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Case report

Olaparib treatment for BRCA-mutant ovarian cancer with leptomeningeal disease

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1. Introduction

Ovarian cancer related brain metastases (BM) are uncommon, the reported incidence ranges from 0.49 to 11.54% and they usually arise two years after diagnosis (Pakneshan et al., 2014). However, rates may be higher as brain imaging is not routinely performed. The cerebellum is the most common site for metastatic spread, while leptomeningeal disease has been reported to only affect 8% of patients with BM.

Leptomeningeal disease is defined as metastatic spread to the cerebrospinal fluid and the leptomeninges. It usually has debilitating consequences, as it can cause cognitive impairment, increased intracranial pressure, cranial nerve palsies and radiculopathies. It is diagnosed by cerebrospinal fluid cytology and contrast-enhanced MRI scans. The optimal treatment for affected patients is unknown (Pakneshan et al., 2014).

Patients with BRCA-mutated high grade serous ovarian cancer (HGSOC) have higher rates of visceral metastases (lung, spleen and liver) compared to sporadic cases where the disease is usually limited to the peritoneum (Gourley et al., 2010). Among patients with HGSOC the rate of BRCA1/2 germline and somatic mutations is about 22% (Cancer Genome Atlas Research Network, 2011). However, homologous recombination defects are present in approximate half of HGSOC patients (Cancer Genome Atlas Research Network, 2011). Poly(ADP-ribose) polymerase (PARP) is involved in the repair of DNA single-strand breaks via the base excision pathway. PARP inhibitors such as olaparib lead to an accumulation of double-strand DNA breaks, resulting in the activation of homologous recombination repair (Ashworth, 2008). Thus, patients with defects in the repair of double-strand DNA breaks by homologous recombination, including those with BRCA1 and BRCA2 mutations are sensitive to PARP inhibition.

There are different indications for the use of olaparib in advanced HGSOC. In Europe, olaparib is approved for maintenance treatment in patients with platinum-sensitive relapsed BRCA-mutated HGSOC with complete or partial response to their most recent platinum-based chemotherapy. In this setting, median progression-free survival is 11.2 months with olaparib maintenance therapy versus 4.3 months with placebo ($p < 0.0001$) (Ledermann et al., 2014). In the U.S., olaparib is approved to treat patients with platinum-sensitive and platinum–resistant advanced BRCA-mutated HGSOC who have received ≥3 lines of chemotherapy, as the median duration of response in these two groups is 8.2 and 8 months, respectively (Domchek et al., 2016).

To the best of our knowledge, herein we report the first case of a patient with BRCA-mutated HGSOC who received the PARP inhibitor, olaparib to treat leptomeningeal disease on a compassionate basis.

2. Case report

A 61 year old lady commenced olaparib for BRCA2-mutated International Federation of Gynecology and Obstetrics (FIGO) stage IVB HGSOC with leptomeningeal disease in the absence of extra-cranial recurrence (Figs. 1 and 2).

She was diagnosed with ovarian cancer six years previously, following presentation with abdominal distension secondary to malignant ascites associated with a serum cancer antigen 125 (CA-125) level of 465 kIU/L. An omental biopsy demonstrated adenocarcinoma infiltration which was positive for cytokeratin 7 (CK7), Wilms tumor gene product (WT1) and CA-125 on immunohistochemistry. Baseline CT staging suggested FIGO stage IVB disease due to pleural nodules and intrathoracic lymphadenopathy. She had no prior medical problems aside from stress incontinence treated by colposupsension. Her daughter had been previously treated for non-Hodgkin lymphoma but there was no other significant family history.

Following 3 cycles of neoadjuvant carboplatin and paclitaxel there was a radiological and CA-125 response (53 kIU/L) and she underwent

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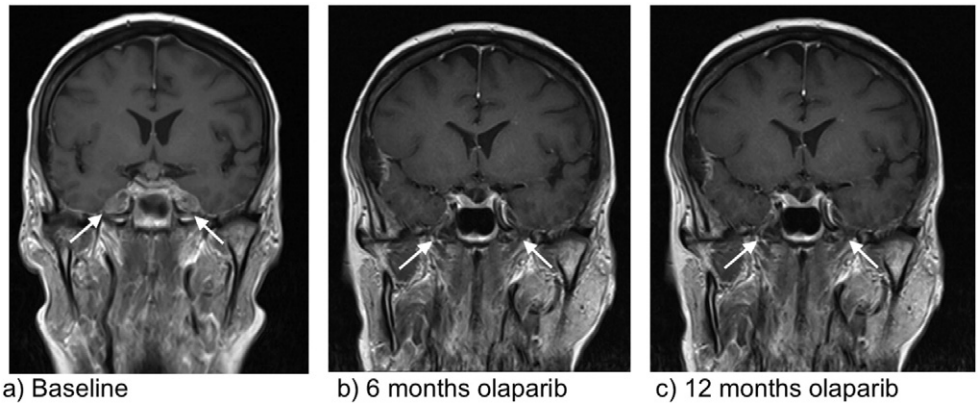

