POLY ADP-RIBOSE POLYMERASE (PARP) INHIBITOR IN THE MANAGEMENT OF RECURRENT OVARIAN CARCINOSARCOMA

Yeoh S[1], Oehler MK[1]
1. Department of Gynaecology Oncology, Royal Adelaide Hospital, Adelaide, SA, Australia
Email: sgjyeoh@gmail.com

BACKGROUND:

Ovarian carcinosarcoma is a
- rare malignancy, 1-4% of all ovarian cancers[1]
- usually more aggressive, faster relapse rate and poorer diagnosis[1]
- overall median survival of less than 2 years[1]
- may be assoc with BRCA mutations from case reports[2]

Treatment for ovarian carcinosaroma has been based mainly on research from high grade serous ovarian carcinoma which is a combination of[1]
- surgical cytoreduction
- platinum and taxane based chemotherapy

Identification and understanding of BRCA mutations have led to improved preventative measures and therapeutic developments such as PARP inhibitors[2]

This is a case report of Olaparib (PARP inhibitor) being used in recurrent ovarian carcinosarcoma.

PARP INHIBITORS IN OVARIAN CANCER:

Mechanism of action: Tumour selective synthetic lethality[2,3]
- BRCA is a tumour suppressor gene that encodes proteins which correct DNA damage by homologous recombination (HR)
- BRCA gene mutations result in defective DNA repair causing tumourgenesis
-PARP is a key regulator of DNA single strand damage repair processes
- combining a PARP inhibitor with cells deficient in BRCA causes significant cellular death compared to cells that are BRCA intact
- well established for high grade serous ovarian cancer, currently little evidence in management of ovarian carcinosarcoma

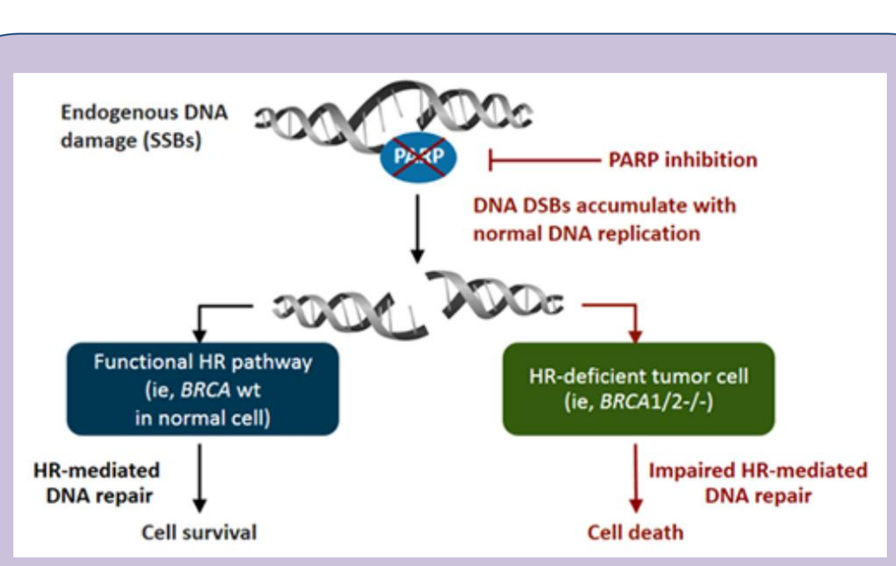

Figure 1: Schematic mechanism of action of PARP inhibitors[3]

Benefits of PARP inhibitors
- prolongs progression free survival in recurrent platinum sensitive high grade serous ovarian cancer with a BRCA mutation[4]
- reduces risk of disease progression if used as adjunct maintenance therapy[5]
- acceptable to patients (oral preparation)[4]
- manageable side effect profile (anaemia, neutropenia, fatigue)[4]

Whilst more research is required specifically on the treatment of ovarian carcinosarcoma, we need to consider that:
- the low incidence of this histological subtype would make a randomised controlled study difficult
- other case reports have shown similar outcomes[6]
- funding for PARP inhibitors be made available for other rarer histological subtypes of ovarian cancer other than high grade serous in Australia

CASE SUMMARY:

63 year old woman with a BRCA 2 gene mutation, presented with lower abdominal pain and urinary frequency
- past history of breast cancer treated with surgery and chemotherapy in 2010
- otherwise no other medical issues

CT showed pelvic mass and ascites

Primary diagnosis and treatment: FIGO stage 3C carcinosarcoma of the ovary
- Surgery: optimal cytoreductive surgery (Oct 2015)
- Adjuvant systemic therapy: 6 cycles of Carboplatin and Paclitaxel, 18 cycles of Bevacizumab completed Jan 2017

