Journal of Cancer Research and Practice

journal homepage: https://journals.lww.com/jcrp

Case Report

Promising Remission with Reduced Bevacizumab and Pembrolizumab Dosage in a Patient with AT-rich Interaction Domain 1A Mutated Ovarian Clear-cell Carcinoma Refractory to Chemotherapy

Cheng-Wei Huang, Ruo-Han Tseng*

Division of Hematology/Oncology, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan

Abstract

Patients with ovarian clear-cell carcinoma have limited treatment choices, because they are resistant to the standard chemotherapeutic agents used in ovarian cancer. The phase II KEYNOTE-100 trial revealed that pembrolizumab monotherapy demonstrated a 15.8% objective response in patients with ovarian clear-cell carcinoma in the subgroup analysis, which is much higher than that of other histology subtypes of ovarian cancer. Immune checkpoint inhibitors may play a new role in the treatment of these malignancies. Genetic analyses revealed a significant proportion of ovarian clear-cell carcinoma carrying the AT-rich interaction domain 1A protein (ARID1A) mutation. The association between a higher frequency of ARID1A mutation and a higher response to immune checkpoint inhibitors in ovarian clear-cell carcinoma opens a new research topic. Herein, we report a patient with ovarian clear-cell carcinoma refractory to platinum-based chemotherapy, who was treated with a reduced dose of bevacizumab and pembrolizumab combination therapy and achieved a complete treatment response.

Keywords: Angiogenesis inhibitor, AT-rich interaction domain 1A, immune checkpoint inhibitor, ovarian clear-cell carcinoma

Introduction

Ovarian cancer is the fifth-most prevalent cancer type and the fourth-most prominent cause of cancer-related death in women globally.[1] Epithelial ovarian carcinoma, accounting for approximately 90% of ovarian cancer, exhibits heterogeneity in histologic subtypes and molecular pathogenesis.[2,3] Ovarian epithelial cancer is categorized into serous, endometrioid, clear cell, and mucinous.[2,3] Ovarian clear-cell carcinoma accounts for approximately 5% of ovarian epithelial cancers.[2] Advanced ovarian clear-cell carcinoma demonstrated worse prognoses than ovarian serous carcinoma.[4] This is because ovarian clear-cell carcinoma appears resistant to standard chemotherapy

Submitted: 31-Jul-2023 **Revised:** 31-Aug-2023
Accepted: 13-Oct-2023 **Published:** 20-Mar-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jcrp

DOI: 10.4103/ejcrp.eJCRP-D-23-00035

Address for correspondence: Dr. Ruo-Han Tseng, Division of Hematology/Oncology, Department of Internal Medicine, Changhua Christian Hospital, No.135, Nanxiao St., Changhua 50006, Taiwan.
E-mail: gwynn514@gmail.com

How to cite this article: Huang CW, Tseng RH. Promising remission with reduced bevacizumab and pembrolizumab dosage in a patient with AT-rich interaction domain 1A mutated ovarian clear-cell carcinoma refractory to chemotherapy. J Cancer Res Pract 2024;11:49-52.

used in ovarian cancer.[4] Its significant proportion carries AT-rich interaction domain 1A protein (ARID1A) mutations.[5] New treatment strategies should be investigated to improve outcomes. Herein, we present the case of a patient with ovarian clear-cell carcinoma treated with a reduced and fixed dose of pembrolizumab and bevacizumab combination and achieved a complete response.

