Annals of Clinical Case Reports

Case Report
Published: 11 Feb, 2019

Regression of Uveal Metastases Following Treatment with PARP-Inhibitor in a Patient with Germline BRCA Mutation and Advanced Breast Cancer

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Abstract

Uveal metastases from breast, lung or gastrointestinal malignancies represent the most frequent intraocular malignancy. We present a case of a 52-year old female patient with metastatic breast cancer with lung and liver involvement, known to be a BRCA2 mutation carrier.

Following a presentation to the emergency service with pain and blurred vision in her left eye, she was diagnosed with uveal metastases. Ten days following this new diagnosis, she was enrolled onto a clinical trial of olaparib, a PARP-inhibitor (Phase 1 Food Effect Study D081ACC00001, NCT01851265). She subsequently developed an improvement in her vision (Snellen visual acuity increased from 1/60 to 6/18 over 6 weeks) and the ocular tumour with its associated retinal detachment was noted to have regressed considerably.

PARP inhibitors are currently involved in several clinical trials for ovarian/breast cancers associated with BRCA mutations. They work by preferentially targeting DNA repair defects in BRCA-positive mutated cancer cells.

In this case olaparib caused regression of ocular metastases in a patient with a BRCA mutation and advanced breast cancer. It supports the case for further research towards offering targeted treatment through gene expression analyses and biomarker functional assays.

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Received Date: *14 Jan 2019*
Accepted Date: *08 Feb 2019*
Published Date: *11 Feb 2019*

Citation:
Jawaheer L, Chadha V, Cauchi P. Regression of Uveal Metastases Following Treatment with PARP-Inhibitor in a Patient with Germline BRCA Mutation and Advanced Breast Cancer. Ann Clin Case Rep. 2019; 4: 1596.

ISSN: 2474-1655

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Introduction

Uveal metastases from breast, lung or gastrointestinal malignancies represent the most frequent intraocular malignancy and the incidence of clinically detectable intraocular metastases in patients dying of cancer has been estimated to be around 1% [1]. Uveal metastases can rarely be the presenting feature in patients with an unknown primary tumour but more commonly manifest in patients with a known primary or with known metastatic disease. In a retrospective case series of 264 patients with uveal metastases secondary to breast cancer by Demirci et al. [2], choroidal metastases were most common, followed by iris and ciliary body metastases. Presenting features of uveal metastases include blurred vision, photopsia, shadows and pain. The average survival after diagnosis of uveal metastases was 21 months, and the five-year survival rate was around 24%.

The aim of treatment is usually to restore visual acuity and hence to improve the quality of life for patients with uveal metastasis. Management options for uveal metastases include localised treatments such as external beam radiotherapy, plaque brachytherapy, photodynamic therapy and enucleation, as well as systemic treatments such as chemotherapy, hormone therapy and immunotherapy.

We present a case where treatment with olaparib, a Poly (ADP-ribose) Polymerase (PARP) inhibitor, resulted in a rapid regression in uveal metastases from a breast primary.

Case Presentation

A 52-year old female presented to the ocular oncology clinic in September 2013 with pain and blurred vision in her left eye. She was a known BRCA2 mutation carrier and had a history of metastatic breast cancer with lung, lymph node and liver involvement. Her visual acuity was 6/5 in the right eye and 1/60 in the left eye. She was subsequently diagnosed with a choroidal metastatic lesion in her left eye (Figures 1A, 2A, 3A and 3B). The anterior segments and right fundus did not show any abnormality.

Table 1: Previous treatment received by patient for bilateral BRCA-positive breast cancer, prior to her presentation to the ophthalmology department in 2013.

Previous treatment for bilateral BRCA-positive metastatic breast cancer	**Surgical**
	Bilateral wide local excision with axillary node clearance
	Radical radiotherapy
	Hormonal agents
	Zoladex (started 2001)
	Tamoxifen (started 2010)
	Chemotherapy
	Fluorouracil/ Epirubicin/ Cyclophosphamide July to October 2011
	Paclitaxel September 2010 to February 2013
	Capecitabine May to August 2013

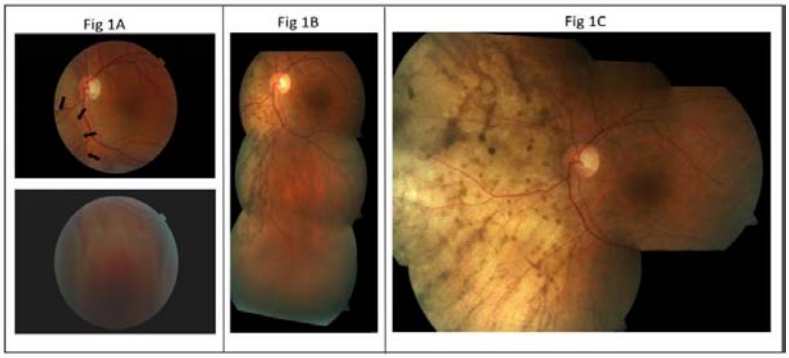

Figure 1: Colour fundal photographs of left eye.
1A: At presentation (September 2013), showing inferonasal choroidal mass with associated inferior retinal detachment. **1B:** After treatment with olaparib (February 2014), showing decrease in exudative retinal detachment. **1C:** October 2014 – no recurrence of lesion.

Her previous treatment for metastatic breast cancer is detailed in Table 1. Ten days following the diagnosis of choroidal metastasis, she was enrolled onto a clinical trial of olaparib capsules (a Phase 1 Food Effect Study D081ACC00001, NCT01851265, study completion date June 2017) [3]. The decision to enrol onto the trial predated her visual symptoms and was unrelated to her diagnosis of choroidal metastasis.