Fig. 1. MRI brain scans demonstrating response of skull base leptomeningeal disease to olaparib (T1 weighted, post gadolinium contrast, coronal sections): a) Enhancing skull base leptomeningeal disease pre-olaparib. b) Significant decrease in volume and enhancement of skull base leptomeningeal disease after 6 months of olaparib. c) Unchanged significant decrease in volume and enhancement of skull base leptomeningeal disease after 12 months of olaparib.

interval debulking surgery (total hysterectomy, bilateral salpingo-oophorectomy, tumor debulking and omentectomy). After 3 cycles of postoperative carboplatin and paclitaxel there was no residual disease on CT scanning and the CA-125 was 35 kIU/L.

Unfortunately, two years later she developed right hemi-dysesthesia and a CT head scan demonstrated a solitary left parietal lesion. She underwent a craniotomy and the resected tumor was CK7 and CA-125 positive carcinoma, thus compatible with the primary disease. A post-operative MRI head scan did not demonstrate any residual disease and she underwent radiotherapy to the tumor bed (20 Gy/5 fractions). She made a good recovery, with only residual paraesthesia in her right foot. A re-staging scan did not demonstrate any extra-cranial disease and serum CA-125 was 36 kIU/L. She underwent stereotactic radiosurgery (SRS) one year post-craniotomy, as a follow up MRI scan identified tumor recurrence within the left parietal resection cavity. The patient was asymptomatic and imaging studies did not reveal any extra-cranial disease.

Over the next few months, she developed problems with balance, right sensorineural hearing impairment and right sided trigeminal dysesthesia. She also developed numbness of her buttocks and left foot, in addition to decreased sensation during micturition and defecation, but she maintained continence. An MRI scan of the brain and spine demonstrated new leptomeningeal thickening, radiological enhancement at the skull base and in the lumbosacral spinal canal (Figs. 1a and 2a). The appearance of the left parietal surgical resection site was stable. Cerebrospinal fluid (CSF) cytology demonstrated atypical cells which stained for MNF116 (pan-cytokeratin antibody), consistent with meningeal infiltration. There was no extra-cranial disease on CT scanning and serum CA-125 had risen to 64 kIU/L.

She commenced treatment with single agent carboplatin but had an hypersensitivity reaction during cycle four. Subsequently, she was switched to a carboplatin 'de-sensitisation' regimen but experienced an anaphylactic reaction and treatment was discontinued. At the end of chemotherapy, her symptoms had improved but she was still troubled by right-sided hearing impairment and right-sided trigeminal dysesthesia. The CSF cytology was negative, serum CA-125 was 45 kIU/L and radiological restaging revealed stable intracranial disease and no extracranial recurrence.

However, there was deterioration in her neurological symptoms at seven months post-carboplatin; at this stage she underwent BRCA testing as it had become publicly-funded for non-mucinous ovarian cancer patients, and she was found to have a deleterious BRCA 2 mutation. Unfortunately, she had bilateral trigeminal dysesthesia, she was unable to open her mouth fully and had difficulty both chewing and swallowing. She had lower back pain and her mobility had deteriorated to the extent that she required walking aids. On repeat MR imaging, there was progressive leptomeningeal disease to account for the patient's worsening neurological symptoms, in the absence of extracranial recurrence on CT staging. In particular, there was leptomeningeal disease, involving Meckel's cave bilaterally, the cisternal portions of the trigeminal nerves bilaterally and right internal auditory meatus, as well as increased intradural extra-medullary disease within the lumbo-sacral spine on MR scanning (Figs. 1a and 2a).