Case Report

A 42-year-old Asian female patient, gravida 2, para 2, presented with lower abdominal pain for some days. Abdominal computed tomography (CT) revealed a large complex cystic mass lesion over the pelvis, an increased infiltrate in the adjacent mesentery, omental soft-tissue nodules, and a thickened peritoneum. She underwent an optimal debulking surgery, and the pathologic report revealed clear-cell carcinoma with bilateral ovaries (left side: 7 cm × 7 cm × 2.5 cm in size, right: 5 cm × 4.3 cm × 2.9 cm in size), omentum, peritoneum, bilateral fallopian tubes, and one right para-aorta lymph node. The pathologic staging was pT3cN1a and the International Federation of Gynecology and Obstetrics (FIGO) stage IIIc. The cancer antigen (CA)-125 level was 309.1 U/mL at diagnosis [Figure 1]. She received two adjuvant chemotherapy cycles with carboplatin (area under the curve [AUC]: 5)/paclitaxel (175 mg/m^2) on Day 7 and 29 postoperatively. Follow-up abdominal sonography (for annual chronic hepatitis B infection evaluation) revealed a lesion at S4a of the liver, and further abdominal CT revealed enlarged lymph nodes in the bilateral iliac, retroperitoneal, hepatoduodenal, and lower mediastinal regions, as well as a new metastatic lesion at S4a of the liver [Figures 2 and 3]. We changed the chemotherapy regimen to liposomal doxorubicin (30 mg/m^2)/carboplatin (AUC: 4)/docetaxel (60 mg/m^2) combination on Day 64 postoperatively. We used FoundationOne CDX, a next-generation sequencing-based assay for genetic analysis, which revealed the ARID1A T1917fs*22 mutation [Table 1]. Some studies revealed that ARID1A mutation in ovarian clear-cell carcinoma caused shorter progression-free survival and chemoresistance,[6] as in our patient; thus, we discussed the chemotherapy-free regimen together. Several case reports revealed a successfully treated ovarian clear-cell carcinoma with an ARID1A mutation with immune checkpoint inhibitor-based therapy. In addition, one study reported that nine cancer types, including ovarian clear-cell carcinoma, harboring ARID1A-altered tumors, have longer median progression-free survival after checkpoint inhibitor treatment, and ARID1A mutation status was independent of microsatellite instability or mutational burden.[7] The patient agreed to pembrolizumab/bevacizumab combination therapy after discussion, and she understood that pembrolizumab was not a Food and Drug Administration-approved ovarian cancer treatment. The doses of pembrolizumab (100 mg, 2 mg/kg) and bevacizumab (400 mg, 8 mg/kg) were reduced, and fixed doses were administered every 3 weeks on Day 86 postoperatively. The CA-125 level was normal on Day 128 postoperatively after two pembrolizumab/bevacizumab cycles. She received bevacizumab of 400 mg (8 mg/kg) and pembrolizumab of 100 mg (2 mg/kg) every 3 weeks for three cycles, which was then reduced to 300 mg (6 mg/kg) and 100 mg (2 mg/kg), respectively, every 3 weeks for extra six cycles, with a longer dosing interval (up to 8 weeks) due to the patient's financial considerations [Figure 1]. Follow-up abdominal CT revealed a partial response to stable disease [Figures 2 and 3], partial response, and complete remission after 4, 8, and 12 cycles of bevacizumab/pembrolizumab combination therapy, respectively. We held the treatment regimen due to the financial consideration of the patient and follow-up on the CA-125 levels at least monthly which were all within normal ranges. A follow-up abdominal CT (123 days after the last cycle of bevacizumab/pembrolizumab combination, day 537 postoperatively) revealed complete resolution of the abdominal lymph nodes, liver metastasis, and peritoneal carcinomatosis, except for an enlarged metastatic lymph node in the left external iliac region. We restarted bevacizumab/pembrolizumab combination therapy on Day 551 postoperatively and arranged radiotherapy to improve local control.

Table 1: Genomic analysis (FoundationOne CDx, next-generation sequencing-based assay) result of ovarian specimen

Biomarker findings:	Result	
Loss of Heterozygosity Score	6.1%	
Microsatellite Status	MS-stable	
Tumor Mutation Burden	3 Muts/Mb	
Genomic findings:	**Result**	**% VAF**
ARID1A	T1917fs*22	13.5%
TERT promoter	124C>T	23.2%
EPHB1	G714W-subclonal	0.93%

