Ovarian Cancer Research Review™

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Issue 40 - 2024

In this issue:

Welcome to the latest issue of Ovarian Cancer Research Review.

We begin this issue with an interim analysis from a phase 3 clinical trial evaluating paclitaxel and carboplatin versus bleomycin, etoposide and cisplatin (BEP) for chemotherapy-naïve stromal ovarian tumours. This is followed by a post hoc analysis of the Japanese Gynaecologic Oncology Group (JGOG) international phase 3 3017 trial that investigated ovarian clear cell carcinoma (OCCC) recurrence patterns after initial treatment in order to optimise follow-up protocols, and a Slovenian single-centre report that details the impact of BReast CAncer (*BRCA*) gene variant type and location on the safety and efficacy of olaparib maintenance monotherapy in patients with platinum-sensitive relapsed ovarian cancer (PSROC). Next, the final overall survival (OS) analysis of the SOC-1 phase 3 trial suggests that secondary cytoreduction may provide a survival benefit over salvage chemotherapy alone in select patients with platinum-sensitive ovarian cancer in first relapse and analysis of pooled data from 10 Ovarian Cancer Association Consortium studies finds a link between regularly drinking green tea prior to an ovarian cancer diagnosis and better survival. We conclude this issue with data from the phase 3 ANITA European trial that, consistent with other studies in this space, fails to find any benefit to the addition of immunotherapy to chemotherapy in recurrent ovarian cancer.

We hope you enjoy this update in Ovarian Cancer research, and we welcome your comments and feedback.

Kind Regards,

Associate Professor Philip Beale
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Abbreviations used in this issue:

AGO = Arbeitsgemeinschaft Gynäkologische Onkologie; ***BRCA*** = BReast Cancer gene; **CI** = confidence interval; **HGSOC** = high-grade serous ovarian carcinoma; **HR** = hazard ratio; **HRD** = homologous recombination deficient; **OCCC** = ovarian clear cell carcinoma; **OS** = overall survival; **PARP** = poly (ADP-ribose) polymerase; **PD-L1** = programmed death-ligand 1; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSROC** = platinum-sensitive relapsed ovarian cancer; **SCST** = sex cord-stromal tumours.

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Independent commentary by Associate Professor Philip Beale

Philip Beale is a medical oncologist who practices at the Concord Hospital in Sydney. He has had a long history of involvement in clinical research into gynaecological cancers, having been the chair of ANZGOG and now a board member, as well as part of the RAC. He has been the principal investigator in many studies and has over 140 peer-reviewed publications. He also has an interest in gastrointestinal cancers and is a member of AGITG.

Results of a randomized phase II trial of paclitaxel and carboplatin versus bleomycin, etoposide and cisplatin for newly diagnosed and recurrent chemonaive stromal ovarian tumors: An NRG oncology/ gynecologic oncology group study14

Authors: Brown J et al.

Summary: Interim futility results from the first 63 patients randomised in the multi-centre US Gynaecologic Oncology Group Study 14 trial failed to find any significant difference in efficacy between paclitaxel and carboplatin versus bleomycin, etoposide and cisplatin (BEP) for chemotherapy-naïve ovarian sex cord-stromal tumours (SCST), but was unsuccessful in demonstrating statistical non-inferiority and led to early trial accrual termination. Patients enrolled to the trial between 2010 and 2020 with either a newly diagnosed advanced (stage 2A-4) tumour – predominantly granulosa cell tumour - or with biopsy-proven recurrent disease of any stage that has never been treated with cytotoxic chemotherapy were administered six cycles of paclitaxel and carboplatin (n=31) or four cycles of BEP (n=32). The non-inferiority of paclitaxel and carboplatin versus BEP could not be demonstrated by the primary outcome measure of progression-free survival (PFS; 27.7 vs 19.7 months; hazard ratio [HR] 1.11), with the hazard ratio exceeding the prespecified boundary of 1.10. A more tolerable profile was noted in the paclitaxel and carboplatin arm with fewer ≥ grade 3 adverse events compared to BEP (77% vs 90%) and the study authors concluded that either regimen may be a reasonable option in this population.

