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Case Report

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Complete Response following Treatment with Olaparib in a Patient with *BRCA*-Mutant High Grade Serous Ovarian Cancer and Central Nervous System Metastases

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Introduction

Ovarian cancer is the leading cause of death from gynecological cancers worldwide. High grade serous ovarian cancer is the most frequent and aggressive sub-type of ovarian cancer. Despite recent improvements in treatment, the 10-year survival rate for HGSOC is <30%. While brain metastasis is a frequent occurrence in breast, lung, and melanoma, it is rarely observed in OC. The exact incidence of brain metastasis in OC is unknown but is estimated at 1.34%. Brain metastasis represents a rare but life threatening complication due to the lack of effective drugs that are able to across the blood brain barrier. It is proposed that the risk of brain metastasis in BRCA-mutated OC is three-fold higher than non-mutated BRCA. Treatment options include radiotherapy, systemic therapy, and rarely surgery. In patients with brain metastases treated with systemic chemotherapy, the median survival is poor, ranging from 2.5 to 7 months. Poly-ADP-ribose-polymerase (PARP) inhibitors take advantage of the homologous recombination deficiency in patients with BRCA mutation leading to synthetic lethality. PARP inhibitors are now approved as maintenance therapy in platinum sensitive mutated BRCA OC in both upfront and recurrent disease setting. We present a case of a 48-year-old woman with relapsed brain metastasis from high-grade serous ovarian cancer that was treated with olaparib with a complete intra-cranial response remaining free of disease progression from 2018 until the present time. The patient provided written informed consent for the publication of the case study.

Case

A 48 year old female presented to the Gynecology department in December 2016 with symptoms of vaginal bleeding and abdominal distension. Family history was suspicious for hereditary breast and ovarian cancer syndrome with her mother diagnosed and treated for breast cancer at age 60 and sister diagnosed with breast cancer at the age of 46. Abdominal and pelvic ultrasound showed right ovarian mass highly suspicious for ovarian cancer with low volume ascites. CA 125 at presentation was 562U/mL. Biopsy of peritoneum showed high grade serous ovarian cancer consistent with primary ovarian adenocarcinoma. She underwent primary debulking surgery on the 14th of February 2017 in a private hospital. Histopathology revealed high grade serous ovarian cancer with lymph node metastases staged as FIGO IIIC. She proceeded to adjuvant chemotherapy with three weekly Carboplatin AUC 6 and Paclitaxel 175mg/m^2 for 6 cycles from April 2017 to July 2017. Post chemotherapy computerized tomography (CT) scan showed complete response and no evidence of disease. The patient was referred for germline genetic testing and was found to have germline *BRCA2* mutation.

On the 10th of March 2018, the patient presented acutely with left hemiparesis to a private hospital. Magnetic resonance imaging (MRI) of the brain showed multiple enhancing lesions in both cerebral hemispheres (figure 1). PET-CT scan showed no evidence of FDG-avid disease extra-cranially. CA-125 remained normal at 13U/mL. She was started on oral dexamethasone 8mg once daily for 3 days then tapered down to 4mg once daily. Olaparib was started at a dose of 400mg twice daily. Her symptoms improved within two weeks and she continued Olaparib. The patient sought a second opinion abroad. On the 5th of May 2018, a repeat MRI was done at another institution which showed a near complete resolution of the brain metastasis. She received ablative stereotactic radiotherapy to the persistent lesion in the right posterior frontal lobeby cyberknife with total dose of 20Gy and continued on Olaparib. Subsequent follow up imaging of brain MRI shows continued response to Olaparib with no evidence of progression. At the time of writing 3 years later, the patient remains in complete remission with no recurrence intra- or extra-cranially.

