Oncology Case Reports Journal

Case Report
Published: 21 Aug, 2023

Rucaparib in Platinum-Resistant High-Grade Serous Ovarian Cancer: Case Report

Sharma M[1] and Bharat S[2]*

[1]*Department of Oncology, Institution-Action Cancer Hospital, India*

[2]*Institution-Zydus Lifesciences LTD, Gujarat, India*

Abstract

High-Grade Serous Ovarian Carcinoma (HGSOC) is the most frequent type of ovarian cancer and has a poor outcome. A 57-year-old menopausal patient with hypertension, type 2 diabetes mellitus, and hypothyroidism presented with a complaint of pain in the abdomen for the duration of 2 to 3 weeks along with abdominal distention, alternating constipation and diarrhea, and nausea with a history of cholecystectomy and breast cancer. The patient's condition was further complicated by dilated cardiomyopathy of the left ventricle that led to congestive heart failure, most probably due to chemotherapy given for breast cancer. Histopathological examination confirmed the diagnosis of high-grade serous ovarian carcinoma, and the patient received neoadjuvant chemotherapy, interval debulking surgery, and adjuvant chemotherapy. Positron Emission Tomography-Computed Tomography (PET/CT) scan showed no evidence of disease post-chemotherapy. Genetic testing revealed that the patient was mutation-positive in germline Breast Cancer Gene 2 (BRCA2). The patient's CA-125 level started to rise after three months of the last platinum-based chemotherapy (Platinum resistant); hence, Rucaparib 600 mg BID was started, and the patient remained progression-free for almost a year.

Keywords: Ovarian cancer; Platinum resistant HGSOC; Rucaparib; CA-125

Introduction

High-Grade Serous Ovarian Cancer (HGSOC) is the most common and aggressive form of ovarian cancer, accounting for approximately 70% of all cases [1,2]. HGSOC typically presents at an advanced stage, making treatment challenging and often requiring surgery and chemotherapy [3,4]. Risk factors for developing HGSOC include family history, age, and mutations in Genes involved in double-strand DNA repair (Homologous recombination) like BRCA1, BRCA2, etc. [1]. Ovarian cancer risk by the age of 70 is 40% for BRCA1 and 18% for BRCA2 mutation carriers [5].

The first line of treatment is usually surgery, followed by platinum and taxane-based combination therapy. In patients having a low likelihood of cytoreduction, Neoadjuvant Chemotherapy (NACT) with debulking surgery are standard approaches for stage IIIc and IV ovarian cancers, sometimes inadvertently leading to secondary platinum resistance [6]. However, the relapse rate for the last three decades has been stagnant, being about 30% to 40% 5-year survival rate due to failure of chemotherapy. A major challenge in the management of ovarian cancer is the occurrence of platinum resistance, which is defined as recurrence within 6 months of the last platinum-based chemotherapy, as per the European Society for Medical Oncology (ESMO) and European Society of Gynecological Oncology (ESGO) consensus conference recommendations on ovarian cancer [7]. Numerous studies have revealed a correlation between Epithelial-Mesenchymal Transitions (EMT) in resistant ovarian cancer cell lines and the appearance of novel marker expressions discovered through proteomics. This modified gene expression pattern has been observed to lead to diminished effectiveness of subsequent chemotherapeutic treatments [8]. However, suppose the relapse is more than 12 months. In that case, the prognosis and secondary response are better [9]; the Initial Platinum Resistance (IPR) is also a challenge in ovarian cancers occurring in nearly 20% to 30% of the patients [10]. Mostly 15% to 20% of patients have BRCA1/2 somatic or germline alterations, leading to their improved efficacy to platinum-based regimens [11].

The present case study illustrates the comorbidities and complicated medical background of a patient diagnosed with High-Grade Serous Ovarian Carcinoma (HGSOC) having BRCA2 mutation but developing platinum resistance.

