SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 13: 73-75, 2020

Long-term response to Olaparib in carcinomatous meningitis of a *BRCA2* mutated ovarian cancer: A case report

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Received May 10, 2019; Accepted February 18, 2020

DOI: 10.3892/mco.2020.2035

Abstract. PARP inhibitors are considered as a treatment revolution in ovarian cancer management. Leptomeningeal metastasis is a rare event with poor prognosis. The present report presents an exceptional history of long term survival for a young patient treated with olaparib for carcinomatous meningitis. A 54-year-old woman was diagnosed with ovarian cancer. After Paclitaxel and Carboplatin treatment, followed by a debulking surgery and several lines of chemotherapy due to progression, the patient's disease evolved into carcinomatous meningitis within 6 months after the end of treatment. During care, exome analysis on brain lesions was performed. Exome analysis was performed with a mean coverage of 80X by a paired-end sequencing on an Illumina NextSeq500 device. Following bioinformatics alignment and variant annotation, a pathogenic *BRCA2* mutation, c.7617+1G>T, was observed, and this was already detected in her family. Additionally, the allelic frequency observed indicated that the mutation was present at the homozygous status in tumor cells. Due to the presence of a pathogenic mutation and a loss of wild-type *BRCA2* allele, a maintenance treatment by Olaparib was initiated after radiotherapy and Cisplatin monotherapy. The patient received olaparib treatment for 14 months with a very good disease control and an excellent tolerance. Despite long control, the patient succumbed to meningeal and peritoneal progression.

Introduction

Over the world, ovary cancer is the 5th cause of death by cancer in women and the first cause of death among gynecological cancers. Despite a good response to platin-based first line treatment, >70% of patients will progress within 2 years following diagnosis. PARP inhibitors are drugs that inhibit DNA repair, with a maximum efficiency in homologous repair deficient cells. The complete blockage of PARP enzymes in homologous repair deficient cells triggers cell death by a phenomenon called synthetic lethality. The development of PARP inhibitors has revolutionized the management of *BRCA* mutated ovary tumors. Indeed, the first available PARP inhibitor, Olaparib, showed dramatic increase of progression free survival at metastatic stage, and as a maintenance treatment for newly diagnosed patients (1,2). In parallel, other PARP inhibitors, Niraparib and Rucaparib, also showed efficiency on *BRCA* mutated tumors and also on *BRCA* wild-type tumors for Niraparib (3,4). As the efficiency of PARP inhibitors was observed in tumors presenting a complete or partial response to platin salt, its therapeutic use is limited to these platin sensitive tumors. Cerebral progression of ovary cancer is a rare event with a dark prognosis, death happening within a few weeks. Here, we report the case of a *BRCA* mutated patient who has lived >1 year with carcinomatous meningitis thanks to Olaparib treatment.

Case report

A 54-year-old woman was diagnosed with ovarian cancer in 2010. After an initial treatment with neoadjuvant chemotherapy (Paclitaxel, Carboplatin), she underwent optimal debulking surgery. In 2012, she presented a first peritoneal relapse and received numerous lines of chemotherapy until August 2014. Oxaliplatin was the last platinum salt administered, since the patient developed a Carboplatin allergy. In the absence of any detectable disease, the treatment was stopped and clinical survey was initiated.

Six months later, patient complained of headaches, and magnetic resonance imaging (MRI) revealed nodular meningitis (Fig. 1A). Lumbar puncture confirmed carcinomatous cell presence. Additionally, computed tomography (CT) scan showed peritoneal progression (Fig. 1B) without other lesions.

Due to her young age and to the pathogenic *BRCA2* mutation (c.7617+1G>T) identified in her family, a germline genetic test was initiated and revealed that patient carried the familial pathogenic *BRCA2* mutation. Upon confirmation of tumor cells presence by a pathologist, lumbar puncture DNA was extracted using the Maxwell 16 FFPE Plus LEV DNA purification kit (Promega Corporation) according to manufacturer's protocol.