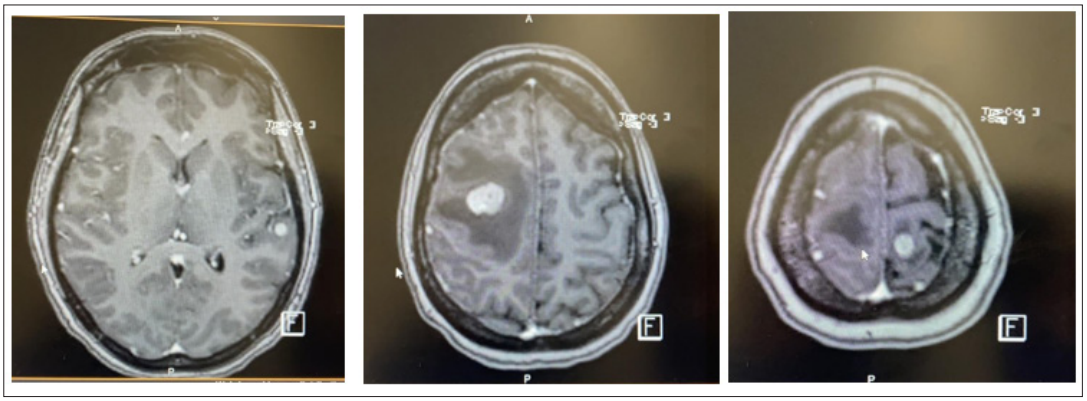

Figure 1: MRI brain March 2018 (Axial view) showing multiple metastatic lesions in both hemispheres with largest lesion in the right posterior frontal lobe measuring 2cm with mass effect and a 2.6mm midline shift.

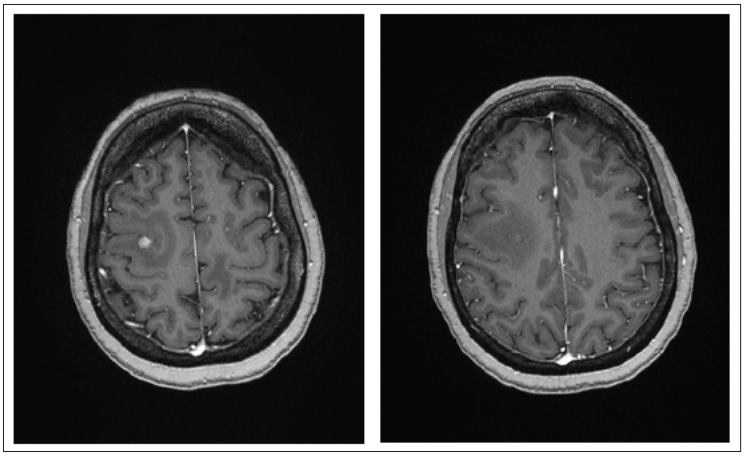

Figure 2: MRI brain May 2018 after treatment 2 months of treatment with Olaparib showing resolution of all lesions except the right posterior frontal lobe lesion.

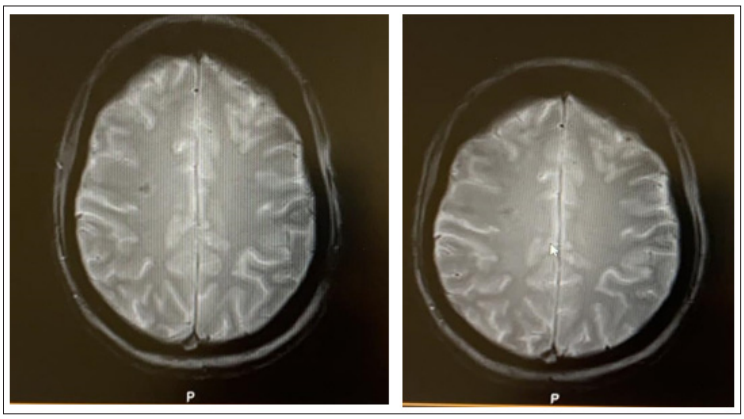

Figure 3: MRI Brain March 2020 (left) and March 2021 (right) (axial view) showing stable disease of the brain metastasis (which is now calcified) with no new metastasis.

Discussion

Ovarian cancer (OC) is the leading cause of death from gynecological cancers worldwide. High grade serous ovarian cancer (HGSOC) is the most frequent and aggressive sub-type of ovarian cancer. Despite recent improvements in treatment, the 10-year survival rate for HGSOC is <30% [1]. While CNS involvement is common in breast, lung, and melanoma, it is rarely observed in OC. The exact incidence of brain metastases (BM) in OC is unknown but is estimated at 1.34% [2]. BM can occur as a result of hematogenous dissemination. Rarely, OC cells can invade the meninges via direct invasion from bone or lymphatic spread [3]. BM represents a rare but life threatening complication due to the lack of effective drugs that are able to across the blood brain barrier (BBB). It is proposed that the risk of BM in BRCA-mutated OC is three-fold higher than BRCA wild type. Surgery, radiotherapy, and systemic chemotherapy are the main options of treatment. The prognosis of women with OC and BM remain dismal with a median OS of 10.1 months [4]. Few case reports have described improved progression free survival in patients who were BRCA positive with PARP inhibitors.