1st Recurrence: 2 months after completing 1st line chemotherapy
- 2nd line chemotherapy: 9 cycles of Carboplatin and 4-weekly Liposomal Doxorubicin, completed Nov 2017

2nd Recurrence: 9 months after completing 2nd line chemotherapy
- CT showed a 10cm pelvic mass and multiple liver metastasis
- 3rd line chemotherapy: 10 cycles weekly Paclitaxel
- Restaging CT showed a reduction in the size of the pelvic disease and largely stable liver deposits
- Then commenced on Olaparib (PARP inhibitor) for maintenance therapy

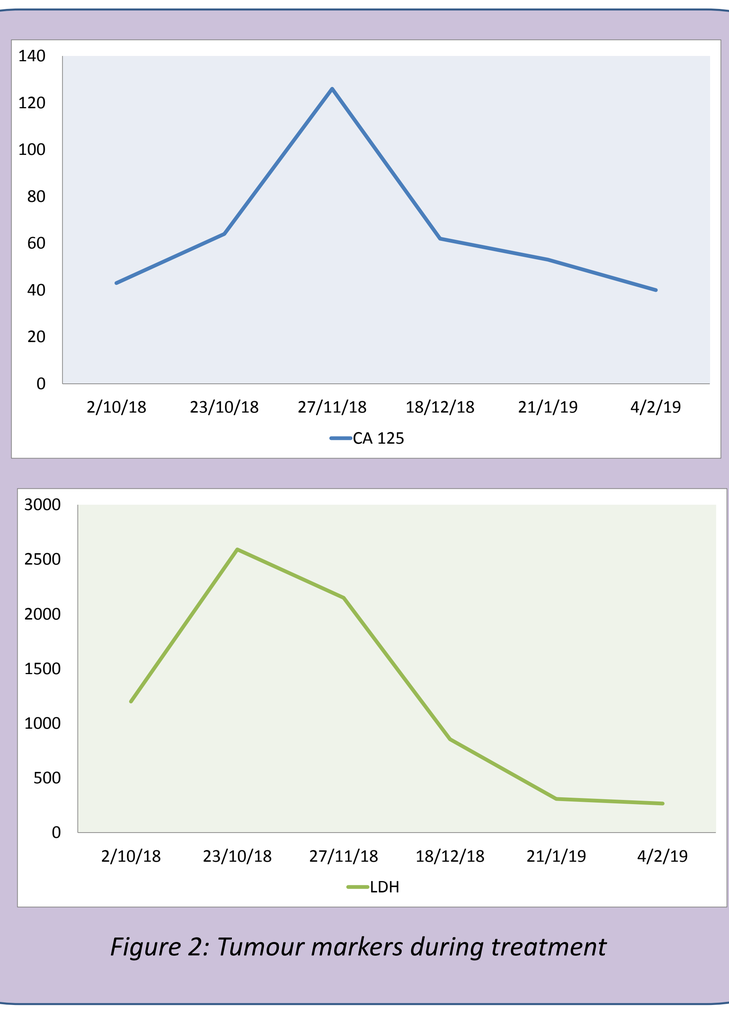

Figure 2: Tumour markers during treatment

CONCLUSION:

This case shows the benefit of using Olaparib in recurrent ovarian carcinosarcoma
At time of writing, she continues to:
- be asymptomatic
- tumour markers decreasing
- no evidence of tumour regrowth on follow up imaging

These are promising results and therefore we should be considering PARP inhibitors in women diagnosed with ovarian carcinosarcoma, especially those with an inherited germline mutation

REFERENCES:
1. Rauh-Hain JA, Birrer M and Del Carmen MG. Carcinosarcoma of the ovary, fallopian tube, and peritoneum: Prognostic factors and treatment modalities. Gynaecol Oncol 2016 Aug;142(2):248-54
2. Neff RT, Senter L and Salani R. BRCA mutation in ovarian cancer: testing, implications and treatment considerations. Ther Adv Med Oncol 2017;9(8):519-531
3. Iglehart JD and Silver DP. Synthetic lethality - a new direction in cancer-drug development. N Engl Med. 2009 Jul 9;361(2):189-91
4. Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015 Jan;16(1):87-97
5. Moore K, Colombo N. Scambia G, Kim BG, Oaknin A et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018;379:2495-2505
6. Chandran EA and Kennedy I. Significant Tumor Response to the Poly (ADP-ribose) Polymerase Inhibitor Olaparib in Heavily Pretreated Patient with Ovarian Carcinosarcoma Harboring a Germline RAD51D Mutation. JCO Precision Oncology DOI:10.1200/PO.18.00253 (accessed 5/7/19)

Royal Adelaide Hospital