

Complete Response of a Mutated *BRCA2* Metastatic Clear Cell Endometrial Adenocarcinoma to the Poly (ADP ribose) Polymerase (PARP) Inhibitor Olaparib

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Abstract. *Background: Cancer of the endometrium is the most common gynecologic malignancy in developed countries and the second most common in developing countries. Endometrioid tumors tend to have a favorable prognosis and typically present at an early stage with abnormal uterine bleeding. Clear cell carcinoma as well as serous endometrial carcinoma are associated with a poorer prognosis. Patients with metastatic endometrial cancer are treated with systemic therapy either following surgery or as primary therapy. As far as second-line chemotherapy is concerned, there are no general agreements on the chemotherapy to be used. Furthermore, to the best of knowledge, there are no studies on the use of poly (ADP ribose) polymerase (PARP) inhibitors in endometrial cancer even in BRCA mutated tumors. Case Report: We here present the case report of an 81-year-old woman with a mutated BRCA2 metastatic clear cell endometrial adenocarcinoma that showed an excellent clinical and radiological response to the PARP inhibitor olaparib. Conclusion: Olaparib could be successfully used in this patient setting.*

Endometrial cancer is the most common gynecological cancer in developed countries; its incidence is gradually increasing due to the increased prevalence of obesity and

population ageing. In contrast to the declining trends for many common tumors, mortality remained more or less the same during the last decades (1, 2).

Although endometrial cancer is often diagnosed at an early stage and prognosis is generally good, a small (but significant) percentage of patients have or develop soon after diagnosis metastatic or recurrent diseases, not susceptible to localized therapies. These women have an unfavourable prognosis.

Case Report

Here, we present the case of a 81-year-old woman with abnormal vaginal bleeding. The endometrial biopsy revealed the presence of endometrial adenocarcinoma. Therefore, on May 2017, she received total laparoscopic hysterectomy (TLH). The final histology showed a clear cell endometrial carcinoma, involving the cervical stroma, with negative margins, and negative for the presence of emboli. The lesion was 4 cm (maximum diameter), infiltrating the myometrium for 0.3/1.3 mm. Outbuildings and omentum were negative. Due to the stage of the disease, the patient underwent periodic follow-up without any further treatment.

We met the patient again one year and a half later, when a pelvic magnetic resonance imaging (MRI) revealed the appearance of a 1.5 cm recurrence nodule on the vaginal dome. A positron emission tomography-computed tomography (PET-CT) scan revealed fluorodeoxyglucose avidity (FDG) not only in this area but also in 4 metastatic lung nodules, already highlighted by a CT, carried out after a pelvic MRI.

A month later, on 18.10.2018, the patient underwent a surgical removal of the nodule of recurrence at the expense of the vaginal dome. Definitive histological examination showed an endometrial clear cell adenocarcinoma. Adjuvant pelvic radiotherapy was excluded because of past radiotherapy pelvic treatment for rectal cancer (5 Gy × 5 fractions) 15 years ago.

Systemic chemotherapy has been therefore started with: Carboplatin/Paclitaxel/Avastin. After 3 cycles, a PET/TC

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re-evaluation showed that 3 out of 4 lung nodules disappeared, with the one at the middle lobe still lasting. Therefore, she received fractionated stereotactic body radiation therapy (FSBRT) on the metastatic lung nodule of the middle lobe with the use of the Cyber Knife (CK) technique (Total dose: 54 Gy in 3 sessions of 18 Gy each), which finished on 15/03/2019. The patient was then treated with Bevacizumab until re-evaluation.

A PET-CT carried out in May 2019 showed further recurrence of the vaginal dome. A detailed genomic testing c/o ONCOLOGICA (Cambridge) was carried out on the surgical specimen, revealing the presence of the *BRCA2* mutation p.K3326*/c.9976A>T. Due to the *BRCA2* mutation, the Oncology Team discussed the opportunity of administering the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib, starting at 600 mg Per Os (PO) Bis In Die (BID) (150 mg per pill). After at least 5 months of treatment, a PET/CT showed complete remission (CR). Unfortunately, 3 months later, an MRI showed two cerebral brain metastases in the right fronto-parietal lobe. Then, multi fraction-stereo radio surgery (mf-SRS), 9 Gy × 3, through CK was started, in conjunction with olaparib, at the same dosage as before. Twenty four months from starting olaparib treatment, and 15 months after the end of mf-SRS, the patient is in complete remission.

Discussion

The incidence of endometrial cancer is around 1 to 2% in the United States and is the fourth most common cancer in women in the United States. The incidence picks between 16 and 60 years of age, but 2 to 5% occurs before the age of 40. Endometrioid tumors tend to have a favorable prognosis and typically present at an early stage with abnormal uterine bleeding. Clear cell carcinoma as well as serous endometrial carcinoma are associated with a poorer prognosis (2).

