Ovarian Cancer Research Review™

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Issue 24 - 2022

In this issue:

Welcome to the latest issue of Ovarian Cancer Research Review.

Results from a SOLO2 ancillary study reported in *Annals of Oncology* should reassure oncologists and their patients with platinum-sensitive, recurrent ovarian cancer that clinical outcomes are not adversely impacted by dose interruptions/reductions of olaparib maintenance, finding comparable survival across different levels of treatment adherence. Adavosertib combined with chemotherapy agents, especially carboplatin, may have merit as a novel therapeutic strategy for primary platinum-resistant high-grade serous ovarian cancer with a phase 2 AstraZeneca study reporting promising preliminary efficacy. Data from other trials assessing other adavosertib-based combination regimens are eagerly awaited. In contrast to the Japanese Gynaecologic Oncology Group (JGOG) 3016 trial, final results from the international ICON8 trial in *The Lancet Oncology* with an almost six-year follow-up fail to demonstrate any survival benefit to front-line dose-dense chemotherapy versus conventional three-weekly administration in newly diagnosed epithelial ovarian cancer, leading the authors to conclude that in a Caucasian population, at least, standard of care dosing for front-line chemotherapy as part of a multimodal approach should remain as three-weekly. The benefit of poly (ADP-ribose) polymerase (PARP) inhibition in the maintenance setting for advanced ovarian cancer was demonstrated in ATHENA-MONO with a significant extension of progression-free survival (PFS) and it is worth contrasting this study with the Gynaecologic Oncology Group 0212 (GOG 0212) study which investigated single-agent taxane maintenance and published results after meeting prespecified futility thresholds.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

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Abbreviations used in this issue:

AUC = area under the curve; **CI** = confidence interval;
CRS = Chemotherapy Response Score; **FIGO** = International Federation of Gynaecology and Obstetrics;
HGNMOC = high-grade nonmucinous ovarian cancer; **HR** = hazard ratio;
HRD = homologous recombination deficient; **ICU** = intensive care unit;
OR = odds ratio; **ORR** = objective response rate; **OS** = overall survival;
PARP = poly (ADP-ribose) polymerase; **PFS** = progression-free survival; **RDI** = relative dose intensity.

Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal cancer treatment (ICON8): overall survival results from an open-label, randomised, controlled, phase 3 trial

Authors: Clamp A et al.

Summary: Final data from the international ICON8 trial (ClinicalTrials.gov Identifier: NCT01654146) have been published in the July edition of *The Lancet Oncology*. The phase 3, three-arm trial accrued 1,566 women with newly diagnosed International Federation of Gynaecology and Obstetrics (FIGO) system stage 1C-4 epithelial ovarian cancer (including fallopian tube carcinoma and primary peritoneal carcinoma of Müllerian histological type) from sites in the UK, Australia, New Zealand, Mexico, South Korea and Ireland to assess the clinical benefit of dose-dense chemotherapy when administered in either the adjuvant or neoadjuvant setting with primary surgery. Two front-line dose-dense doublet chemotherapy regimens, all administered for six 21-day cycles – weekly paclitaxel plus three-weekly carboplatin (80 mg/m^2 and area under the curve [AUC]5 or AUC6, respectively; n=523) and weekly paclitaxel plus weekly carboplatin (80 mg/m^2 and AUC2; n=521) – were compared to standard three-weekly paclitaxel/carboplatin (175 mg/m^2 and AUC 5/6; n=522). Study participants had a median age of 62 years, disease was predominantly (71%) advanced-stage and most (69%) patients had high-grade serous histology. At a median follow-up of almost six years (69 months), crude median overall survival (OS) in both dose-dense treatment arms was at least six months longer compared to the standard-of-care three-weekly regimen, however the difference did not reach statistical significance to demonstrate superiority (54.8 & 53.4 vs 47.4 months; hazard ratio [HR] 0.87 and 0.91). The co-primary endpoint of PFS also failed to find a benefit to either dose-dense regimen versus the three-weekly control (25.3 vs 24.8 vs 23.9 months). Grade 3/4 adverse events were predominantly haematological and more common in the dose-dense versus three-weekly dosing schedules (neutropenia, 36% vs 30% vs 15%; leukopenia, 16% vs 14% vs 4%; anaemia, 13% vs 5% vs 5%). Seven treatment-related fatalities were reported, two in the control arm and five in the two experimental arms combined.