Comment: Randomised trials in this space are very hard to complete and so the investigators should be congratulated in recruiting as many patients as they did. Still, this was only achieved after 10 years of recruitment. While not meeting its endpoint of demonstrating paclitaxel and carboplatin was not inferior to BEP in this patient group it has not demonstrated superiority of one regimen over another. However, the median PFS was 27.7 months for paclitaxel and carboplatin and 19.7 months for BEP. This was not statistically significant. OS was immature but favoured paclitaxel and carboplatin. In addition, grade 3 and above toxicity was significantly better with paclitaxel and carboplatin compared with BEP. Overall, this suggests that paclitaxel and carboplatin is the preferred regimen in this setting and this is reflected in the National Comprehensive Cancer Network (NCCN) guidelines which state that paclitaxel and carboplatin as the "preferred regimen" and BEP as "useful in certain circumstances" for advanced and recurrent SCST prior to this publication.

Reference: Gynecol Oncol. 2024:190:283-90
Abstract

Investigating the timing and site of recurrence for ovarian clear cell carcinoma: Analysis of the JGOG/GCIG trial-JGOG 3017-A3

Authors: Yunokawa M et al.

Summary: Japanese researchers conducted an unplanned post hoc analysis of data from the Japanese Gynaecologic Oncology Group (JGOG) international phase 3 3017 trial in order to characterise recurrence patterns of ovarian clear cell carcinoma (OCCC) after initial treatment and develop best practice follow-up protocols. Analysis included 619 women who underwent primary debulking surgery followed by adjuvant combination chemotherapy with either irinotecan plus cisplatin or paclitaxel plus carboplatin. Utilising kernel smoothing curves to determine the hazards for PFS and OS over time, the study found maximal risk for each at 12- and 18-months post-treatment, respectively, with events predominantly occurring within two to four years. Major sites of disease metastasis included the lungs, liver, spleen and peritoneum, with risk for dissemination greatest during the first 12-18 months after initial treatment and events predominantly observed before 24 months. The highest risk for pelvic malignancy recurrence was found to be at six months, with events primarily occurring within two years. Based on these findings the authors propose that close monitoring for the first two years after initial treatment followed by a less rigorous schedule of follow-up visits may be optimal, with individualisation depending on site of recurrence.

Comment: The frequency of OCCC in Europe and the United States ranges from 5% to 12.2%, while the frequency in Japan is as high as 25%, hence the best data on outcomes from this rare subtype will come from Asian studies. This study provides a very useful analysis on the behaviour of clear cell carcinoma of the ovary. The study highlights that the highest risk of recurrence occurs in the first 12 months after completion of treatment and the most common sites of first recurrence are the peritoneum, abdominal lymph node, liver, pelvis, distant lymph node and lung. Survival is very much influenced by stage at diagnosis, which has been described previously. The paper also comments on the possible follow-up schedules for these patients given the pattern of recurrence, emphasising the differences between recommendations in Europe/US versus Japan. However, what is not clear is whether changing the frequency of visits will truly change survival for these patients. Better treatment pathways are required, especially for those who relapse early.

Reference: Gynecol Oncol. 2024:190:113-18
Abstract

Exploring the impact of *BRCA1* and *BRCA2* mutation type and location on olaprib maintenance therapy in platinum-sensitive relapsed ovarian cancer patients

Authors: Škof E et al.