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Key words: olaparib, BRCA2, carcinomatous meningitis, ovary cancer

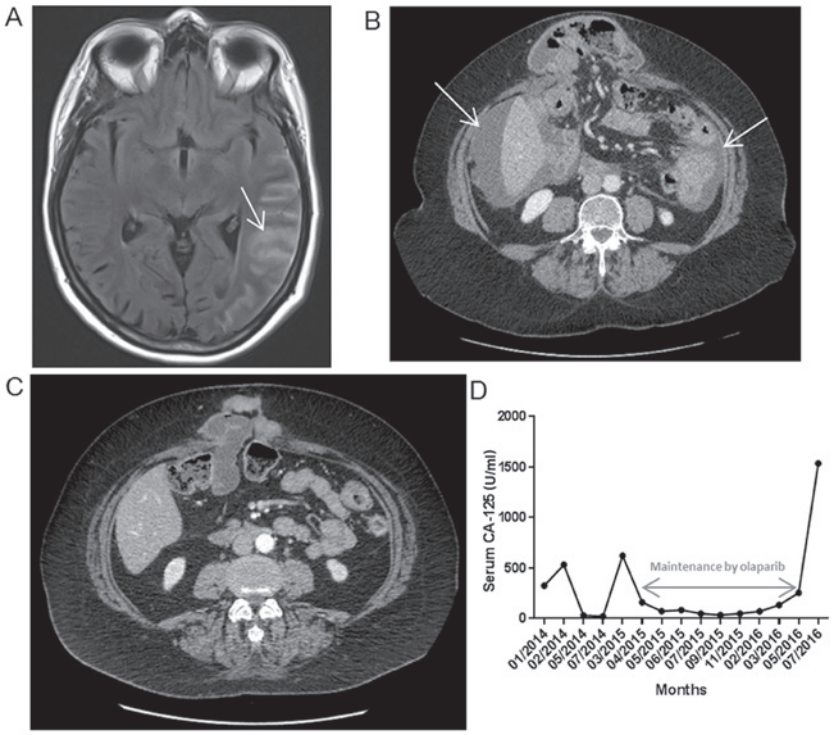

Figure 1. Imagery and biological exams performed throughout medical care. (A) MRI showing nodular meningitis (white arrow). (B) CT scan exam indicating the presence of an abundant ascites liquid quantity (white arrows). (C) CT scan exam showing the complete disappearance of ascites after platin-based chemotherapy. (D) Serum CA-125 dosage throughout the maintenance by olaparib treatment. MRI, magnetic resonance imaging; CT, computed tomography.

Corresponding normal DNA was extracted from 500 μl EDTA blood samples with the Maxwell 16 Blood DNA Purification system (Promega Corp.) according to manufacturer's instructions. DNA quality was assessed by spectrophotometry with absorbance at 230, 260 and 280 nm. DNA was quantified using a fluorimetric assay with a Qubit device.

Genomic DNA from meningeal cells was fragmented with a Covaris device to obtain fragments around 180-200 bp. Subsequently, libraries were constructed and captured by using SureSelect Human All Exon v5 kit (Agilent Technologies, Inc.) following manufacturer's protocol. Paired-end (2x151 bases) sequencing was performed on a NextSeq500 device (Illumina, Inc.). Obtained sequences were aligned and annotated with the human Hg19 genome based on SureSelect Human All exon v5 manifest by using BWA and GATK algorithms. Only sequences with a read depth of 10X and a mutation allele frequency superior to 5% were analyzed. Exome analysis on meningeal cells confirmed the presence of the pathogenic *BRCA2* mutation. Moreover, the tumor homozygous pathogenic *BRCA2* mutation status (mutated allele frequency of 98%) suggested a loss of wild-type allele in tumor cells. Whole brain radiotherapy was carried out and Cisplatin monotherapy treatment was administrated from March to June 2015. CT scan confirmed a positive response to chemotherapy (Fig. 1C) and Olaparib treatment was proposed. This treatment allowed a 14 month disease control (Fig. 1D) with a good quality of life. Standard dose was administered without any modification due to excellent tolerance.

On August 2016, meningeal and peritoneal progression was diagnosed. Platinum based chemotherapy was tried without improvement. Patient died on September 2016.