In a review of BM in OC, 79% of all OC were found to have high grade serous OC as primary tumour subtype, followed by endometroid, mucinous and clear cell. Furthermore, the majority

of patients (86%) had advanced FIGO stage at diagnosis. Age < 50 years at primary tumour diagnosis and Karnofsky performance status ≥70 were associated with an improved outcome. Sehouli et al. reported that platinum sensitivity of the primary tumour is associated with a better prognosis (HR 0.23, 95%CI 0.12-0.48) [3]. Factors associated with worse survival are the presence of more than one brain lesion and the number of previous extra-cranial relapses before a diagnosis of BM [4].

Clinical presentation of BM depends on the location and the number of metastasis. Headache is the most common symptom and is present in approximately 50% of cases. Up to 40% of patients present focal neurological deficit and 15-20% develop seizures. Most of patients with BM are symptomatic at diagnosis and most cases (58.1%) have multiple lesions. In a large case series by Marchetti et al.up to 26% of patients did not have any symptoms at diagnosis possibly suggesting that patients who are high risk of BM, more judicious surveillance might be necessary.

MRI of the brain with gadolinium contrast is the gold standard for diagnosis of BM as it allows better resolution and examination of the posterior fossa and the assessment of leptomeningeal disease [2]. It is unclear whether CA-125 plays a role in diagnosis of BM. In our case, the levels of CA-125 were normal reflecting perhaps the absence of systemic relapse in which elevation of CA-125 is expected.

Radiotherapy can achieve local control of BM and in the presence of multiple brain metastases, whole brain radiotherapy (WBRT) is the often the treatment of choice. Cohen et al. reported the improved median survival in patients who received WBRT in combination with surgery in comparison to patients who received WBRT or surgery alone (23 months, 5.33 months, and 6.9 months respectively) [5]. However, side effects of WBRT such as cognitive impairment can have significant impact on patients' quality of life. More recently, stereotactic radiosurgery (SRS) is the preferred option for local control in patients with single or limited BM and in patients who are not candidates for surgical resection. Lee et al. reported improved outcomes of patients treated with SRS in comparison to WBRT regardless of the number of BM (29 months vs. 6 months; p=0.00061) [6].

In a very selective group of patients, surgical excision might be considered particularly in the presence of raised intra-cranial pressure. One advantage is the histological confirmation of the tissue hence the analysis of prognostic and predictive biomarkers. Surgery combined with radiotherapy and/or chemotherapy lead to improved median OS (21.8 and 20.15months) compared to a single modality treatment by surgery or radiotherapy alone (6.5 months and 5.4 months respectively) [4].

Although platinum therapy is the corner stone of treatment in OC, its role in BM is controversial. In theory, patients with BM, the BBB have been breached by cancer cells. Yet, many drugs fail to cross the BBB and reach the CNS in adequate concentrations. In patients with BM, who were treated with systemic chemotherapy, the median survival is poor ranging from 2.5 to 7 months. The exact role of chemotherapy is not well defined in this population due to the rarity of BM occurrence in OC.

The Cancer Genome Atlas Research project revealed that up to 50% of HGSOC display deficiency in homologous repair pathways. Germline and somatic *BRCA1/2* mutations are well-known causes of homologous repair deficiency (HRD). However, there are other genetic abnormalities of the HR repair pathway that could cause HRD. These are measured by genomic scar scores and are currently part of the myChoice HRD test with an accepted threshold of 42 for a positive HRD score. Poly-ADP-ribose-polymerase (PARP) inhibitors leads to synthetic lethality by inhibition of DNA single-stranded break repair mechanisms. *BRCA1/2* mutant OC are exquisitely sensitive to platinum-based chemotherapy, and those patients have significantly improved OS in comparison to non-*BRCA* mutated tumours [7]. Currently, three PARPi (rucaparib, niraparib and olaparib) are approved by the FDA for the treatment of OC as maintenance therapy in *BRCA* mutated platinum sensitive relapsed HGSOC and as upfront maintenance therapy in *BRCA* mutated HGSOC after partial or complete response to platinum therapy.