Comment: ICON8 was a pivotal clinical trial and, although a negative trial changed practice. Many centres around the world had adopted the dose-dense schedule of weekly paclitaxel based on the striking findings of clinically significant increased PFS as well as OS in the JGOG 3016 trial. ICON8 was a confirmatory trial of dose-dense scheduling versus conventional three-weekly carboplatin and paclitaxel in a predominantly Caucasian population of patients with stages 1C-4 ovarian cancer. The PFS results were published in 2019 and demonstrated no difference in PFS between the arms which was quite different to JGOG 3016. The ICON8 investigators, which included multiple Australian sites, have now reported both updated PFS and OS – the median OS was 4 -4.5 years with no significant difference between the three arms. This reaffirms that three-weekly treatment with intravenous carboplatin and paclitaxel is the standard of care and has not changed for over 25 years despite numerous clinical trials. Depressing but reality. Progress has been made with maintenance therapies but in my view the next generation of trials should focus on the 50% of patients with homologous proficient cancers as high-grade serous cancers, in particular, include a number of distinct molecular subtypes where there is a high unmet need.

Reference: Lancet Oncol 2022;23(7):919-30
Abstract

Delay in adjuvant chemotherapy administration for patients with FIGO stage I epithelial ovarian carcinoma is associated with worse survival; an analysis of the National Cancer Database

Authors: Nasioudis D et al.

Summary: Dimitrios Nasioudis and colleagues interrogated the US National Cancer database to elucidate whether delayed post-surgical chemotherapy initiation deleteriously impacts survival in women with early-stage epithelial ovarian cancer. Analysis included 8,549 women diagnosed with FIGO stage I disease over the 12-year period spanning 2004 to 2015. All women received adjuvant combination chemotherapy, two-thirds (67.7%) commenced adjuvant treatment within six weeks of surgery and the other one-third (32.3%) received delayed chemotherapy (6-12 weeks post-surgery). Log-rank test of Kaplan-Meier curves found a 4% higher survival rate at five-years in patients who received chemotherapy within six weeks of surgery (five-year OS, 89.7% vs 85.7%; $p<0.001$) and this benefit was extended to 6.7% in subgroup analysis of patients with high-grade serous tumours (five-year OS, 88.6% vs 81.9%; $p<0.001$). Cox regression modelling adjusted for age, race, comorbidities, insurance status, tumour histology and grade, performance of lymphadenectomy and substage and time of chemotherapy commencement identified delayed adjuvant chemotherapy as a negative independent prognostic factor for survival, conferring a 25% increased risk of mortality compared to immediate chemotherapy treatment after surgical resection (HR 1.25; 95% confidence interval [CI], 1.10-1.42).

Comment: Although there are limitations and caveats with database audits, the large numbers of patients in a "real-world" setting provides confidence with the findings, which are supported by other studies. This study included over 8,000 patients and showed that a delay in commencing adjuvant chemotherapy beyond six weeks from surgery in patients with stage 1 ovarian cancer was associated with inferior survival. There are a number of reasons for delaying chemotherapy which include patient-related factors such as comorbidities, slow recovery from surgery, frailty and older age as well as health system factors including limited access to care and timely commencement of treatment. However, even when controlling for patient-related factors, the association persisted. A delay in treatment had the highest impact in patients with stage 1c or high-grade serous histology which makes sense as they have the highest risk of recurrence and the most to gain from adjuvant chemotherapy. These findings are very consistent with what has been reported in patients with advanced ovarian cancer. A 2017 meta-analysis that included 14 studies found a significant association with delay in starting chemotherapy and OS. In this analysis, relative OS decreased by 4% for each week in delay of initiating adjuvant chemotherapy. Similar findings have been observed in other studies in advanced ovarian cancer but this is the first such study in stage 1 ovarian cancer. The take home message is: commence adjuvant chemotherapy as early as possible in all stages.

Reference: Gynecol Oncol 2022;166(2):263-68
Abstract

Ovarian Cancer Research Review™

Independent commentary by Professor Michael Friedlander

Michael Friedlander is conjoint Professor of Medicine at the University of NSW and a senior medical oncologist at the Prince of Wales Hospital and Royal Hospital for Women. He has a broad range of research interests with a focus on clinical trials for women with breast and gynaecologic cancers as well as incorporating patient reported outcomes as endpoints into clinical trials and to inform clinical practice.