Discussion

The most frequent metastasis site of ovarian cancer is the peritoneum. Meningeal and cerebral metastases seem to be a rare event. Jernigan *et al* (5) have found an incidence of 2.58% of central nervous system metastasis in their series. Cerebral metastasis incidence seems to be correlated to *BRCA* mutation. Sixty seven percent of patients with CNS metastasis had a familial history of hereditary breast and ovarian cancer (5). Carcinomatous meningitis leads to poor prognosis and treatments are limited. The FRENCH ANOCEF group has published recently online guidelines on the treatment of carcinomatous meningitis (6).

PARP inhibitors are described as a major therapeutic advance in ovarian cancer (1,7). The first drug of this pharmaceutical class is Olaparib. Olaparib is only indicated in platinum sensitive recurrent ovarian cancer with *BRCA* mutation. Nevertheless, several other agents such as Rucaparib or Niraparib are in development and nearly available (2,4). These molecules seem to be active in tumors with homologous recombination deficiency, independently of *BRCA* status (2,4). Studies showed good tolerance and the most described side effect is hematological toxicity such as anemia. Meningeal efficacy has not been described to date. This case report shows long-term survival despite CNS metastases (20 months with 14 months under Olaparib treatment) with a good clinical control. In the literature, the median survival without treatment ranges between four to six weeks and 15.9 weeks with intrathecal treatment (6), which was not used in our case. Therefore it seems that Olaparib, a small molecule, is able to cross the leptomeningeal barrier.

This is the first report on the efficacy of a PARP inhibitor on meningeal disease of a *BRCA* mutated ovarian cancer. This case report also illustrates that exome or Next Generation Sequencing (NGS) analysis can be performed on a small amount of cells with a good overlap with germinal *BRCA* abnormalities. Moreover, this kind of analysis revealed its complementarity with germline analysis, as the somatic second hit could be observed. In this case report, the strong efficiency of Olaparib could be explained by the homozygous status of the pathogenic *BRCA2* mutation in cancer cells.

In conclusion, carcinomatous meningitis is a rare event with a poor prognosis in ovarian cancer. We illustrated a good response with Olaparib, the first PARP inhibitor available in clinical practice, suggesting efficient meningeal diffusion. NGS could be performed in a small number of cells obtained from lumbar puncture, with a good overlap with germ line mutations, allowing complementary information on tumor status and pathogenic mutation characterization. This first encouraging result should be confirmed in clinical practice. Results should be confirmed using other PARP inhibitors.

Acknowledgements

The authors would like to thank Dr Isabel Gregoire (Georges-François Leclerc Anticancer Center, Dijon, France) for manuscript editing.

Funding

No funding was received.

Availability of data and materials

The datasets generated and/or analyzed during the present study are not publicly available due to presence of identifying genetic information but are available from the corresponding author on reasonable request.

Authors' contributions

LF, GT and LBL treated the patient. RB performed genetic analysis. LF, RB, and LBL wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The paper was read and validated by the local Ethics Committee of the Centre Georges-François Leclerc (Dijon, France).

Patient consent for publication

The local Ethics Committee of the Centre Georges-François Leclerc waives the necessity of consent for publication by the patient because the patient has died, and the content of the publication does not provide any identifying data on the patient and the establishment does not wish to disturb the patient's family in these unfortunate circumstances.

Competing interests

The authors declare that they have no competing interests.

References

1. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira-Frommer R, Safra T, *et al*: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 366: 1382-1392, 2012.
2. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, *et al*: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 379: 2495-2505, 2018.
3. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, *et al*: Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 375: 2154-2164, 2016.
4. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, *et al*: Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390: 1949-1961, 2017.
5. Jernigan AM, Mahdi H and Rose PG: Epithelial ovarian cancer metastatic to the central nervous system and a family history concerning for hereditary breast and ovarian cancer-a potential relationship. Int J Gynecol Cancer 25: 1232-1238, 2015.
6. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T and Ettinger DS: Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern cooperative oncology group. J Clin Oncol 11: 561-569, 1993.
7. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, Korach J, Huzarski T, Poveda A, Pignata S, *et al*: Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 18: 1274-1284, 2017.