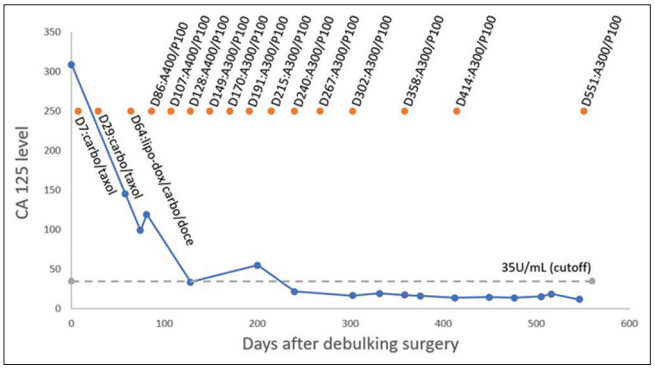

Figure 1: Serum CA-125 level (U/mL, cut-off value: 35 U/mL) according to postdebulking surgery. Day 0 is when the patient receives optimal debulking surgery. Carbo/taxol: Carboplatin and paclitaxel combination; Lipo-Dox/carbo/doce: Liposomal doxorubicin, carboplatin, and docetaxel combination; A400: Bevacizumab of 400 mg; A300: Bevacizumab of 300 mg; P100: Pembrolizumab of 100 mg

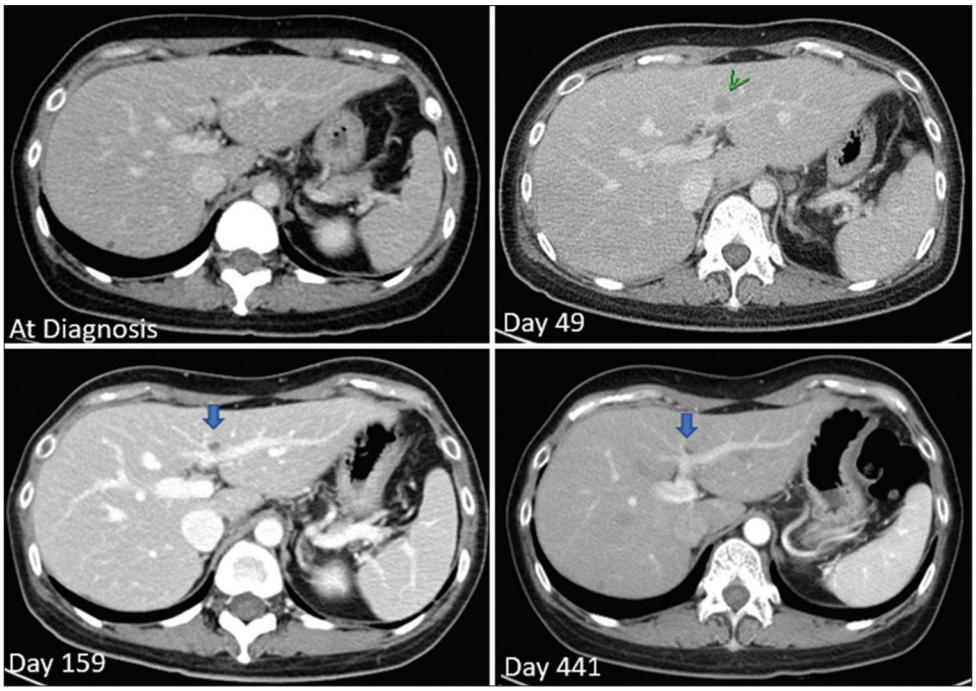

Figure 2: Serial computed tomography scan of liver metastatic lesion: Day 0 is when the patient underwent optimal debulking surgery. Left upper: no liver metastatic lesion at diagnosis; right upper: new liver metastatic lesion after two cycles of carboplatin-containing chemotherapy; left lower: partial response after four cycles of pembrolizumab/bevacizumab combination therapy; right lower: complete remission after 12 cycles of pembrolizumab/bevacizumab combination therapy