OPEN ACCESS

Correspondence:
Manish Sharma, Department of Oncology, Institution-Action Cancer Hospital, Paschim Vihar, New Delhi, India, Tel: 9717718836

Received Date: *28 Jul 2023*
Accepted Date: *11 Aug 2023*
Published Date: *21 Aug 2023*

Citation:
Sharma M, Bharat S. Rucaparib in Platinum-Resistant High-Grade Serous Ovarian Cancer: Case Report. Oncol Case Report J. 2023; 6(2): 1058.

ISSN: 2641-9173

Case Presentation

In July 2020, a 57-year-old menopausal female patient with a known case of hypertension, type 2 diabetes mellitus, and hypothyroidism presented with a complaint of pain in the abdomen for 2 to 3 weeks, along with abdominal distention, alternating constipation, diarrhea, and nausea besides the history of cholecystectomy 20 years ago. In 2010, the patient was diagnosed with infiltrating ductal carcinoma in her right breast (Estrogen Receptor negative, Progesterone Receptor negative, Human Epidermal Growth Factor Receptor 2 negative) T2N0M0, for which breast conservation surgery with latissimus dorsi flap reconstruction was done. Adjuvant chemotherapy consisting of four cycles of doxorubicin hydrochloride (Adriamycin) and cyclophosphamide was done, followed by four cycles of paclitaxel every three weeks. After 5 to 6 months, the patient was diagnosed with dilated cardiomyopathy of the left ventricle with an ejection fraction of 25%, likely caused by Adriamycin presenting as congestive heart failure (Figure 1).

A complete physical examination was followed by a whole abdomen CT, which showed ascites with omental infiltration. As the CT was suggestive of carcinoma, a biopsy of the omental infiltration was performed. The histopathological examination revealed the presence of high-grade serous ovarian carcinoma of the female genital tract.

Once the diagnosis of HGOSC was confirmed, the patient received neoadjuvant chemotherapy with eight weekly cycles of paclitaxel and carboplatin. Genetic testing revealed that the patient was mutation-positive in Germline Breast Cancer Gene 2 (BRCA2). Post the chemotherapy, interval debulking surgery was performed; adjuvant chemotherapy with paclitaxel and carboplatin was later started. After about two-three months, the patient developed a severe allergic reaction to carboplatin at the end of the cycle (difficulty breathing, chest pain, and nausea). However, Positron Emission Tomography-Computed Tomography (PET/CT) scans showed no evidence of disease. For maintenance therapy, Olaparib has suggested that patients refused that due to financial constraints; hence the patient was administered Tamoxifen 20 mg OD. The patient's CA-125 level started to rise, post three months of treatment with Tamoxifen from 18.3 IU/ml to 207.1 IU/ml and then to 358.2 IU/ml (Figure 1); hence Rucaparib 600 mg BID was started. The patient achieved complete remission and remained free from progression for around one year, emphasizing the significant value of Rucaparib in cancer with impaired double strand DNA repair mechanism like in BRCA mutated ovarian cancer. However, the patient later complained of fatigue and developed grade 3 anemia, for which packed red blood cell transfusions were given. Therefore, the Rucaparib dosage was reduced to 300 mg BID after ten months. A PET/CT scan was then performed, revealing no lesion. In April 2022, the patient showed disease progression as indicated by increased serum CA-125 levels despite continued treatment with Rucaparib, which was discontinued. However, the patient achieved complete remission for a year.

Due to increased CA-125 values (342 U/ml) (Figure 2), bevacizumab and gemcitabine were initiated as alternative chemotherapy agents in August 2022 to control the level of CA-125. In the later stages of chemotherapy treatment, the patient developed chemotherapy-induced thrombocytopenia, for which gemcitabine and bevacizumab were discontinued for a short duration and Romiplostim 250 mcg stat was administered once weekly for two weeks to improve the platelet counts. During chemotherapy, the patient continued to be on medication for hypertension, DM type 2, hypothyroidism, and dilated cardiomyopathy with decreased EF (20% to 25%). The patient was on Carvedilol, venlafaxine, torsemide, sacubitril and valsartan, digoxin for the treatment of CHF and DM, metformin, voglibose, and included pregabalin, febuxostat, ropinirole and thyroxine for the treatment of hypothyroidism.

