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Case report

Non-surgical management of advanced ovarian cancer with maintenance PARP inhibitors

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A B S T R A C T

The standard of care for advanced ovarian cancer is cytoreductive surgery followed by a platinum-taxane combination with PARP inhibition as a maintenance strategy. In practice, many advanced ovarian cancer patients are older and are either not candidates for surgery or decline surgical intervention. There are limited data for using PARP inhibitor maintenance in the non-surgical patient population. We describe two cases of patients with advanced-stage ovarian cancer who received platinum-taxane chemotherapy and declined surgical debulking. They were continued on maintenance PARP inhibitors and have no evidence of disease for over four years.

1. Introduction

In 2023, 19,710 people were diagnosed with ovarian cancer and about 13,270 died from ovarian cancer. The median age at diagnosis was 63 years (American Cancer Society, 2023). The standard of care for advanced ovarian cancer is cytoreductive surgery and platinum-taxane combination chemotherapy (Network, 2023). In patients with high disease burden, neoadjuvant chemotherapy followed by interval cytoreductive surgery (ICS) was non-inferior to primary cytoreductive surgery followed by adjuvant chemotherapy (Vergote et al., 2010; Kehoe et al., 2015; Fagotti et al., 2020). With the advent of PARP inhibitors (PARPi), upfront treatment has been followed by maintenance therapy with PARPi and/or bevacizumab (Tew et al., 2020). However, many women diagnosed with ovarian cancers are older and some are poor surgical candidates. While in most trials these patients were still eligible to receive PARPi irrespective of surgical intervention, the magnitude of benefit from PARPi in these non-surgical patients has not been fully described. At this point, the management of these patients has been dependent on subgroup analysis of randomized trials, prospective real-life population-based studies, and retrospective studies (Rousseau et al., 2023 Sep). Here, we describe two cases of advanced ovarian cancer in which the patients received chemotherapy and PARPi maintenance but did not undergo cytoreductive surgery. Both of these patients are now more than four years from diagnosis with no evidence of disease.

2. Cases

The first patient was a 79-year-old woman with type 2 diabetes, hypertension, and latent tuberculosis with a family history of breast cancer who initially presented with abdominal pain. Imaging on presentation showed a 7.2 cm ovarian mass, paraaortic lymphadenopathy, mild hydronephrosis and possible liver lesions. Biopsy demonstrated high-grade adenocarcinoma of Mullerian origin. Her CA-125 was 122 U/mL. She initially started carboplatin AUC 5 for cycle one to assess tolerability and paclitaxel 175 mg/m^2 was added for cycle two. For cycle three, the patient received reduced dose paclitaxel (140 mg/m^2) for neuropathy. After three cycles, she underwent interval imaging which illustrated a decrease in the left ovarian mass, lymphadenopathy, and resolution of left hydroureteronephrosis. She was offered interval cytoreductive surgery, which she declined citing personal preference. She then completed chemotherapy with three cycles of single-agent carboplatin, as paclitaxel was held for progressive neuropathy. After the completion of six cycles of chemotherapy, imaging demonstrated an interval decrease in the size of the left ovarian mass and ongoing improvement in the left periaortic lymphadenopathy. CA-125 was 18 U/mL. Germline genetic testing demonstrated a BRCA2 mutation. Four weeks after her last dose of chemotherapy, per SOLO1, she was started on olaparib 200 mg twice daily which was dose reduced for baseline impaired kidney function. She underwent routine lab checks biweekly, which were later extended to monthly. CA-125 has been monitored every three months. She has remained on olaparib without evidence of disease and stable CA-125 for 4.5 years (Fig. 1).

