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A Case Report of Combination Maintenance Therapy with Olaparib and Bevacizumab in Advanced Ovarian Cancer: A Promising Approach

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Abstract

Epithelial Ovarian Cancer (EOC) is a common and often deadly disease among women, with High-Grade Serous Ovarian Carcinoma (HGSOC) making up about 75% of cases. Standard treatment includes surgery and platinum-based chemotherapy. Recent studies highlight the effectiveness of Poly (ADP-Ribose) Polymerase (PARP) inhibitors, especially for patients with BRCA1/2 mutations or Homologous Recombination Deficiency (HRD). HRD status is a key biomarker for predicting PARP inhibitor success, even without BRCA mutations. Genomic signatures can detect HRD independently. Healthcare professionals assess HRD by evaluating genomic instability and recommend PARP inhibitors for patients with an HRD score of 42 or higher. Combination maintenance therapy with Olaparib and Bevacizumab has shown improved survival for HRD-positive or BRCA-mutated patients. A case report of a 36-year-old woman with advanced ovarian cancer showed a positive treatment response and tumor-free lymph nodes after neoadjuvant chemotherapy, surgery, and targeted therapy. Combination maintenance therapy with a PARP inhibitor and Bevacizumab is crucial in advanced ovarian cancer treatment.

In conclusion, a combination of a PARP inhibitor and bevacizumab for maintenance therapy is essential in the treatment of advanced ovarian cancer. Patients in stages 3 and 4 gain significant benefits from this approach, which is customized according to their initial treatment, BRCA mutation status, and Homologous Recombination Deficiency HRD status.

Keywords: Epithelial Ovarian Cancer, High Grade Ovarian Carcinoma, Homologous Recombination Deficiency, Olaparib Bevacizumab

Introduction

Epithelial ovarian cancer (EOC) is a widespread and often deadly illness that affects women all over the world. Approximately 75% of all EOC cases are due to high-grade serous ovarian carcinoma (HGSOC). Unfortunately, most patients are not diagnosed until the disease has progressed to an advanced stage (III-IV). The typical treatment for newly diagnosed EOC

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usually involves surgery to remove as much of the tumor as possible, followed by chemotherapy using platinum-based drugs. However, recent clinical trials have shown that maintenance therapy with Poly (ADP-ribose) polymerase (PARP) inhibitors can be beneficial, especially for patients with BRCA1/2 mutations or homologous recombination deficiency (HRD). HRD status is an important biomarker that can help identify patients without BRCA mutations who could still benefit from PARP inhibitors as a first-line maintenance treatment.

Epithelial ovarian cancer EOC is a prevalent and often fatal disease affecting women worldwide. high-grade serous ovarian carcinoma HGSOC accounts for approximately 75% of all EOC cases. Unfortunately, most patients are diagnosed at an advanced stage (III-IV) (1-7). The standard treatment for newly diagnosed EOC typically involves cytoreductive surgery followed by systemic platinum-based chemotherapy [8,9]. However, recent clinical trials have underscored the benefits of maintenance therapy with Poly (ADP-ribose) polymerase PARP inhibitors, especially for patients with BRCA1/2 mutations or homologous recombination deficiency HRD As a critical predictive biomarker, HRD status helps identify BRCA wild-type patients who may benefit from PARP inhibitors in the first-line maintenance setting (10-14) .

Approximately 50% of EOC cases exhibit HRD due to alterations in homologous recombination repair (HRR) pathway genes, making HRD a significant predictive biomarker for ovarian cancer treatment (15, 16). Genomic scar signatures can indicate the presence of HRD even in the absence of BRCA mutations, though the incidence of BRCA1/2 mutations in EOC is only around 30% (17-19).

Healthcare professionals calculate an HRD score by assessing three measures of genomic instability: Loss of heterozygosity (gLOH), which is the permanent loss of one allele copy of a gene; the number of telomeric allelic imbalances (TAI), referring to regions with allelic imbalances; and large-scale transitions (LST), which involve genomic alterations associated with chromosome breakages. An HRD score of 42 or greater is considered positive, indicating that a patient may be a candidate for targeted treatment with PARP inhibitors, regardless of BRCA1/2 mutation status (20).

Given that ovarian cancer patient who are HRD-positive or have BRCA mutations benefit from combination maintenance therapy with olaparib and bevacizumab, which has been shown to improve overall survival and progression-free survival, we utilized this combination maintenance therapy for the patient, in this case, report (21).

Case presentation

A 36-year-old woman presented with abdominal pain that had persisted for 9 months. After an initial ultrasound examination, a CT scan was recommended. The CT scan revealed a heterogeneous lesion measuring 62 x 40 millimeters, with adhesions and pressure on the intestinal loop. The primary probable origin was thought to be tubo-ovarian. Additionally, the left ovary appeared enlarged and contained multiple cysts.