Discussion

The case report above illustrates the complexity of managing patients with multiple comorbidities. The patient had dilated cardiomyopathy and congestive heart failure, which were complications of chemotherapy for breast cancer and relapsed platinum-resistant ovarian cancer. The patient was prescribed rucaparib, a poly (ADP-ribose) Polymerase (PARP) inhibitor, as a maintenance therapy based on the ATHENA-MONO trial, which showed its superiority over placebo in improving progression-free survival in the first-line maintenance setting for ovarian cancer [12]. Rucaparib is a targeted therapy that inhibits DNA repair in cancer cells, especially those with BRCA mutations or other homologous recombination deficiencies [13]. It is approved by the FDA for the treatment of advanced ovarian cancer with BRCA mutations or deleterious genomic alterations after two or more prior lines of chemotherapy, and for the maintenance treatment of recurrent ovarian cancer after response to platinum-based chemotherapy, irrespective of BRCA status or biomarker status [14]. The efficacy of

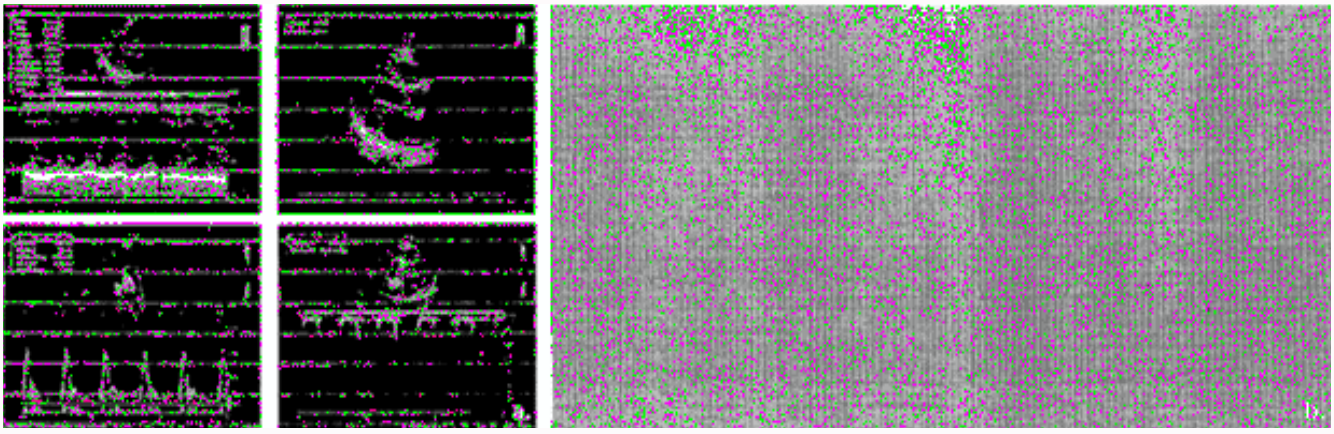

Figure 1: (a, b) With echocardiography and electrocardiogram (EKG), the patient was diagnosed with Congestive Cardiac Failure of the left ventricle with an ejection fraction of 25% with global hypokinesia and dilated cardiomyopathy probably induced by Adriamycin.