Due to the location, distinct biology, and limited treatment options, CNS metastasis is associated with poor survival. Masoodi et al. evaluated the molecular profile of eight OC patients with BM using next generation sequencing. Interestingly, seven out of the eight cases harbored BRCA1/2 mutations. All samples showed somatic or germline mutations in at least one gene involved in DNA repair (*BRCA1/2*, ATM, CHK2) [8]. Sekine et al. and Szarszewska et al. both reported a high prevalence of BRCA1 protein loss in patients with BM from OC [9,10]. For PARPi to achieve a therapeutic benefit they need to cross the BBB and the brain metastasis should present homologous recombination deficiency [11]. Diossy et al. examined the levels of HRD scores in patients with breast cancer brain metastasis to their corresponding primary tumors. They reported that 14 out of 16 cases of brain metastasis had higher myChoice HRD score than the primary tumor and for four cases of brain metastasis had switched from low myChoice HRD score (HRD-) primary tumor to a high myChoice HRD score (HRD+). Furthermore, there was a significant correlation between the changes in the scores and the time elapsed from the detection of the primary tumor and presence of brain metastasis. The author proposed that the significant increase in HRD scores in BM may arise from two distinct mechanisms. One is the clonal selection of tumor cells with higher HRD scores as these are more genomically unstable and able to adjust to a distinct environment such as the brain. Secondly, it is also possible that growing brain metastases become gradually more genomically unstable due to some unidentified mechanism [11].

PARP Inhibitors in CNS Metastasis

More recent work showed that in rodent models with disrupted BBB, PARP inhibitors have adequate CNS penetration [12.13]. Despite the finding that rucaparib, another PARP inhibitor, has limited brain activity in murine models with intact BBB, anti-tumour effects were observed in *BRCA* 1 mutant intracranial murine model [12]. PARPi are has utilized as a therapeutic strategy in combination with chemotherapy or radiation in the management of gliomas. DNA repair mechanisms have been implicated in temozolamide resistance and PARP enzyme plays an important role in repairing DNA damaged caused by temozolamide thus reducing its efficacy. Inhibition of PARP has shown significant activity in various preclinical and clinical studies of glioma. Olaparib has also been shown to increase radiosensitivity in glioma cell lines [14]. A study by Chalmer et al. showed that in patients with recurrent glioblastoma multiforme (GBM), olaparib reached the tumor site. Similarly, rucaparib was shown to penetrate the brain and in human GBM xenografts. Co-administration of rucaparib with temozolmide in preclinical models demonstrated complete regression of tumors >60 days. A newer third generation PARPi, pamiparib, has also showed ability to penetrate the brain in animal models and significantly improved survival time when administered with temozolomide [14]. These observations suggest

that there is a potential role for PARP inhibitors in patients with intra-cranial metastases.

In the OlympiAD trial, a randomized phase III trial of olaparib vs. treatment of physician choice in patients with metastatic breast cancer and *BRCA* mutation, patients with treated stable measurable CNS disease were included in the trial. A PFS benefit was seen (HR=0.58; 95% CI 0.43-0.80, p <0.001) but no brain metastasis specific analysis was performed [13].

The Phase III EMBRACA trial evaluated another PAPP inhibitor, talazoparib, in patients with advanced or metastatic breast cancer with *BRCA* mutation in which patients were randomized to talazoparib vs. standard chemotherapy in the first to fourth line setting. A significant benefit of talazoparib was observed with a median PFS of 8.6months vs 5.6 months (HR=0.54, 95% CI 0.41-0.71, p<0.001). In the trial, 15% of patients on talazoparib had stable/treated CNS disease at baseline. In a subgroup analysis comparing patients on talazoparib to chemotherapy, a PFS benefit was observed even in comparison to those without brain metastasis (HR=0.32, 95% CI 0.15-0.68 and HR 0.58, 95% CI 0.43-0.78, respectively) suggesting CNS activity of the drug [13].

Conclusion

As we see subset of women living longer, we would expect a different trajectory with more distant relapses. There is no particular guidance as to how to follow up these patients that would be at higher risk of developing BM given that up to 26% of them maybe asymptomatic at diagnosis. Earlier identification of intra-cranial disease can lead to improved outcomes in this cohort of patients. There is limited evidence to support the use of PARP inhibitors in BM however our case suggests that some patients experience sustained remission over many years with multi-modality treatment including PARPi and targeted radiosurgery.

Author contribution

Maha Al Sendi: Manuscript drafting and editing, Ali Madan: Review of literature, Hanadi Malik: Editing

Declaration of Competing Interest

Maha Al Sendi, Ali Madan, and Hanadi Malik declare that there is no conflict of interest.

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