She commenced olaparib capsules 400 mg twice daily with symptomatic benefit within two weeks, including complete resolution of back pain, decreased facial pain, improved swallowing and full mouth opening. The dose was reduced to 200 mg twice daily by month three due to severe treatment-related fatigue, which was significantly

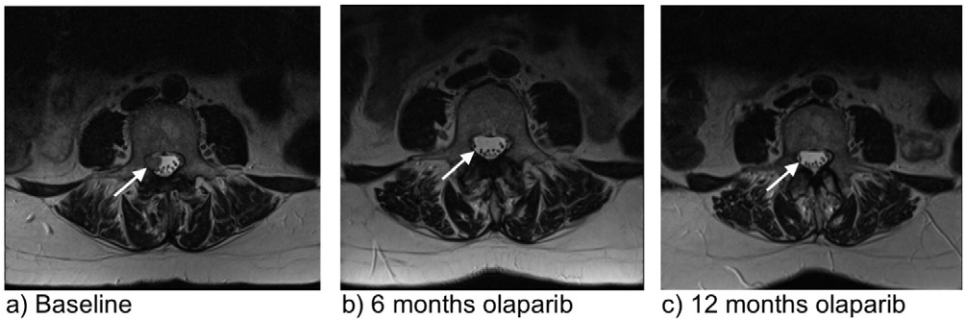

Fig. 2. MRI spine scans demonstrating complete resolution of leptomeningeal disease at the L4 vertebral with olaparib treatment (T2 weighted, axial sections). a) Enhancing leptomeningeal disease at the L4 vertebral level prior to olaparib. b) Normal appearances at the site of the previous spinal leptomeningeal disease after 6 months of olaparib. c) Normal appearances at the site of the previous spinal leptomeningeal disease after 12 months of olaparib.

impacting on her quality of life. After six months of olaparib, facial sensation, bladder sensation and balance had all improved but had not fully resolved. In addition, she was able to walk short distances without walking aids. However, the right hearing impairment was unchanged. The clinical response was consistent with MR imaging. Intracranially, there was a dramatic decrease in leptomeningeal disease at the skull base (Fig. 1b). Intraspinally, the leptomeningeal disease had decreased to the point that it was no longer visible on MR imaging (Fig. 2b). These findings were associated with a fall in CA-125 from 62 to 37 kIU/L.

Unfortunately, after twelve months of olaparib, surveillance MR scanning demonstrated a new 2 cm deposit within the right occipital lobe which was not associated with any symptoms, the serum CA-125 had risen to 66 kIU/L. The left parietal resection cavity was unchanged and the intracranial leptomeningeal disease remained stable aside from progressive hypothalamic disease. Furthermore, there was no recurrence of the intra-spinal or extra-cranial disease. The patient is now scheduled to undergo SRS and has discontinued olaparib.

3. Discussion

The patient presented had a sustained clinical and radiological response to olaparib for leptomeningeal metastases related to BRCA2 mutant HGSOC. Based on data from pooled case series, the median overall survival (OS) for patients with ovarian cancer BM is 6.4 months (Piura and Piura, 2011).

There are several prognostic indices for patients with BM arising from solid malignancies which take into account various factors, such as size and number of BM, patients' age, performance status and primary disease status (Sperduto et al., 2008). Retrospective studies have demonstrated that the indices can be applied to ovarian cancer patients (Chen et al., 2005). For patients with ovarian cancer BM, progressive primary disease and presence of multiple BM are associated with worse survival outcomes (Chen et al., 2005). In general, prognostic indices can help to stratify patients, in order to identify patients who will benefit most from a proactive treatment approach.

Currently, there is no agreed consensus regarding the optimal treatment for HGSOC central nervous system (CNS) metastases (Divine et al., 2016). Treatment options for parenchymal BM include whole brain radiation therapy (WBRT), surgery or SRS in combination with WBRT and SRS alone, as well as systemic chemotherapy (Walter et al., 2015). Retrospective studies suggest that multimodal therapy could offer a survival advantage compared to WBRT alone (Piura and Piura, 2011). However, treatment options for HGSOC leptomeningeal disease are more limited and include partial or WBRT and chemotherapy (systemic and or intrathecal) (Teckie et al., 2013; Yust-Katz et al., 2013). The reported median OS for patients from diagnosis of HGSOC leptomeningeal disease is <4 months and the benefit of conventional treatments are uncertain.

This patient gained significant symptomatic benefit from olaparib with an associated improvement in her quality of life and treatment was well tolerated following a dose reduction for treatment-related fatigue. In addition, it was possible to avoid WBRT which is associated with neurocognitive deficits, that can arise within a few months of treatment (Walter et al., 2015).