Results

Her Snellen visual acuity in the affected left eye improved from 1/60 at its worst to 6/18 six weeks after having been started on olaparib. The choroidal metastasis and its associated retinal detachment were noted to have regressed considerably, both clinically and on ultrasound scan (Figures 1B, 1C, 3C and 3D) in February 2014 (22 weeks from start of olaparib), and also later on in September 2014 on repeat CT scan (Figure 2B). At last follow-up in August 2015, visual acuities were 6/5 in the right eye and 6/9 in the left eye. Unfortunately in spite of the improvement in her ocular condition and some initial improvement in the liver lesions with olaparib, the patient eventually developed more advanced disease in the liver and lymph nodes. She was taken off olaparib and subsequently enrolled onto another clinical study of Liposomal Eribulin (November 2014 to February 2015), followed by palliative chemotherapy with carboplatin (February 2015 to April 2015) and vinorelbine (started in April 2015). The patient passed away in October 2015.

Discussion

External Beam Radiotherapy (EBRT) remains the most commonly used treatment modality for uveal metastases with success rates of up to 86% in restoring visual acuities [1]. It is easily accessible but time consuming and usually involves several trips to the hospital over a period of 3 weeks to 4 weeks. Its side effects include cataract formation and radiation retinopathy.

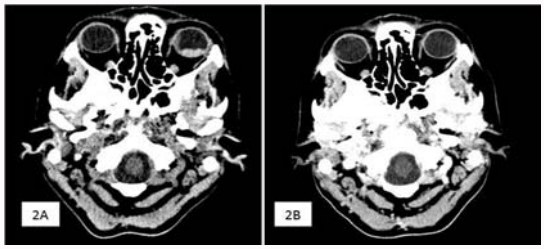

Figure 2: Axial CT head images: **2A** in November 2013, showing left uveal metastasis, **2B** in September 2014 (after treatment with olaparib) and showing evidence of regression of disease.

Systemic chemotherapy is also commonly used - its effects are often slower than with radiotherapy [1]. Photodynamic therapy can be used for shallow, well circumscribed metastases and has been successfully used in a case where the metastatic lesion was refractory to treatment with radiotherapy or chemotherapy [4]. Hormonal treatments used include tamoxifen or aromatase inhibitors such as anastrozole, letrozole or exemestane for oestrogen-receptor positive tumours [5]. Successful use of intravitreal anti-VEGF treatment has also been reported [6,7].

Demirci et al. [2] described the management and prognosis of patients with uveal metastases from breast cancer. The types of treatment for choroidal metastases included EBRT (59% of patients), systemic chemotherapy (29%), hormonal therapy (9%),

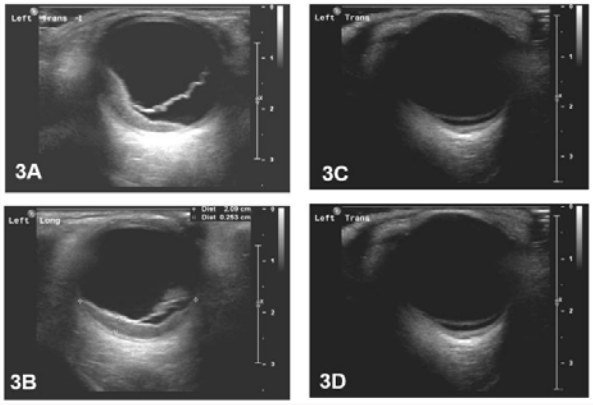

Figure 3: Ultrasound scan images of left eye - transverse & longitudinal views: 3A & 3B - September 2013, 3C & 3D - February 2014 (after treatment with olaparib).

plaque radiotherapy and enucleation (3%). They noted a 12% rate of recurrence of choroidal metastasis following treatment and a 10% rate of active choroidal metastasis in spite of treatment. 53% of the study patients had developed ocular metastases while on systemic chemotherapy or immunotherapy, indicating that these might not be sufficient for preventing ocular metastases. Tumour responses to treatment therefore remain variable and new agents are being researched.

PARP-inhibitors such as olaparib, which target BRCA-positive tumour cells, are one of the newer agents being investigated as treatment for BRCA-positive ovarian/breast cancers [8-10]. They offer an alternative option to women who develop resistance to chemotherapy following a relapse of initially treated cancer. They have shown promising results as anticancer agents, both in monotherapy and as chemo-potentiating agents.

PARP-inhibitors work by preventing cancer cells from repairing their DNA [8]. BRCA1 & 2 is tumour suppressor genes that serve an important function in DNA repair. BRCA-positive cancers often show poor response rates with traditional agents, and therefore tailored therapies on basis of biomarker screening are being developed. PARP 1 is an important component of base excision repair involved in the repair of DNA single-strand breaks which would otherwise be converted into DNA double-stranded breaks. Cells with inactive BRCA genes are heavily dependent on PARP 1 for DNA repair. PARP-inhibitors therefore selectively target the BRCA-positive cancer cells while normal cells, in which DNA repair is still carried out by the active BRCA genes, are spared [8,9].

Conclusion

In this case olaparib caused regression of ocular metastases in a patient with a BRCA mutation and advanced breast cancer. It supports the case for further research towards offering targeted treatment through gene expression analyses and biomarker functional assays. The hope is that prompt delivery of targeted treatment at the time of diagnosis will help prevent the emergence of drug resistant cancer sub-populations. More research is required to further assess the relative risks and benefits of treatment with olaparib.

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