequencing, her tumor showed microsatellite stability (MSS), with a low tumor mutational burden score. With few reported exceptions (Bellone et al., 2018) It is known that both pembrolizumab and lenvatinib alone have had limited utility in treating recurrent endometrial cancer that is pMMR or MSS (Vergote et al., 2020; Marabelle et al., 2020). However, in combination, pembrolizumab and lenvatinib (vs. standard chemotherapy) have been shown to confer improved progression free and overall survival in patients with advanced or recurrent endometrial cancer, of all histologic subtypes. The KEYNOTE-775 trial, that evaluated this combination, included 47 patients with uterine CCC, and was majority pMMR/MSS. While the authors do report specifically on pembrolizumab/lenvatinib's efficacy among the pMMR population, results based on histologic subtype were not provided (Makker et al., 2022). While ovarian CCC is known to have immunophenotypic differences from uterine CCC, there may be some similarities that suggest potential for similar responses to cytotoxic therapies (Ju et al., 2018).

The safety profile of pembrolizumab/lenvatinib (at a dose of 200 mg q3wks/20 mg/day) has been proven in numerous Phase II-III studies (Makker et al., 2022). The most common Grade 3–4 adverse events are hypertension, hypothyroidism, diarrhea, and nausea. In the KEYNOTE-775 trial, 45.6% of patients had two or more dose reductions of lenvatinib, much like our patient presented here, suggesting that lenvatinib doses less than 20 mg/day remain efficacious (Makker et al., 2022). Our patient is currently on her 7th month of this chemotherapy regimen. In the KEYNOTE-775 trial, the median duration of treatment with pembrolizumab/lenvatinib was 7.6 months (range of 1 to 27 months), however 27% of patients continued treatment for longer than 12 months (Makker et al., 2022). This suggests that this combination can be used for prolonged periods of time with appropriate management of treatment-related adverse events.

The combination of pembrolizumab and lenvatinib may represent a novel, highly effective treatment option for patients with recurrent and treatment-resistant ovarian CCC.

4. Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest

A.D.S. reports grants from PUMA, grants from IMMUNOMEDICS, grants from GILEAD, grants from SYNTHON, grants and personal fees from MERCK, grants from BOEHINGER-INGELHEIM, grants from GENENTECH, grants and personal fees from TESARO and grants and personal fees from EISAI. The other authors declare no conflict of interest.

Author contributions

Blair McNamara, Stefania Bellone, Cem Demirkiran, Tobias Hartwich, and Alessandro D. Santin participated in drafting and revising this manuscript. Blair McNamara provided materials for the figures. All authors read the manuscript and approved its submission.

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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