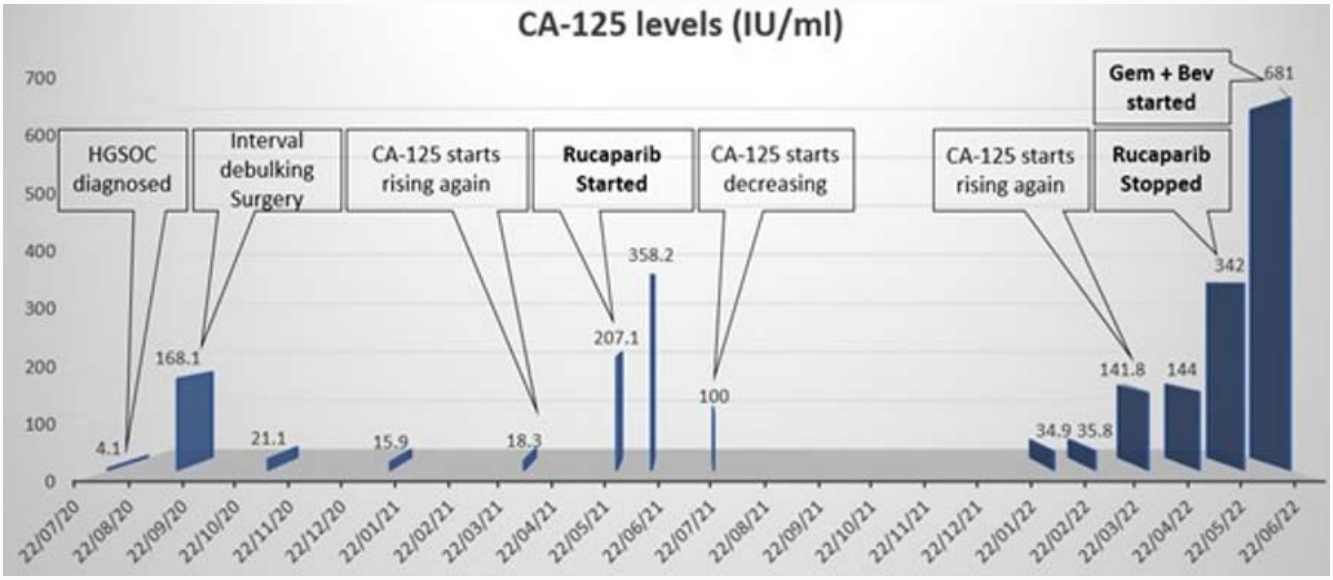

Figure 2: Patient journey of CA-125 levels; CA 125: Cancer Antigen 125; HGSOC: High-Grade Serous Ovarian Cancer; IU: International Unit; GEM: Gemcitabine; Bev: Bevacizumab.

rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy was demonstrated by the ARIEL3 trial, which compared rucaparib with placebo in women with recurrent ovarian cancer who had responded to platinum-based chemotherapy. Rucaparib demonstrated significant efficacy in prolonging disease progression-free time, particularly in patients with BRCA mutations. Additionally, rucaparib exhibited favorable tolerability, with predominantly mild to moderate and manageable adverse effects. The trial concluded that rucaparib holds promise as a potential new standard of care for women with recurrent ovarian cancer who have responded to platinum-based chemotherapy [15]. In the present case, the patient also developed adverse effects such as fatigue and anemia, which may be attributed to the inhibition of PARP in normal cells, which may compromise DNA repair and cause cytotoxicity. Therefore, patients receiving rucaparib should have their doses adjusted and their hematological parameters closely monitored [16], necessitating a dose reduction of rucaparib to 300 mg BID. This is consistent with another case study that reported improvement in anemia and fatigue after reducing the dose of rucaparib [17]. Despite achieving complete remission with rucaparib, the patient experienced disease progression one year later as a platinum-resistant HGSOC patient, leading to discontinuation of rucaparib due to elevated CA-125 levels. She was then switched to alternative chemotherapy agents, such as bevacizumab and gemcitabine, which she is currently receiving for HGOSC while being on multidrug therapy. A similar case of HGSCO reported a partial response with a decrease in CA-125 levels after six cycles of gemcitabine plus bevacizumab. This combination may have synergistic effects by targeting both tumor cells and tumor vasculature [18]. Patient also developed, Chemotherapy induced thrombocytopenia, most probably induced by Gemcitabine, and was treated with Romiplostim, which is recommended by National Comprehensive Cancer Network (NCCN) in 2022 [19].

This case underscores the importance of monitoring patients with multiple comorbidities and managing adverse effects promptly. Adjusting drug doses as needed is essential to optimize treatment while minimizing adverse effects. Rucaparib has shown promising results in clinical trials, but its use may be limited by adverse effects, as demonstrated in this case. Further research is needed to identify the optimal treatment strategies for patients with ovarian cancer who have multiple comorbidities and complex medical histories.