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Phase III randomised trial of maintenance taxanes versus surveillance in women with advanced ovarian/tubal/peritoneal cancer

Authors: Copeland L et al.

Summary: A Gynaecologic Oncology Group 0212:NRG Oncology study (ClinicalTrials.gov Identifier: NCT00108745) assessing single-agent taxane maintenance for advanced ovarian cancer has published early survival data after the fourth interim analysis revealed that the prespecified futility threshold had been exceeded. A total of 1,157 women with advanced disease who achieved a complete response with no radiographic evidence of persistent cancer following primary surgical resection and platinum-taxane-based combination chemotherapy were accrued from more than 300 US sites. After a more than eight-year median follow-up, 12 cycles of paclitaxel or paclitaxel poliglumex maintenance did not improve OS, the primary outcome measure of the trial, compared to surveillance (56.8 vs 60 vs 58.3 months, respectively; both $p>0.05$). A modest but statistically significant improvement in PFS with median extensions of over five and three months in the paclitaxel and paclitaxel poliglumex treatment arms, respectively (18.9 vs 16.3 vs 13.4 months; HR 0.80 and HR 0.85; both $p\leq0.05$), was reported compared to surveillance but at the expense of more frequent gastrointestinal and neurological toxicity (≥ grade 2 gastrointestinal adverse events, 27% vs 20% vs 11%; ≥ grade 2 neurological adverse events, 36% vs 46% vs 14%).

Comment: The main reason for including this trial is to compare and contrast with contemporary trials of maintenance therapy with PARP inhibitors after response to first-line therapy. This was a large trial that included over 1,100 patients with advanced ovarian cancer who had responded to first-line treatment (all were in complete response after primary surgery) when they were randomised to maintenance therapy with paclitaxel, paclitaxel poliglumex or surveillance alone. The median PFS was increased with maintenance taxanes (18.9 months for paclitaxel poliglumex; 16.3 for paclitaxel vs 13.4 m with surveillance) but no difference in median OS which was about five years in all arms. As expected, progression of sensory neuropathy was the most significant adverse effect of both taxanes, although surprisingly only 11% ceased treatment for neuropathy despite 30-40% having grade 2 -3 neuropathy. The HR for PFS was about 0.8 for both taxanes, which is similar to maintenance bevacizumab and pazopanib. The PFS for the control is very similar to the placebo arms in contemporary PARP maintenance trials. Unfortunately, there are no data on *BRCA* status or homologous recombination deficiency (HRD) so cross trial comparison is not possible. In the first-line PARP inhibitor trials the HR for PFS in the intent-to-treat analysis was around 0.6 -0.7 with HR for PFS much lower in the *BRCA* (0.3) and HRD (0.4) populations. The five-year OS is a good benchmark for comparison with the PARP inhibitor trials. The authors concluded that maintenance taxanes are unlikely to play a role in management of patients, which most would agree with.

Reference: J Clin Oncol 2022; Jun 27 [Epub ahead of print]
Abstract

A randomised, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45)

Authors: Monk B et al.

Summary: Clovis Oncology's international, phase 3 ATHENA trial (NCT03522246) aimed to elucidate the benefit of single-agent PARP inhibition, single-agent checkpoint inhibition or dual combination PARP/checkpoint inhibitor front-line maintenance for previously untreated, advanced ovarian cancer. Monk et al report outcomes from two of the four front-line maintenance trial arms – rucaparib monotherapy versus placebo – in *Journal of Clinical Oncology*. Patients with newly diagnosed FIGO stage 3-4 epithelial ovarian, fallopian tube or primary peritoneal cancer who had attained a response to primary or interval debulking surgery (including at least a bilateral salpingo-oophorectomy and partial omentectomy) plus front-line platinum-based chemotherapy were enrolled from sites across North America, Europe and Asia and randomised 4:1 to maintenance with oral rucaparib (600 mg twice-daily; n=427) or placebo (n=111). Trial inclusion criteria permitted enrolment by a broad patient population including those with high-risk features such as *BRCA1/2* mutations or other HRD. The trial demonstrated efficacy of rucaparib monotherapy maintenance in the overall intention-to-treat population with an almost one-year extension of PFS compared to placebo (20.2 vs 9.2 months; HR 0.52; 95% CI, 0.40-0.68; $p<0.0001$). The benefit was most pronounced in the HRD population with a more than 17-month prolongation of median PFS and a 53% reduced risk of disease progression or death versus placebo (28.7 vs 11.3 months; HR 0.47; $p=0.0004$). A significant PFS benefit was also revealed in the HRD-negative population (12.1 vs 9.1 months; HR 0.65). Adverse events were predominantly haematological and were more prevalent with rucaparib (≥ grade 3 anaemia, 28.7% vs 0%; neutropenia, 14.6% vs 0.9%).