In a review of ovarian cancer BM published in 2011, <600 cases were reported in the literature (Piura and Piura, 2011), Given the paucity of cases it will not be feasible to conduct a clinical trial of PARP inhibitors in patients with leptomeningeal disease, thus, highlighting the importance of sharing case reports in the literature. However, future clinical trials could focus on a larger group of patients with BM related to BRCA mutated breast or HGSOC to assess the use of PARP inhibitors in this setting.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Conflict of interest

JAL was the Chief Investigator for AstraZeneca study 19 and is the Co-Chief Investigator for the Clovis Oncology ARIEL3 trial. He has participated in Advisory Boards for both companies but has not received any personal remuneration. He has participated in interest AstraZeneca sponsored symposia and received travel costs to attend.

MB, RG and HW declare they have no conflicts of interests.

References

Ashworth, A., 2008. A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J. Clin. Oncol. 26 (1), 3785–3790.

Cancer Genome Atlas Research Network, 2011 Jun 29. Integrated genomic analyses of ovarian carcinoma. Nature 474 (7353), 609–615. http://dx.doi.org/10.1038/nature10166 Erratum in: Nature. 2012 Oct 11;490(7419):298. PMID: 21720365 Free PMC Article.

Chen, P.G., Lee, S.Y., Barnett, G.H., Vogelbaum, M.A., Saxton, J.P., Fleming, P.A., Suh, J.H., 2005. Use of the radiation therapy oncology group recursive partitioning analysis classification system and predictors of survival in 19 women with brain metastases from ovarian carcinoma. Cancer 104 (1), 2174–2180.

Divine, L.M., Kizer, N.T., Hagemann, A.R., Pittman, M.E., Chen, L., Powell, M.A., Mutch, D.G., Rader, J.S., Thaker, P.H., 2016. Clinicopathologic characteristics and survival of patients with gynecologic malignancies metastatic to the brain. Gynecol. Oncol. (1).

Domchek, S.M., Aghajanian, C., Shapira-Frommer, R., Schmutzler, R.K., Audeh, M.W., Friedlander, M., Balmana, J., Mitchell, G., Fried, G., Stemmer, S.M., Hubert, A., Rosengarten, O., Loman, N., Robertson, J.D., Mann, H., Kaufman, B., 2016. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol. Oncol. 140 (1), 199–203.

Gourley, C., Michie, C.O., Roxburgh, P., Yap, T.A., Harden, S., Paul, J., Ragupathy, K., Todd, R., Petty, R., Reed, N., Hayward, R.L., Mitchell, P., Rye, T., Schellens, J.H., Lubinski, J., Carmichael, J., Kaye, S.B., Mackean, M., Ferguson, M., 2010. Increased incidence of visceral metastases in scottish patients with BRCA1/2-defective ovarian cancer: an extension of the ovarian BRCAness phenotype. J. Clin. Oncol. 28 (1), 2505–2511.

Ledermann, J., Harter, P., Gourley, C., Friedlander, M., Vergote, I., Rustin, G., Scott, C.L., Meier, W., Shapira-Frommer, R., Safra, T., Matei, D., Fielding, A., Spencer, S., Dougherty, B., Orr, M., Hodgson, D., Barrett, J.C., Matulonis, U., 2014. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 15 (1), 852–861.

Pakneshan, S., Safarpour, D., Tavassoli, F., Jabbari, B., 2014. Brain metastasis from ovarian cancer: a systematic review. J. Neuro-Oncol. 119 (1), 1–6.

Piura, E., Piura, B., 2011. Brain metastases from ovarian carcinoma. ISRN Oncol. 2011 (1), 527453.

Sperduto, P.W., Berkey, B., Gaspar, L.E., Mehta, M., Curran, W., 2008. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int. J. Radiat. Oncol. Biol. Phys. 70 (1), 510–514.

Teckie, S., Makker, V., Tabar, V., Alektiar, K., Aghajanian, C., Hensley, M., Beal, K., 2013. Radiation therapy for epithelial ovarian cancer brain metastases: clinical outcomes and predictors of survival. Radiat. Oncol. 8 (1), 36.

Walter, A.C., Gunderson, C.C., Vesely, S.K., Algan, O., Sughrue, M., Slaughter, K.N., Moore, K.N., 2015. Central nervous system metastasis in gynecologic cancer: symptom management, prognosis and palliative management strategies. Gynecol. Oncol. 136 (1), 472–477.

Yust-Katz, S., Mathis, S., Groves, M.D., 2013. Leptomeningeal metastases from genitourinary cancer: the University of Texas MD Anderson Cancer Center experience. Med. Oncol. 30 (1), 429.