Further evaluation included tumor markers, which showed elevated CA-125 levels (96). A PET-CT scan was performed, revealing an irregularly bordered cystic lesion in the left adnexa and hypermetabolic subcapsular lesions in hepatic segment VII. Extensive peritoneal metastasis involving the small bowel wall was also observed, suggesting a possible origin from the adnexa or colon (Figure1).

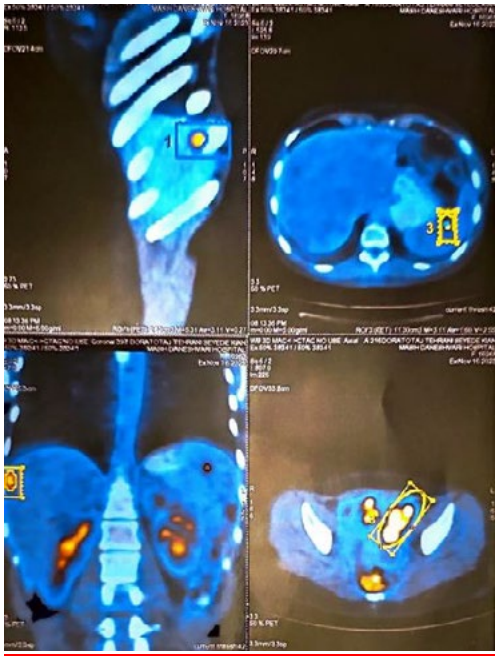

Fig 1. The patients' PET scan results.

Following a diagnostic laparoscopy, the patient had signs of ascites and peritoneal involvement. Biopsies from the omentum and peritoneum, as well as the cytology of the ascitic fluid, were unable to identify the exact kind of tumor. After immunohistochemistry, positive markers that are indicative of high-grade Müllerian serous carcinoma were found. The diagnosis was validated by molecular analysis by next-generation sequencing. The patient started neoadjuvant treatment with carboplatin and paclitaxel after being staged as per FIGO stage IIIc. When the therapy response was evaluated by MRI after three cycles, a partial response was seen. After six rounds of neoadjuvant chemotherapy, the patient underwent bilateral hysterectomy and oophorectomy. The subsequent cycles proceeded. High-grade serous carcinoma encompassing the ovaries, liver, and

omentum was found in the postoperative pathology. The cervical, iliac, and obturator areas as well as the aortocaval lymph nodes. Considering the final NGS results, the patient was a candidate for PARP inhibitor therapy (due to the unavailability of type 3 inhibitors) in combination with bevacizumab.Lymph nodes in the iliac, obturator, and aortocaval regions, as well as cervical tissue, were tumor-free. Based on the final NGS results.

Three months into treatment, a PET-CT scan confirmed a complete metabolic response. Therefore, the combined therapy was continued (Figure2).

Fig 2. The patients' PET scan results.

Discussion

In this case, the significant role of combination maintenance therapy with a PARP inhibitor and bevacizumab in advanced ovarian cancer has been highlighted. Maintenance therapy is standard for patients with ovarian cancer in stages III to IV, and the specific type is determined based on the patient's initial treatment, BRCA mutation status, and homologous recombination deficiency HRD status (22).

Generally, patients with stage 3 and 4 ovarian cancers may have more benefit from neoadjuvant therapy compared to primary surgery. The initial neoadjuvant therapy for these patients includes a platinum-based chemotherapy regimen. Adding bevacizumab to the neoadjuvant treatment regimen has been investigated in various studies and may be added based on the patient's condition, tumor characteristics, and the physician's discretion (23). In the GOG-0218 and ICON7 trials, patients who received carboplatin and paclitaxel in combination with bevacizumab, followed by maintenance therapy with bevacizumab alone, showed an increase in median progression-free survival (PFS) (24, 25).

In general, for ovarian cancer patients, it is particularly important to plan maintenance therapy for those at higher risk. This includes patients with stage IV disease, inoperable stage III, suboptimally debulked stage III (with residual disease greater than 1 cm), poor performance status, high-grade serous histology, and elevated pretreatment CA-125 levels (26-28).

Both the GOG-0218 and ICON7 trials found that patients receiving bevacizumab during chemotherapy had a slight decline in quality of life (QOL). However, this decline did not continue into the maintenance phase (24, 25).

Randomized trials have recently investigated the use of PARP inhibitors as maintenance therapy after first-line chemotherapy for patients with newly diagnosed and histologically proven FIGO stage III/IV ovarian, fallopian tube, or primary peritoneal cancer (29) .