Summary: A single centre report from the Institute of Oncology Ljubljana in Slovenia details the impact of *BRCA* gene variant type and location on the safety and efficacy of single-agent olaparib maintenance therapy in patients with PSROC. Retrospective analysis included 100 women with relapsed *BRCA1* or *BRCA2* mutated (germline, 90%; somatic, 10%; *BRCA1* mutated; 76%, *BRCA2* mutated, 24%) PSROC. The study cohort almost exclusively had high-grade serous histology and most were in first relapse. The median age of patients was 60 years (range, 31-84) and the median follow-up duration was almost five years. The study found significantly different survival outcomes in women undergoing olaparib monotherapy according to specific *BRCA1/2* mutation type (large deletions, insertions, frameshift, missense or nonsense pathogenic variants) and location, but no impact of germline versus somatic variant. Specifically, the presence of a pathogenic variant in *BRCA1* was associated with an inferior prognosis, with median PFS and OS both more than two years shorter in this subgroup compared to patients with *BRCA2* mutated disease (PFS: 14 vs 38.8 months; OS: 21.8 vs 62 months). In addition, the intragenic location of the mutation in *BRCA1* influenced survival, with variants in the RING (Really Interesting New Gene) domain associating with inferior PFS versus variants in the DNA binding domain and C terminal domain (12.4 vs 23 months). Finally, the authors noted a higher incidence of olaparib discontinuation in patients with *BRCA1* mutated versus *BRCA2* mutated disease (84% vs 52%; p=0.015) and differences in reasons for treatment termination between patients with germline and somatic mutations (most commonly due to serious adverse events and disease progression, respectively).

Comment: This is a great paper that tells us very clearly that not all *BRCA* mutations are the same when it comes to prognosis and response to treatment. The *BRCA* gene has several functional domains that include: (1) a highly conserved N-terminal RING domain with an E3 ubiquitin ligase activity; (2) a DNA-binding domain; and (3) a C terminal domain of *BRCA1* (BRCT) that facilitates phosphoprotein binding. The main finding in this paper was the difference in response to maintenance olaparib with different mutations. There was a shorter survival in those harbouring a *BRCA1* RING domain mutation compared with other sites and patients with *BRCA2* mutations had a much better outcome compared with *BRCA1* mutation carriers. These findings are consistent with analysis from the PAOLA1 study, which showed that although all patients with *BRCA* mutated ovarian cancer derive benefit from olaparib maintenance therapy, the magnitude of benefit varied by *BRCA* mutation type. The greatest benefit was observed in patients with *BRCA1* mutations located in the DNA-binding domain, where the 24-month PFS rate was improved by almost six-fold by the addition of olaparib to bevacizumab maintenance (89% vs 15%). However, what is missing in that study is to see whether olaparib and bevacizumab is better than olaparib alone in some *BRCA* mutation carriers by site of the mutation.

Reference: Gynecol Oncol. 2024:190:104-12
Abstract

Surgery versus no surgery in platinum-sensitive relapsed ovarian cancer

Authors: Jiang R et al., & the SOC-1 Investigators

Summary: Final overall survival analysis of the SOC-1 randomised phase 3 trial suggests that secondary cytoreduction may provide a survival benefit over salvage chemotherapy alone in select patients with platinum-sensitive ovarian cancer in first relapse. A total of 357 adult patients with first relapsed platinum-sensitive epithelial ovarian, primary peritoneal, or fallopian tube cancer with a platinum-free interval of at least six months and disease deemed suitable for complete resection were enrolled to the Chinese multicentre, open-label, phase 3 trial and received six cycles of second-line chemotherapy alone (control cohort; n=175) or chemotherapy in the postoperative setting following secondary cytoreduction (n=182). Analysis in the intention-to-treat population at a median follow-up of nearly seven years revealed a six-month prolongation in absolute median OS with surgery that did not reach statistical significance (58.1 vs 52.1 months; HR 0.80; 95% confidence interval [CI], 0.61-1.05; *p*=0.11). A sensitivity analysis excluding the 35% of patients who crossed over from the control arm to the surgical arm after disease relapse found that surgery conferred a 24% reduced risk of death compared to salvage chemotherapy alone (HR 0.76; 95% CI, 0.58-0.99). The longest survival duration was found in patients who attained a complete resection (median, 73 months). Signficantly more patients in the surgical versus control cohort were alive and relapse-free at five years (13.2% vs 2.9%).