Systemic therapy in chemotherapy naive patients. Patients with metastatic endometrial cancer are treated with systemic therapy either as adjuvant treatment or as primary therapy. The benefit of multiagent chemotherapy for advanced, recurrent, or metastatic endometrial cancer was shown in a metaanalysis of 220 trials that compared the administration of a combination of multiagents (more intensive regimens with less intensive combinations, 3 vs. 2 agent combinations, or 2 agents vs. 1 agent). The major findings of this analysis included:

First, compared with the administration of less intensive regimens, the use of more intensive regimens (8 trials) resulted in an improvement in progression-free survival (PFS) from six months with less intensive regimens to seven months with more intensive ones (HR=0.82) and an overall survival (OS) from 9 to 10.5 months (HR=0.86). Trials that compared doxorubicin with or without additional drugs favoured the

arms incorporating additional chemotherapy. Second, the administration of more intensive chemotherapy regimens also increased the risk of serious nausea and vomiting. Further data, especially from the GOG 209 study, supported the use of carboplatin plus paclitaxel combination (3).

GOG 209 phase 3 randomized trial aimed to demonstrate the non-inferiority of the experimental chemotherapy regimen over the standard regimen. A total of 1,300 chemotherapy naive patients treated for recurrent endometrial cancer were randomly assigned to carboplatin plus paclitaxel or TEP (taxol-epirubicin-paclitaxel). This regimen was administered every three weeks, for a total of 7 cycles. Based on the results of GOG 209, the comparison between the two arms indicated: 1) similar overall response rate; 2) similar PFS; 3) similar OS; 4) statistically significant reduction in the incidence of grade 2 or 3 toxicities including sensory neuropathy, thrombosis, emesis, diarrhea, and metabolic derangements.

As far as second-line chemotherapy is concerned, there are no specific guidelines on the chemotherapy to be used. Usually, in patients with a long platinum-free interval (more than six months) the same association of carboplatin with paclitaxel can be used, whereas in patients with a short platinum-free interval, other drugs have been traditionally used (doxorubicin, topotecan, *etc.*) (4-6).

Bevacizumab. The anti-VEGF monoclonal antibody bevacizumab (15 mg per kg, injected intravenously every 3 weeks) seems to be effective in endometrial cancer both as a single agent and when combined with chemotherapy, but up to now, it has not become the standard first or second-line therapy.

In first-line treatment, bevacizumab in combination with chemotherapy has been evaluated in a 3 arm randomized phase 2 NRG Oncology study/GOG 86 P trial, which randomly assigned 349 patients (over 80% of whom had received prior radiation therapy) to treatment to one of 3 arms using: 1-carboplatin and paclitaxel plus bevacizumab, 2-carboplatin and paclitaxel plus temsirolimus, or 3-carboplatin and ixabepilone plus bevacizumab. The main results were compared with the historical reference from GOG 209, discussed above.

There was no statistically significant difference in PFS compared with the historical reference for any of the arms, but median OS was improved with the addition of bevacizumab to chemotherapy (7).

Investigational agents - molecular or genetic based drugs. With the advance of the extensive molecular and genetic profiling of tumors, several pathways have been identified. Among them, P13K/PTEN/EKT/mTOR pathway inhibitors have been used with some results. HER2 over-expressing tumors have been successfully treated with trastuzumab plus chemotherapy until progression of disease.

Moreover, mismatch repair (MMR) deficient tumors or MMR/Microsatellite instability (MSI)-h or tumor mutation burden (TMB) have been used to select immune check point inhibitors usage with very important results. The case of this patient is a case of a *BRCA* mutated tumor.

Parp inhibitors. To the best of our knowledge, there are no studies using PARP inhibitors in endometrial cancer even in *BRCA* mutated tumors. Up to now, PARP inhibitors have been approved as a standard treatment for ovarian cancer and metastatic breast cancer. More recently, olaparib obtained (FDA and EMA) approval for:

- 1) *BRCA* mutated metastatic pancreatic adenocarcinoma and
- 2) *BRCA* mutated and homologous recombinant deficient (HDR) advanced and metastatic hormone-sensitive prostate cancer.

The only published results on olaparib treatment in endometrial adenocarcinoma derive from the case report of a 58 woman with brain metastasis from endometrial adenocarcinoma (8) where a clear reduction in brain lesions (plus subjective improvement of symptoms) after 10 weeks was shown. After disease progression, a biopsy showed loss of PTEN, a known tumour suppressor gene linked with HRD, functionally linked to *BRCA* 1/2 somatic mutations, both targeting DNA repairs.

Finally, three large studies are ongoing with PARP inhibitors in endometrial recurrent or metastatic cancer: a phase 2 study using niraparib in 44 patients (NCT03016338) (8) and two randomized control studies with rucaparib and olaparib in metastatic endometrial cancer patients (NCT03617679 and NCT03745950) (8).

Conclusion

In our case, 3 months of olaparib therapy (cps 50 mg) at 800 mg PO BID obtained CR. Unfortunately, due to several grade 3-4 toxicities, treatment had to be discontinued and 9 months after, an MRI documented 2 cerebral secondary brain lesions. At this point, combined treatment with radiotherapy using CK at 9 Gy \times 3 fractions and olaparib (150 mg tablet) 600 mg per OS BID was administered. However, olaparib was stopped after 3 months of treatment due to patient refusal because of grade 2-3 toxicity. Sixteen months after the appearance of brain metastasis the patient is still in CR. Despite the use of radiation therapy, the clear effect of olaparib can still be observed.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

Authors' Contributions

All Authors actively participated in the data collection. The article was written by Dimitri Anzellini and revised by Sergio Del Bianco.

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