Comment: This is the fourth trial which has demonstrated that maintenance therapy with a PARP inhibitor following response to first-line chemotherapy in advanced ovarian cancer was associated with a significant increase in PFS, particularly in the *BRCA* and HRD population of patients. In ATHENA –MONO patients were randomised to rucaparib versus placebo (4:1) and the results are very similar to what has been reported in other trials with PARP inhibitors. Although there was a PFS benefit observed in the intent-to-treat population the greatest benefits were in the HRD subset who made up 50% of patients. Tumour HRD status (*BRCA* mutated and genomic loss of heterozygosity was determined with Foundation One CDx assay). Treatment interruptions occurred in 60% of patients; dose reductions in 49% and treatment discontinuation in 12% of patients on rucaparib. Similar to the PRIMA trial, but in contrast to PAOLA, there was a benefit observed in patients with HRP tumours. The absolute benefits were much greater in the HRD population (PFS 28.7 vs 11.3 months) as opposed to 12.1 vs 9.1 months in the HRP population. It would be interesting to know what the PFS with weekly paclitaxel would be in a HRP subgroup based on the abstract above but it is unlikely this will ever be looked at in trial. This study also includes ATHENA-COMBO which compares nivolumab with rucaparib versus rucaparib and placebo and the results are eagerly awaited.

Reference: J Clin Oncol 2022; Jun 6 [Epub ahead of print]
Abstract

Phase Ib study of navicixizumab plus paclitaxel in patients with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer

Authors: Fu S et al.

Summary: This phase 1b study (NCT03030287) reports promising anti-tumour activity of the first-in-class, bispecific, antiangiogenic antibody navicixizumab in combination with paclitaxel for recurrent platinum-resistant, advanced epithelial ovarian cancer. The single-arm trial, sponsored by OncoMed Pharmaceuticals, enrolled 44 American women with a residual tumour at least 1 cm in diameter and progressive disease within six months of platinum-based chemotherapy. All women were administered intravenous navicixizumab (3 mg/kg every second week in dose-expansion phase; median of 8 doses) plus paclitaxel (80 mg/m2 weekly). The objective response rate (ORR) was 43.2% (19/44) and was comprised predominantly of partial responses and a single complete response. The median duration of response was six months and the median PFS 7.2 months. Substantially better outcomes were noted in bevacizumab-naïve versus bevacizumab-exposed patients with a two-fold higher response rate (64.3% vs 33.3%) and longer PFS (7.6 vs 5.4 months). An exploratory retrospective analysis in 33 tumour samples utilising an RNA-based diagnostic panel revealed a superior response rate and disease-control rate in patients with an angiogenic or immune-suppressed tumour microenvironment, indicating that these may be predictive biomarkers to anti- vascular endothelial growth factor (VEGF) therapy. The safety profile was manageable with hypertension (40.9%), neutropenia (6.8%) and thrombocytopenia (4.5%) the most frequent grade 3/4 treatment-emergent adverse events.

Comment: It is unusual for phase 1 trials in platinum resistant ovarian cancer to be published in the *Journal of Clinical Oncology* and this attests to the potential implications of the results. The investigators evaluated the safety and efficacy of navicixizumab, a delta –like ligand 4 and VEGF bispecific antibody, in a heavily pre-treated group of patients many of whom had progressed after multiple lines of treatment including PARP inhibitors and bevacizumab. Given that the AURELIA trial demonstrated improved outcomes in combination with paclitaxel in platinum-resistant ovarian cancer, the investigators combined navicixizumab with paclitaxel in a dose finding and escalation study. The most important adverse effect of navicixizumab was hypertension (40% grade 3) as well as pulmonary hypertension (18%). The response rate was 43% and median PFS 7 months which is a lot higher than expected – whether this reflects patient selection or efficacy can only be determined in a phase 3 trial. Importantly, the response rate was 45% in patients who had progressed on a PARP inhibitor. They also reported a potential biomarker (angiogenic/immune suppressed based on mRNA expression of 100 genes) to identify the subset of patients more likely to respond. A phase 3 trial is planned and clearly careful selection of patients and close monitoring for adverse effects will be critical as will the translational component evaluating the biomarker.