In the SOLO-1 trial, olaparib as a single agent significantly improved progression-free survival (PFS) compared to placebo when used as maintenance therapy. This benefit was seen in patients with either germline or somatic BRCA1/2 mutations who had achieved a complete or partial response after first-line platinum-based chemotherapy. A later subgroup analysis confirmed that the PFS benefit was significant for both BRCA1 and BRCA2 mutation types (30) .

In the PAOLA-1 trial, progression-free survival (PFS) was dramatically increased by combining olaparib with maintenance bevacizumab. Patients with advanced ovarian cancer who responded completely or partially to bevacizumab and platinum-taxane treatment in the first line saw this advantage. PAOLA-1 comprised individuals with and without BRCA1/2 mutations, in contrast to SOLO-1. Subsequent sub-analysis revealed that whether the BRCA mutation was BRCA1 or BRCA2, the PFS benefit of adding olaparib to bevacizumab maintenance was the same (21) .

Patients without BRCA1/2 mutations were further categorized based on Genomic Scar Analysis (GSA) results. PFS was significantly improved for those with homologous recombination deficiency (HRD) but not for those without it. with the availability of next-generation sequencing (NGS) technology, tumor molecular analysis should be recommended for all patients (18-21).

In the mentioned patient, considering the early stage, neoadjuvant therapy was initiated. Due to concerns about the adverse effects of bevacizumab (such as bleeding and gastrointestinal perforation), a combination of dual chemotherapy (carboplatin and paclitaxel) was chosen (31) .

Based on the post-surgery pathology results, which indicated residual disease, high risk criteria,

and positive genomic markers (BRCA wild-type and positive HRD), the decision was made to proceed with maintenance therapy using the combination of bevacizumab and olaparib. Three months after starting the treatment, a follow-up PET scan showed that the patient was in complete metabolic response. Therefore, the continuation of treatment with the same combination was planned (32).

Conclusion

In advanced ovarian cancer, combination maintenance therapy with a PARP inhibitor and bevacizumab plays a crucial role. Patients in stages 3 to 4 benefit from maintenance therapy, tailored based on initial treatment and BRCA mutation and HRD status. Neoadjuvant therapy may offer more advantages than primary surgery for stage 3 and 4 ovarian cancer patients. Adding bevacizumab to neoadjuvant treatment has shown promise, but individualized decisions are essential. Genomic scar analysis (GSA) further informs treatment decisions. Overall, tumor molecular analysis using next-generation sequencing NGS should be recommended for all patients (33).

Statements and Declarations

Consent to participate and Publication

The patient provided informed consent for participation in this case report and publication. She understood the purpose, risks, and benefits of sharing her medical information for scientific and educational purposes. Confidentiality was maintained, and her initials were used to protect privacy. We seek to share this unique case to contribute to medical knowledge and improve patient care.

Availability of data and materials

The availability of data and materials is subject to institutional policies, patient consent, and legal constraints. Researchers should follow established protocols and guidelines when requesting access to clinical information.

Ethics approval and consent to participate

Ethical considerations guided decision-making, ensuring patient autonomy, safety, and adherence to best practices.

Conflicts of Interest

The authors affirm that they have no conflict of interest.

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References

1.American Cancer Society. Treatment of Invasive Epithelial Ovarian Cancers, by Stage (https://www.cancer.org/cancer/ovarian-cancer/treating/ Invasive Epithelial Ovarian Cancers, by Stage.html)

2.Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.

3.Ghaemmaghami F, Karimi-Zarchi M, Modares-Gilani M, et al. Clinical outcome of Iranian patients with advanced ovarian cancer with neoadjuvant chemotherapy versus primary debulking surgery. Asian Pac J Cancer Prev. 2008;9:719–24.

4.Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30. 4. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66:115–32.

5. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017;14:9–32.

6.Seidman JD, Horkayne-Szakaly I, Haiba M, et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. Int J Gynecol Pathol. 2004;23:41–4.

7. Prat J. Ovarian carcinomas: fve distinct diseases with diferent origins, genetic alterations, and clinicopathological features. Virchows Arch. 2012;460:237–49.

8.National Comprehensive Cancer Network (NCCN)--Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer.

9. Matulonis UA, Sood AK, Fallowfeld L, et al. Ovarian cancer Nat Rev Dis Primers. 2016;2:16061.

10. Jose Alejandro Perez-Fidalgo, Fernando Gálvez-Montosa2 et all. SEOM–GEICO clinical guideline on epithelial ovarian cancer . Clinical and Translational Oncology 2023.

. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379:2495–505.

12.Kristeleit R, Lisyanskaya A, Fedenko A, et al. Rucaparib versus standardof-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, openlabel, randomised, phase 3 trial. Lancet Oncol. 2022;23:465–78.

13.Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375:2154–64.