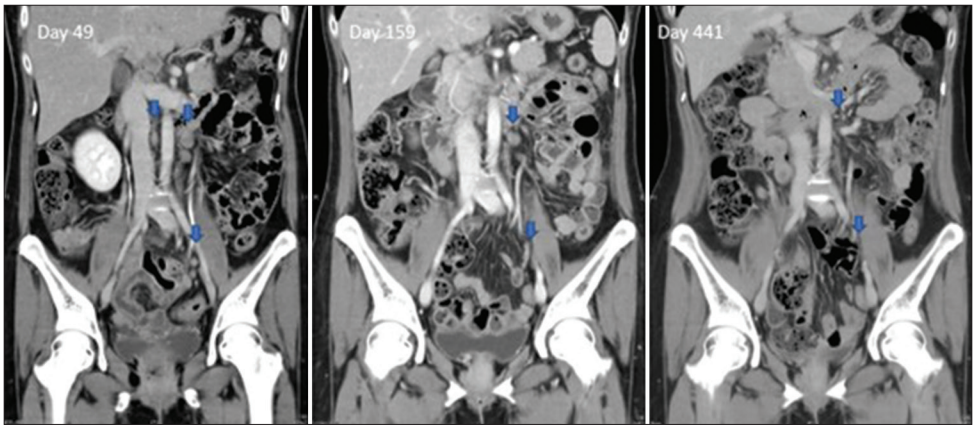

Figure 3: Serial computed tomography scan of metastatic lymph nodes: Day 0 is when the patient underwent optimal debulking surgery. Left: several enlarged lymph nodes at left iliac, and paraaortic regions after two cycles of carboplatium-containing chemotherapy; middle: decreased size (partial response) after four cycles of pembrolizumab/bevacizumab combination therapy; right: complete remission of enlarged metastatic lymph nodes after 12 cycles of pembrolizumab/bevacizumab combination therapy serial

Discussion

The treatment of ovarian clear-cell carcinoma is challenging for clinicians. Ovarian clear-cell carcinoma prognosis is staged dependent, with a 5-year overall survival for FIGO stages III and IV disease of 52%, much lower than high-grade ovarian serous carcinoma.[4] Only approximately 11%–27% of patients with ovarian clear-cell carcinoma respond to platinum-based chemotherapy.[4]

ARID1A protein, ARID1A, a key component of the mammalian BAF SWI/SNF chromatin remodeling complex, is the most frequently mutated SWI/SNF complex member.[8] Approximately 46%–57% of ovarian clear-cell carcinoma carries ARID1A mutation, much higher than other ovarian cancer subtypes (30% of endometrioid carcinomas and none of the 76 high-grade serous carcinomas).[5,8] Some studies revealed worse progression-free survival in ARID1A-deficient ovarian clear-cell carcinoma.[6] ARID1A recruits the mismatch repair gene MSH2 to chromatin during DNA replication. Loss of function of ARID1A correlated with mismatch repair deficiency.[8,9] Interestingly, severe case reports revealed promising responses in patients with ARID1A-mutated

ovarian clear-cell carcinoma, and most patients harbored microsatellite stability.[10-14] One study that analyzed patients who had tumor tissue next-generation sequencing among nine cancer types revealed a longer median progression-free survival after immune checkpoint inhibitor in patients with ARID1A-altered tumor, and the result was independent of microsatellite instability or mutational burden.[7] The mechanism by which ARID1A-mutated ovarian clear-cell carcinoma responds well to immunotherapy-based treatment is a new topic to study.

The phase II KEYNOTE-100 trial focused on the role of immune checkpoint inhibitor, pembrolizumab, in ovarian cancer.[15] The trial enrolled 376 patients with recurrent ovarian cancer for pembrolizumab monotherapy. The objective response rate was 8.0%, and progression-free survival was 2.1 months. However, subgroup analysis revealed a 15.8% (95% confidence interval: 3.4–39.6) objective response rate in 19 patients with ovarian clear-cell carcinoma, which was much higher than that of other histology types of ovarian cancer. This finding indicates the benefit of immune checkpoint inhibitors in patients with ovarian clear-cell carcinoma, which requires further investigation of ARID1A mutation.

