CLINICAL VIGNETTE

PARP Inhibitor Maintenance in Newly Diagnosed Advanced Ovarian Cancer

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Case Report

A 65-year-old female with no significant past medical history presented to oncology for evaluation of newly diagnosed ovarian cancer. She presented to the emergency room two weeks prior with progressive abdominal pain, bloating, and constipation for several months. Physical exam in the emergency room revealed ascites. CT abdomen/pelvis demonstrated bilateral adnexal masses, 10cm on the right and 9cm on the left, widespread peritoneal carcinomatosis, and massive ascites. CT chest showed a 1cm solid left upper lobe nodule and a trace left pleural effusion. The patient underwent paracentesis with 4.3L removed and improvement of symptoms. Pathology from peritoneal fluid revealed adenocarcinoma. She then underwent biopsy of an omental lesion which revealed high-grade serous carcinoma of Mullerian primary. CA-125 was elevated at 2000.

She was referred to medical oncology and surgical gynecologic oncology. She was treated with three cycles of neoadjuvant chemotherapy with carboplatin, paclitaxel, and bevacizumab. Repeat imaging showed marked decrease in peritoneal carcinomatosis and resolution of ascites and adnexal masses. Repeat CA-125 was 15. She underwent interval optimal cytoreduction with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, and tumor debulking of implants followed by three cycles of adjuvant chemotherapy with carboplatin, paclitaxel, and bevacizumab. Pathology confirmed high-grade serous carcinoma with significant treatment effect. Invitae genetic testing was positive for BRCA1. After adjuvant chemotherapy was completed, patient was started on maintenance therapy with bevacizumab and olaparib (a PARP inhibitor).

Discussion

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in the United States with 21,750 estimated new cases in the United States in 2020.[1] The most common presenting symptoms are nonspecific and include pelvic pain or pressure, bloating, urinary urgency or frequency, and gastrointestinal symptoms. As such, most women are diagnosed with advanced stage disease which is associated with high relapse rates. Improved treatment options are needed.

PARP inhibitors are approved for maintenance therapy in advanced ovarian cancer. PARP inhibitors block the repair of DNA *single* strand breaks resulting in cell death due to inadequate DNA cell repair mechanisms. For women with BRCA mutations, which results in dysfunctional repair of DNA *double* strand breaks, the magnitude of benefit of PARP inhibitors is increased.

PARP inhibitors have been FDA approved for use in the maintenance setting for women with ovarian cancer who had a complete or partial response to first-line platinum-based chemotherapy.[2] The SOLO1 trial was a phase III randomized clinical trial that compared olaparib 300mg PO bid maintenance therapy to placebo in 391 women with advanced, high-grade, BRCA-associated serous or endometrioid ovarian cancer that had a complete or partial response to front-line platinum-based chemotherapy.[3] Updated 5 year follow up showed 48.3% of women treated with olaparib had not experienced disease progression compared to 20.5% of those in the placebo arm with a PFS of 56 months vs 13.8 months, respectively.[4] The PAOLA-1 trial was a phase III randomized clinical trial that compared maintenance therapy with olaparib plus bevacizumab vs bevacizumab alone in 806 women with advanced, high-grade, serous or endometrioid ovarian cancer who responded to front-line platinum-based chemotherapy.[5] Among all women, regardless of BRCA mutation, olaparib plus bevacizumab improved PFS compared to bevacizumab alone with a PFS 22.1 months vs 16.6 months, respectively. Among women with BRCA mutations, olaparib plus bevacizumab improved PFS compared to bevacizumab alone with a PFS of 37.2 months vs 21.7 months, respectively. Finally, the PRIMA trial was a phase III randomized clinical trial that compared niraparib to placebo in the maintenance setting after front-line platinum-based chemotherapy in advanced ovarian cancer, regardless of BRCA status, in 733 women.[6] PFS was 13.8 months in the niraparib group vs 8.2 months in the placebo group in all-comers. Subgroup analysis in women with BRCA mutations revealed PFS of 22.1 months in the niraparib arm vs 10.9 months in the placebo arm. Subgroup analysis in women who lacked a mutation revealed PFS of 8.1 vs 5.4 months, respectively.

Overall, PARP inhibitors are well-tolerated. The most common side effects include fatigue, GI symptoms, thrombocytopenia, anemia, and neutropenia. Rare, but significant effects, include AML, MDS, and pneumonitis. Patients should be monitored closely while on PARP inhibitors.

All women diagnosed with ovarian cancer should be sent for genetic testing. Women with newly diagnosed serous or endometrioid ovarian cancer with BRCA mutations or HRD positive tumors who have had a complete or partial response to front-line platinum-based chemotherapy should be offered maintenance therapy with olaparib (with or without bevacizumab) or niraparib. Women with no mutations should be offered maintenance niraparib, bevacizumab, or observation as clinically appropriate.

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