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The second patient was a 79-year-old woman with a history of hemorrhagic stroke, hypertension, and Sjogren's syndrome who presented with shortness of breath, lower extremity edema, and oliguria. Imaging exhibited an eight-centimeter complex right pelvic wall mass, smaller masses along the left pelvic wall, tumor encasing small bowel, omental caking, large volume ascites, hepatic/splenic subcapsular implants, and sclerotic foci on the pelvis and several vertebrae. Labs were notable for a CA-125 of 598 U/mL. Cytology from a paracentesis demonstrated serous carcinoma of gynecologic origin. Gynecologic oncology recommended neoadjuvant chemotherapy with interval scans to determine surgical candidacy, and the patient was referred to medical oncology. Her course was complicated by a bowel obstruction requiring decompression with a venting gastric tube and initiation of total parenteral nutrition. She started on single-agent carboplatin AUC 5 for two cycles in light of her poor functional status. Given clinical improvement, she received two cycles of carboplatin in conjunction with paclitaxel. Interval imaging illustrated disease response, and she was recommended for interval cytoreductive surgery. The patient declined, hoping to receive sufficient benefit from chemotherapy and avoid surgery. She then received three more cycles of carboplatin and paclitaxel. CA-125 was 8 U/mL upon the completion of chemotherapy. Imaging after completion of chemotherapy demonstrated no evidence of disease. She was referred for surgery, and again she declined. Germline testing was negative for BRCA mutation. Homologous recombination status was evaluated via next generation sequencing by Foundation Medicine, but the loss of heterozygosity (LOH) score could not be determined as the sample was not of sufficient quality to confidently define LOH. Per PRIMA, five weeks after her last dose of chemotherapy, she started on niraparib 200 mg daily, dose reduced for her weight (González-Martín et al., 2019) (Fig. 2). PARPi course was complicated by thrombocytopenia and headaches which improved with further dose reduction to 100 mg daily. She has now been on niraparib for three years without signs of disease by CA-125.

Many women diagnosed with epithelial ovarian cancer are older than 65 years of age. While great strides have been made to increase survivorship, the prognosis for older patients with ovarian cancer remains markedly poor. Older age has been reported to be a risk factor for premature death in several population-based studies (Rousseau et al., 2023 Sep). Pectasides et al. reported that age greater than or equal to 70 years is an independent risk factor for premature death, in addition to FIGO stage III-IV disease, high-grade histology, performance status greater than 1, and residual disease greater than two centimeters (Pectasides et al., 2007).

A significant limitation for older patients with ovarian cancer is the feasibility and interest in surgical cytoreduction. Surgical debulking to R0, no residual macroscopic disease, remains a mainstay of ovarian cancer management and is one of the most important predictors of survival (Elattar et al., 2011 Aug). Cheeseman et al. described the characteristics of patients with ovarian cancer in seven cancer centers in six different countries around Europe and Asia (Cheeseman et al., 2023). Across all sites, late-stage patients undergoing debulking surgery were younger, less likely to have stage IV disease, and more likely to have an Eastern Cooperative Oncology Group (ECOG) score of less than two when compared to late-stage patients not undergoing debulking surgery. Marth et al. described the treatment strategies and outcomes for women with newly diagnosed advanced high-grade serous or endometrial ovarian cancer in eight Western countries (Marth et al., 2022). 19.9 % of patients did not receive any cytoreductive surgery, but their outcomes were not presented.

In these two cases, we describe two older patients with advanced disease and reduced functional status requiring dose reductions to chemotherapy and maintenance PARPi. While both patients were offered cytoreductive surgery, they both declined, acknowledging that their treatment would not be standard of care. A BRCA2 mutation was identified for the first patient, and she was started on olaparib. The second patient was started on niraparib without any known genetic or genomic alteration though notably with no evidence of disease on imaging and normalization of CA-125 following chemotherapy alone. While both SOLO-1 and PRIMA included patients who did not receive cytoreductive surgery, they were only a small minority of such patients, 1.5 % in SOLO-1 and an unknown percentage in PRIMA. The completion of surgery was not evaluated in their subgroup analyses. However, SOLO-1 demonstrates that those with residual macroscopic disease after debulking surgery who received PARPi had improved progression-free-survival compared to the placebo group (Moore et al., 2018; González-Martín et al., 2019).

There is limited literature on the use of PARPi without cytoreductive surgery. Shalowitz et al. describe a population of women who did not receive surgery from the National Cancer Database (Shalowitz et al., 2016). Of the 210,667 patients analyzed, 18 % did not receive cytoreductive surgery. Common reasons for the lack of surgical intervention included patient comorbidities contraindicating surgery, refusal by the patient, and death before surgery. Among patients older than 75, 21.5 % received only systemic chemotherapy. The median survival for these women with stage III or IV disease was 10.4 months. This analysis was performed before the FDA approval of olaparib in 2018 (Arora et al., 2021). We would greatly benefit from a repeat analysis given the advent of many new systemic treatments to the ovarian cancer armamentarium.