Comment: This is a follow-up paper after the first publication in 2021 showing a PFS advantage for surgery over no surgery (HR 0.58). In addition, the DESKTOP study showed an improvement in survival of surgery (HR 0.75 using the AGO criteria to exclude unsuitable patients). This trial also demonstrated the need to achieve a complete cytoreduction to get any benefit from debulking surgery. This trial used a different scoring method to determine resectability – the iMODEL score using patient and tumour factors. They also used a positron emission tomography (PET) scan to exclude other patients. Importantly, it did not exclude patients on the basis of a peritoneal carcinoma index. In the intention-to-treat analysis there was no improvement in OS with the addition of surgery but when the analysis was done to exclude those who crossed over or those with > 20 sites of disease there were trends towards a survival advantage. The survival rates documented are very good for this group of patients with relapsed ovarian cancer and I think supports the role of secondary surgery. What is unclear is exactly which criteria to use to exclude patients. I would favour the AGO score with a PET scan and a pre-operative laparoscopy.

Reference: Nat Med. 2024;30(8):2181-88
Abstract

Pre-diagnosis tea and coffee consumption and survival after a diagnosis of ovarian cancer: results from the Ovarian Cancer Association Consortium

Authors: Nagle C et al.

Summary: Regular intake of green tea, but not coffee, prior to a diagnosis of ovarian cancer may protect against death, according to this analysis of data from 10 Ovarian Cancer Association Consortium studies. Researchers evaluated associations between pre-diagnosis tea and coffee consumption and survival via food frequency questionnaires in almost 6,000 women newly diagnosed with ovarian cancer, most commonly advanced high-grade serous carcinoma. Adjusted Cox proportional hazards regression modelling failed to find any correlation between pre-diagnosis consumption of coffee, herbal tea, black tea or caffeine, and survival. Factors identified as negatively impacting survival included advanced disease, older age, residual disease post-surgery, obesity and smoking. Finally, daily intake of at least one cup of green tea was associated with improved OS and ovarian cancer-specific survival (adjusted hazard ratios [HRs] 0.84 and 0.81, respectively), both in pooled analyses and independently in each of five studies that reported ovarian cancer-specific survival.

Comment: The role of natural products in the prevention and possible treatment for cancer is controversial. However, it is clear that certain long-term diets can reduce the risk of cancer (vegetarian and Mediterranean diets in particular). Green tea contains epigallocatechin-3-gallate (EGCG), which is the predominant catechin that has anticancer properties in vitro. Large clinical trials have been quite inconclusive for benefit. A Cochrane meta-analysis in 2020 suggested a relative risk of 1.50 for gynaecological cancer risk in those who drank green tea versus those who did not. The current study suggests that there may be a survival advantage for ovarian cancer patients who drank green tea prior to their diagnosis. It also hypothesises that taking green tea after treatment could improve outcomes but I think this is very uncertain and I would not be advising my patients to do so at this time.

Reference: Br J Cancer. 2024;131(6):1043-49
Abstract

Stereotactic radiotherapy for managing ovarian cancer oligoprogression under poly (ADP-ribose) polymerase inhibitors (PARPi)

Authors: Durante S et al.

Summary: This Italian multicentre retrospective study sought to explicate the efficacy and safety of stereotactic body radiotherapy for advanced epithelial ovarian cancer oligoprogression in patients undergoing poly (ADP-ribose) polymerase (PARP) inhibitor therapy. A total of 46 patients (89 lesions) who received stereotactic body radiotherapy in combination with PARP inhibitor therapy for oligoprogressive disease between 2012 and 2023 were included in the study. The median follow-up was over two years. Most lesions (90%) were located in lymph nodes, with visceral and bone lesions fairly uncommon (9% and 1%, respectively). A median next-line systemic therapy-free interval of 12.4 months was reported, with time to next-line therapy substantially shorter in patients with five or more prior lines of chemotherapy (HR 3.21). Less than one-third of patients remained on PARP inhibitor therapy at the time of analysis, with all other patients initiating a novel systemic therapeutic. At two years, the rate of PFS was 10.7%, local failure-free survival 78.1% and OS 76.5%. The study authors concluded that this combination strategy may be an option for patients with oligoprogressive ovarian cancer although they caution that prospective research to confirm the efficacy and safety is needed.