Reference: J Clin Oncol 2022; Apr 19 [Epub ahead of print]
Abstract

TRACEBACK: Testing of historical tubo-ovarian cancer patients for hereditary risk genes as a cancer prevention strategy in family members

Authors: Delahunty R et al., on behalf of The Australian Ovarian Cancer Study, Ovarian Cancer Prognosis and Lifestyle Study and the TRACEBACK Study

Summary: The pilot Australian TRACEBACK study conducted retrospective genetic testing on women who died of high-grade nonmucinous epithelial carcinoma of the ovary, fallopian tube, or peritoneum (HGNMOC) prior to implementation of regular testing guidelines to evaluate if provision of unsolicited hereditary risk information to family members could mitigate cancer risk. A total of 787 women who died from HGNMOC between 2000 and 2016 without undergoing genetic testing were identified from multiple sources including research cohort studies, relative contact and gynaecologic oncology clinic databases. Assessment of 10 potentially clinically-actionable risk-associated genes (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*) revealed pathogenic variants in 11% (n=84) of the cohort. Of this group of deceased patients with confirmed hereditary cancer risk, almost three-quarters (71%) had identifiable next of kin, 65% of whom were contactable. Most next of kin (90%) were unaware of their increased genetic cancer risk and two-thirds (66%) accepted a referral to a genetic service. The authors noted that next of kin who refused referrals were exclusively male with the proband's death at least ten years prior. The authors concluded that despite substantial ethical and logistical challenges, retrospective genetic testing for the purpose of identifying family members with a genetic predisposition for cancer is feasible.

Comment: This is an important study lead by Rachel Delahunty and David Bowtell with a large number of centres in Australia collaborating and I should declare that I was a co-author. The basis for TRACEBACK was the high likelihood that there were potentially a large number of people with a first degree relative with high-grade ovarian cancer who had not been offered genetic testing in the past and who may have had a germline *BRCA* mutation. Given that up to 20% of women with a high-grade serous cancer have a germline *BRCA* pathogenic variant depending on the age at diagnosis there could be many unsuspecting family members at risk of breast /ovarian cancer. There were enormous hurdles and barriers to overcome to carry out this study and as expected they identified pathogenic variants in 11% of patients who had not been previously tested which has implications for other family members. The criteria for genetic testing have evolved and changed over the last 10 years. We now offer testing to all patients with a high-grade ovarian cancer, irrespective of family history but did not do so in the past, which means that we missed many patients with *BRCA* pathogenic variants – TRACEBACK attempted to address this so should all of us in the clinic if we come across patients who had not been offered genetic testing in the past.

Reference: J Clin Oncol 2022;40(18):2036-47
Abstract

The impact of olaparib dose reduction and treatment interruption on treatment outcome in the SOLO2/ENGOT-ov21 platinum-sensitive recurrent ovarian cancer

Authors: Francis K et al.

Summary: Reduced adherence to olaparib maintenance posology to manage side effects does not affect survival in women with platinum-sensitive, recurrent ovarian cancer according to data from a SOLO2 ancillary study in *Annals of Oncology*. Analysis included 185 women with *BRCA* mutated high-grade serous ovarian cancer who had undergone at least two lines of platinum-based chemotherapy prior to trial enrolment and did not experience disease progression in the first four weeks of olaparib 300 mg twice-daily maintenance treatment in the AstraZeneca SOLO2 trial (NCT01874353). While dose alterations were relatively frequent with dose interruptions in half of patients and dose reductions in 28%, adherence rates were high overall with three-quarters of the study population (n=40) receiving more than 90% relative dose intensity (RDI) and the median RDI in patients who received less than 90% was 76.2%. 12-week landmark Cox regression analysis of patients stratified into three cohorts according to RDI (> 98%, 90-98% and <90%) failed to find any significant difference in OS (49.7 vs 495 vs 54.1 months; p=0.84). Median PFS in the three levels of adherence were 14.2, 19.3 and 34.4 months, respectively, a difference that was not statistically significant (p=0.37). Univariate logistic regression analysis revealed an increased likelihood of lower RDI (<90%) associated with poor performance status (odds ratio [OR] 2.54), nausea (OR 3.17) and body weight of 70 kg or lower (OR 1.86).