In conclusion, we describe two cases of advanced serous ovarian cancer in which patients received neoadjuvant chemotherapy with disease response and declined interval cytoreductive surgery. They both received a PARPi with sustained disease response. The literature describes that about 12 % of women documented with ovarian cancer do not receive cytoreductive surgery, which is associated with worse outcomes, particularly in older adults. However, little is known about the response to PARPi as maintenance therapy in the absence of cytoreductive reductive surgery. Older patients who do not receive cytoreductive surgery are a crucial population that deserves further study in

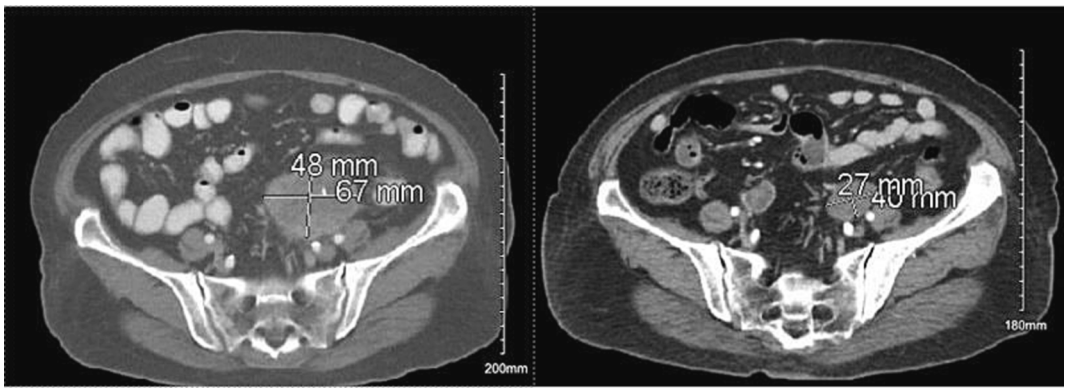

Fig. 1. Case 1 CT abdomen/pelvis. Left: Prior to systemic therapy. Right: After one year of maintenance olaparib.

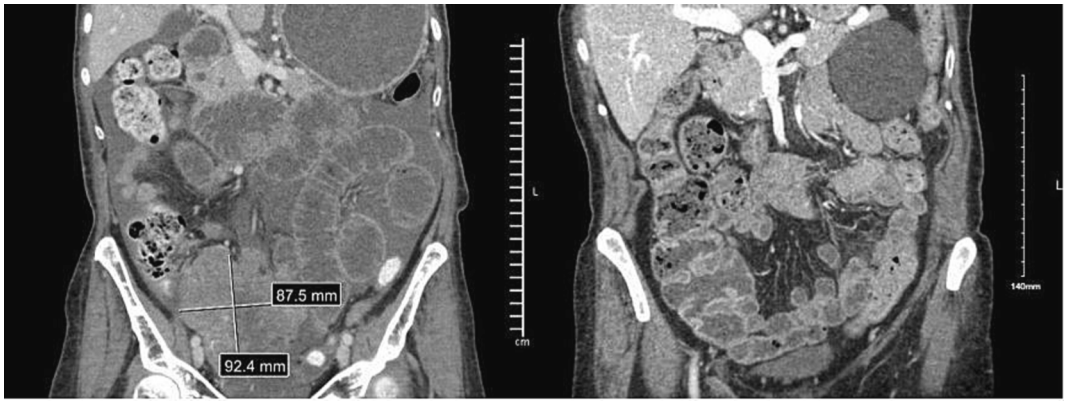

Fig. 2. Case 2 CT abdomen/pelvis. Left: Prior to systemic therapy. Right: After completion of chemotherapy.

the era of PARP inhibition.

CRediT authorship contribution statement

Taliya Lantsman: Writing – original draft, Conceptualization. **Lily Jia:** Writing – review & editing. **Meghan Shea:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Author MS sits on the advisory board of Eisai and GSK.

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