Comment: This is a retrospective study and therefore suffers from several biases. However, this is now a more common problem of how to manage patients with oligoprogression while on maintenance olaparib. Some of these patients are not relevant to our clinical practice as they have had multiple lines of chemotherapy which is not the patient cohort who we treat with olaparib. The key takeaway message is that patients who do progress with isolated lymph node metastases while on olaparib can be safely given radiation to that site and continue with olaparib. It leads to a 12-month delay in time to next systemic therapy, which is important for quality-of-life considerations.

Reference: Int J Gynecol Cancer. 2024;34(8):1232-39
Abstract

Efficacy of chemotherapy after progression during or following PARPi exposure in ovarian cancer

Authors: Xu-Vuillard A et al.

Summary: Xu-Vuillard et al retrospectively analysed the effectiveness of chemotherapy in patients who experience ovarian cancer progression during PARP inhibitor therapy. A real-world international cohort of almost 200 patients (44.7% *BRCA* mutated disease) treated at one of four international centres in a 20-year period spanning 2002 to 2021, inclusively, with platinum- (62.5%) or non-platinum-based chemotherapy (37.5%; most commonly paclitaxel monotherapy) for progressive disease during or after at least one line of chemotherapy and PARP inhibition were included in the study. Most patients received PARP inhibition as a later-line therapy (14.1% in the first-line setting) and had received one or two prior lines of chemotherapy (median, 1; range, 1-7). The study noted a poor prognosis in this patient population overall, with a median PFS and OS from initiation of post-PARP inhibitor chemotherapy of 5.6 and 13.6 months, respectively. They also reported that a platinum-based chemotherapy regimen prolonged PFS and trended towards improving OS compared to a non-platinum-based regimen, with a HR for PFS of 0.52 on multivariable analysis (PFS: 3.7 vs 3.5 months, $p<0.0001$; OS: 14.2 vs 12.9 months; $p=0.13$). Other factors identified as positively associated with longer PFS, independent of *BRCA* status or line of therapy, included a platinum-free interval of more than six months and primary versus interval surgery.

Comment: This study is a retrospective study but gives us good guidance into outcome in this patient group. Increasingly we have patients who progress on PARP inhibition whether in the first-line or second-line setting. The population analysed does include 55% of patients without a mutation in *BRCA* genes, so will include many patients who we would not prescribe a PARP inhibitor for in Australia. However, the results are instructive in what to expect with patients in this setting and highlights the importance of platinum-free interval as a marker of response and survival to subsequent chemotherapy. It also highlights that the survival in this situation is independent of *BRCA* status. The take home message is that we should still prescribe chemotherapy according to the principals of platinum sensitivity to achieve best outcomes for these patients.

Reference: ESMO Open. 2024;9(9):103694
Abstract

Concurrent RB1 loss and *BRCA* deficiency predicts enhanced immunologic response and long-term survival in tubo-ovarian high-grade serous carcinoma

Authors: Saner F et al.