Conclusion

The case study presented a 57-year-old menopausal patient with multiple comorbidities, including hypertension, type 2 diabetes mellitus, and hypothyroidism. The patient also had a history of breast cancer with BRCA2 germline mutation and later developed high-grade serous ovarian carcinoma. Despite severe adverse reactions to various chemotherapy agents, such as carboplatin, the patient has survived for over two years with multiple lines of treatment, including rucaparib for platinum-resistant ovarian cancer. The patient is currently receiving gemcitabine plus bevacizumab for HGSOC and is on multidrug therapy for various comorbidities. This case illustrates the importance of tailored treatment plans for each patient, taking into account their medical history, genetic profile, and response to therapy.

Acknowledgment

The authors thank the patient for agreeing to be a part to this study. The authors also thank Dr Devina Aswal and Prachi Sharma from DHSPL, Ahmedabad, India for their contributions to the study and development of this manuscript.

References

1. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-grade serous ovarian cancer: Basic sciences, clinical and therapeutic standpoints. Int J Mol Sci. 2019;20(4):952.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
3. Hollis RL, Croy I, Churchman M, Bartos C, Rye T, Gourley C, et al. Ovarian carcinosarcoma is a distinct form of ovarian cancer with poorer survival compared to tubo-ovarian high-grade serous carcinoma. Br J Cancer. 2022;127(6):1034-42.

4. Będkowska GE, Gacuta E, Zajkowska M, Głażewska EK, Osada J, Szmitkowski M, et al. Plasma levels of MMP-7 and TIMP-1 in laboratory diagnostics and differentiation of selected histological types of epithelial ovarian cancers. J Ovarian Res. 2017;10(1):39.

5. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329-33.

6. Luo Y, Lee M, Kim HS, Chung HH, Song YS. Effect of neoadjuvant chemotherapy on platinum resistance in stage IIIC and IV epithelial ovarian cancer. Medicine (Baltimore). 2016;95(36):e4797.

7. Colombo N, Sessa C, Du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO–ESGO consensus conference recommendations on ovarian cancer: Pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol. 2019;30(5):672-705.

8. Marino D, Zichi C, Audisio M, Sperti E, Di Maio M. Second-line treatment options in hepatocellular carcinoma. Drugs Context. 2019;8:1-13.

9. Garzon S, Laganà AS, Casarin J, Raffaelli R, Cromi A, Franchi M, et al. Secondary and tertiary ovarian cancer recurrence: What is the best management? Gland Surg. 2020;9(4):1118-29.

10. Flynn MJ, Ledermann JA. Ovarian cancer recurrence: is the definition of platinum resistance modified by PARPi and other intervening treatments? The evolving landscape in the management of platinum-resistant ovarian cancer. Cancer Drug Resist. 2022;5(2):424-35.

11. Mylavarapu S, Das A, Roy M. Role of BRCA mutations in the modulation of response to platinum therapy. Front Oncol. 2018;8:16.

12. Monk BJ, Parkinson C, Lim MC, O'Malley DM, Oaknin A, Wilson MK, et al. A randomized, phase iii trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45). J Clin Oncol. 2022;40(34):3952-64.

13. Shirley M. Rucaparib: A review in ovarian cancer. Target Oncol. 2019;14(2):237-46.

14. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10106):1949-61.

15. Ledermann JA, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): Post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(5):710-22.

16. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol. 2019;20(1):e15-28.

17. Labadie BW, Morris DS, Bryce AH, Given R, Zhang J, Abida W, et al. Guidelines for management of treatment-emergent adverse events during rucaparib treatment of patients with metastatic castration-resistant prostate cancer. Cancer Manag Res. 2022;14:673-86.

18. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and ovarian cancer: A comprehensive review. Cancers. 2020;12(12):3730.

19. Griffiths EA, Roy V, Alwan L, Bachiashvili K, Baird J, Cool R, et al. NCCN guidelines® insights: Hematopoietic growth factors, version 1.2022: Featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2022;20(5):436-42.