14.Miller RE, Leary A, Scott CL, et al. ESMO recommendations on predictive biomarker testing for homologous recombination defciency and PARP inhibitor beneft in ovarian cancer. Ann Oncol. 2020;31:1606–22.
15. Justin Fortune Creeden, Nisha S. Nanavaty, katelyn R. Einloth, et al. Homologous recombination proficiency in ovarian and breast cancer patients, Creeden et al. BMC Cancer (2021) 21:1154
16.Rowan E Miller, Osnat Elyashiv , Karim H El-Shakankery. Ovarian Cancer Therapy: Homologous Recombination Deficiency as a Predictive Biomarker of Response to PARP Inhibitors. OncoTargets and Therapy 2022:15.
17.Angel Chao, Chyong-Huey Lai, Tzu-Hao Wang, Shih-Ming Jung, Yun-Shien Lee, Et alGenomic scar signatures associated with homologous recombination deficiency predict adverse clinical outcomes in patients with ovarian clear cell carcinoma. Journal of Molecular Medicine, 2018, Volume 96, pages 527–536, (2018) .
18. Zheng Feng, Di Shao, Yuhang Cai, Rui Bi, Xingzhu Ju, Dongju Chen , Chengcheng Song et al, recombination deficiency status predicts response to platinum-based chemotherapy in Chinese patients with high-grade serous ovarian carcinoma. Feng et al. Journal of Ovarian Research (2023) 16:53
19. Kelly L. Bolton, Georgia Chenevix-Trench3, Cindy Goh4, Siegal Sadetzki, Susan J. Ramus, Beth Y. Karlan, Diether Lambrechts ,et al. Association Between BRCA1 and BRCA2 Mutations and Survival in Women with Invasive Epithelial Ovarian Cancer. JAMA. 2012 January 25; 307(4): 382–390.
20. Tatiana Kekeeva , Yulia Andreeva , Alexander Tanas , Alexey Kalinkin , Svetlana Khokhlova , Tatiana Tikhomirova , Alexandra Tyulyandina, et al. HRD Testing of Ovarian Cancer in Routine Practice: What Are We Dealing With? Int. J. Mol. Sci. 2023, 24, 10497.
21. Domenica Lorusso , Marie-Ange Mouret-Reynier, Philipp Harter ,Claire Cropet, Cristina Caballero, et al. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ ENGOT-ov25 trial. Int J Gynecol Cancer 2024;34:550–558.
22. Isabelle Ray-Coquard, Patricia Pautier, Sandro Pignata, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 2019;381:2416-2428.
23. Adamantia Nikolaidi , Elena Fountzilas , Florentia Fostira , et al. Neoadjuvant treatment in ovarian cancer: New perspectives, new challenges. Front. Oncol. 12:820128.
24.Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 2015;16:928-936..
25. Norquist BM, Brady MF, Harrell MI, et al. Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: an NRG Oncology/Gynecologic Oncology Group study. ClinCancer Res 2018;24:777-783.
26. Ferriss JS, Java JJ, Bookman MA, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. Gynecol Oncol 2015;139:17-22.
27.Tewari KS, Burger RA, Enserro D, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. J Clin Oncol 2019;37:2317-2328.
28. Burger RA, Enserro D, Tewari KS, et al. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: A NRG oncology/ Gynecologic Oncology Group (GOG) study (abstract). J Clin Oncol 2018;36:abstr 5517.
29.Paul DiSilvestro, Nicoletta Colombo, Philipp Harter, Antonio González-Martín, Isabelle Ray-Coquard and Robert L. Coleman. Maintenance Treatment of Newly Diagnosed Advanced Ovarian Cancer: Time for a Paradigm Shift? Cancers 2021, 13, 5756.
30. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495-2505.
31.Roman Rouzier , Sébastien Gouy , Frédéric Selle , Eric Lambaudie , Anne Floquet , Virginie Fourchotte , Christophe Pomel, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: Results from the ANTHALYA trial. European Journal of Cancer 70 (2017) 133e142.
32.Marco Petrillo, Ida Paris, Giuseppe Vizzielli, Giulia Amadio, Francesco Cosentino, et al. Neoadjuvant Chemotherapy Followed by Maintenance Therapy With or Without Bevacizumab in Unresectable High-Grade Serous Ovarian Cancer: A Case-Control Study. Gynecologic Oncology 03 June 2015,Volume 22, pages 952–958, (2015).
33.Paul DiSilvestro, Nicoletta Colombo, Philipp Harter, et al. Maintenance Treatment of Newly Diagnosed Advanced Ovarian Cancer: Time for a Paradigm Shift? Paul DiSilvestro, Nicoletta Colombo, Philipp Harter, et al. Cancers 2021, 13(22), 5756.