Summary: This study examined ovarian carcinoma tumour samples from the Ovarian Tumour Tissue Analysis consortium to investigate the prevalence of RB1 protein expression loss in each histology and investigate the impact of concurrent *BRCA* deficiency plus RBI loss in high-grade serous ovarian carcinoma (HGSOC). Analysis of RB1 expression in formalin-fixed, paraffin-embedded tumour samples from almost 7,500 patients diagnosed with invasive epithelial ovarian cancer by immunohistochemistry found RB1 loss in 16.4% of HGSOCs, significantly more often than the incidence of RB1 expression loss in any other histotype (endometrioid ovarian carcinoma, 4.1%; clear cell ovarian cancer, low-grade serous carcinoma and mucinous ovarian cancer, 2% each). Multivariate analysis of molecular alterations and OS found RB1 expression loss to be a positive prognostic factor in HGSOC, prolonging median OS by more than one year versus patients with retained RB1 expression (4.7 vs 3.6 years; HR 0.74). In contrast, RB1 protein expression loss associated with poorer survival in patients with an endometrioid ovarian carcinoma (HR 2.17). Subsequent analysis in a subset of patients with HGSOC with other molecular or immune data available revealed that the improved prognosis conferred by RB1 loss may be homologous recombination deficient (HRD)-dependent, with the best prognosis observed in patients with both RB1 expression loss plus mutated *BRCA1/2*. Finally, *in vitro* experiments in *BRCA1/2* mutated HGSOC cell lines employing CRISPR-Cas9 to knockout *RB1* revealed improved response to chemotherapy and immune stimulation.

Comment: This study is important in our understanding of the value of assessing RB1 loss in HGSOC. It seems to stratify patients into good and poor prognostic groups when combined with *BRCA*/HRD status. This may be due to increased chemotherapy sensitivity, as described in the paper, but it may also be due to an enhanced immune response in the most favourable tumours. The way forward may be to use this information to target treatments in the first or subsequent lines of therapy. Also, it may open up new lines of treatment, either exploring novel immune pathways or combining with other targeted therapies. Some of these cited in the paper include casein kinase 2 inhibitors, which have been reported to enhance the sensitivity of RB1-deficient triple-negative breast cancer and HGSOC cells to carboplatin and niraparib, Aurora kinase A and B inhibition, which is synthetically lethal in combination with RB1 loss in breast and lung cancer cells, and WEE1 inhibition in TP53 mutant triple-negative breast cancer and patient-derived HGSOC xenografts. The *BRCA1*-altered cell line AOCS7.2 with induced *RB1* knockout was more sensitive to olaparib, suggesting that RB1 loss may also predict responses to PARP inhibitors in HGSOC.

Reference: Clin Cancer Res. 2024;30(16):3481-98
Abstract

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Atezolizumab combined with platinum and maintenance niraparib for recurrent ovarian cancer with a platinum-free interval >6 months: ENGOT-OV41/GEICO 69-O/ANITA phase III trial

Authors: González-Martín A et al.

Summary: The European phase 3 ANITA trial has failed to demonstrate any clinical benefit to the addition of atezolizumab to a carboplatin chemotherapy doublet prior to maintenance niraparib in patients with recurrent ovarian cancer with a platinum-free interval of at least six months. Adult patients with measurable high-grade serous, endometrioid or undifferentiated recurrent ovarian cancer after one or two lines of platinum-based chemotherapy with a platinum-free interval of six months or more enrolled to the trial (n=417) received six cycles of carboplatin in combination with either paclitaxel, gemcitabine or pegylated liposomal doxorubicin ± atezolizumab followed by single-agent niraparib maintenance. The addition of atezolizumab did not prolong PFS versus doublet chemotherapy alone in an investigator-assessed analysis with a median follow-up of over two years (11.2 vs 10.1 months). This finding was consistent across subgroups including by programmed death-ligand 1 (PD-L1) status. In addition, no difference in objective response rates was found between trial arms (45% vs 43%).

Comment: Unfortunately, this trial adds to a long list of negative studies of using immune check point inhibition in ovarian cancer. This study is in platinum-sensitive recurrent disease adding atezolizumab to a carboplatin doublet. There was no difference in response rate or PFS. In addition, there was no hint that using PD-L1 as a marker for response was helpful. In some of the earlier studies there was a hint that high PD-L1 expression may lead to a slightly higher response rate, but this was not meaningful when PFS or OS was analysed. So, unless we do find more useful biomarkers, or we have novel targets in the immune pathway, immune checkpoint inhibitors should not be used in serous carcinoma of the ovary.

Reference: J Clin Oncol. 2024; Sep 18. Online ahead of print.
Abstract

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