Herein, we report a patient with clear-cell carcinoma harboring the ARID1A mutation refractory to platinum-based chemotherapy, evidenced by enlarged lymph nodes, a new metastatic lesion in the liver, and CA-125 level elevation. Therefore, exploring new treatment approaches is essential for improving disease control and survival. Immune checkpoint inhibitor pembrolizumab-based therapy is a potential therapeutic strategy to treat the patient. The objective response rate was 15.8% ovarian clear-cell carcinoma after pembrolizumab monotherapy. Pembrolizumab-based combination therapy may be a new approach. Several case reports were published using pembrolizumab-based combination therapy, with published partner medications, including lenvatinib, olaparib, and bevacizumab.[10-13] Reduced and mixed pembrolizumab (2 mg/kg) and bevacizumab (8 mg/kg) doses were administered every 3 weeks as a cycle due to financial and adverse effects considerations. We tried longer dosing intervals (up to 8 weeks) for disease control due to partial response after 8 cycles of treatment, which achieved a complete treatment response.

In conclusion, reduced and fixed bevacizumab and pembrolizumab doses may be beneficial to patients with ARID1A mutated ovarian clear-cell carcinoma. Further case reports and clinical trials are needed to confirm these novel treatment strategies.

Declaration of patient consent

The authors certify that all appropriate patient consent forms were obtained. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Chan JK, Cheung MK, Husain A, Teng NN, West D, Whittemore AS, *et al.* Patterns and progress in ovarian cancer over 14 years. Obstet Gynecol 2006;108:521-8.
3. McCluggage WG. Morphological subtypes of ovarian carcinoma: A review with emphasis on new developments and pathogenesis. Pathology 2011;43:420-32.
4. Mackay HJ, Brady MF, Oza AM, Reuss A, Pujade-Lauraine E, Swart AM, *et al.* Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. Int J Gynecol Cancer 2010;20:945-52.
5. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, *et al.* ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 2010;363:1532-43.
6. Katagiri A, Nakayama K, Rahman MT, Rahman M, Katagiri H, Nakayama N, *et al.* Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma. Mod Pathol 2012;25:282-8.
7. Okamura R, Kato S, Lee S, Jimenez RE, Sicklick JK, Kurzrock R. ARID1A alterations function as a biomarker for longer progression-free survival after anti-PD-1/PD-L1 immunotherapy. J Immunother Cancer 2020;8:e000438.
8. Caumanns JJ, Wisman GB, Berns K, van der Zee AG, de Jong S. ARID1A mutant ovarian clear cell carcinoma: A clear target for synthetic lethal strategies. Biochim Biophys Acta Rev Cancer 2018;1870:176-84.
9. Shen J, Ju Z, Zhao W, Wang L, Peng Y, Ge Z, *et al.* ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. Nat Med 2018;24:556-62.
10. Lin YC, Wen KC, Sung PL, Chou YT, Liew PL, Chen LY, *et al.* Complete remission of heavily treated ovarian clear cell carcinoma with ARID1A mutations after pembrolizumab and bevacizumab combination therapy: A case report. J Ovarian Res 2020;13:143.
11. Meng L, Zhang Z, Zhang X, Zhang X, Wei Y, Wu B, *et al.* Case report: Local cryoablation combined with pembrolizumab to eliminate lung metastases from ovarian clear cell carcinoma. Front Immunol 2022;13:1006500.
12. Calo CA, Levine MD, Brown MD, O'Malley DM, Backes FJ. Combination lenvatinib plus pembrolizumab in the treatment of ovarian clear cell carcinoma: A case series. Gynecol Oncol Rep 2023;46:101171.
13. Zhao Y, Jiang Y. Remarkable response to the triplet combination of olaparib with pembrolizumab and bevacizumab in the third-line treatment of an ovarian clear cell carcinoma patient with an ARID1A mutation: A case report. Onco Targets Ther 2022;15:323-8.
14. McNamara B, Bellone S, Demirkiran C, Max Philipp Hartwich T, Santin AD. Pembrolizumab and lenvatinib in recurrent ovarian clear cell carcinoma resistant to chemotherapy. Gynecol Oncol Rep 2023;48:101218.
15. Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, *et al.* Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: Results from the phase II KEYNOTE-100 study. Ann Oncol 2019;30:1080-7.