Comment: This paper was written by Katherine Francis who also carried out the analyses on the impact of dose reductions and interruptions with maintenance olaparib in the SOLO2 trial and I should declare that I was a co-author. Most dose reductions and interruptions occur in the first 12 weeks of commencing olaparib and she focused on this time period. The take home message is that protocol mandated dose interruptions and delays or dose reductions of olaparib in patients enrolled in SOLO2 did not appear to be detrimental and patients can be reassured that this does not impact on overall outcomes. This is important as many patients and clinicians may have concerns regarding dose modifications. Following protocol mandated dose modifications is appropriate and does not compromise the potential benefit of treatment. For those who are interested, this paper was accompanied by a thoughtful editorial by Rob Coleman.

Reference: Ann Oncol 2022;33(6):593-601
Abstract

Adavosertib with chemotherapy in patients with primary platinum-resistant ovarian, fallopian tube, or peritoneal cancer

Authors: Moore K et al.

Summary: An open-label, four-arm, phase 2 study sponsored by AstraZeneca (NCT02272790) provides preliminary evidence to support the novel therapeutic combination of adavosertib plus chemotherapy for primary platinum-resistant ovarian cancer. A cohort of 94 patients with advanced (stage 3/4) recurrent disease within six months of surgical debulking and systemic platinum-based chemotherapy were enrolled and received adavosertib (175-225 mg twice-daily) in combination with either gemcitabine, paclitaxel, carboplatin or pegylated liposomal doxorubicin. Retrospective analysis of archival tumour samples proved *TP53*-mutation status. The ORR was 31.9% (30/94) and included three complete responses. Of the four combination regimens carboplatin plus adavosertib elicited the highest response rate (66.7%) with no cases of progressive disease (disease control rate 100%). The median PFS in this cohort was 12 months. Severe neutropenia was reported in half of patients and anaemia and thrombocytopenia in approximately one-third.

Comment: Adavosertib, a small molecule inhibitor of the tyrosine kinase WEE1, is the "new kid on the block" and is attracting a lot of interest as it has efficacy as a single agent as well as in combination with other drugs such as carboplatin or paclitaxel, as reported in this paper, as well as with PARP inhibitors, amongst others. There are an increasing number of studies being carried out in platinum-resistant ovarian cancer with adavosertib. Last year there was a phase 2 randomised trial reported of adavosertib plus gemcitabine or placebo plus gemcitabine (Lancet. 2021; 397: 281-292). PFS was 4.6 months in the adavosertib arm, compared with 3.0 months for the gemcitabine only, for a HR of 0.55 (95% CI, 0.35-0.90; p=0.015). There are many studies in progress, including the IGNITE trial in Australia lead by George Au Yeung, recruiting patients with cyclin e amplified /overexpressed platinum-resistant ovarian cancers. This is an active agent but can be associated with significant myelosuppression and diarrhoea. George reported a response rate of 53% with adavosertib as a single agent at the American Society of Clinical Oncology (ASCO) Annual Meeting 2022 and the trial is still recruiting. Expect to hear a lot more about adavosertib and it is likely that it will find a place in the management of patients with recurrent ovarian cancer.

Reference: Clin Cancer Res 2022;28(1):36-44
Abstract

BRCA status and platinum sensitivity in advanced ovarian cancer according to Chemotherapy Response Score

Authors: Ergasti R et al.

Summary: This single-centre retrospective study from the Gynaecologic Oncology Unit of the Catholic University of the Sacred Heart in Rome, Italy investigated the relationship between *BRCA* status and Chemotherapy Response Score (CRS) in advanced epithelial ovarian cancer. Analysis included 172 women with unresectable disease who received neoadjuvant chemotherapy and interval debulking in a five-year period between 2016 and 2020. Higher rates of good histopathologic response (CRS 3) were found in the 40% of patients with *BRCA*-mutated disease versus *BRCA* wild-type disease (43.5% vs 29.1%). CRS was prognostic for outcome exclusively in *BRCA* wild-type disease, with a significantly longer PFS in CRS 3 versus CRS1/2 (22 vs 15 months; p=0.003) and a trend towards improved survival that did not reach statistical significance (60 vs 44 months; p=0.06).

Comment: Although we would expect that there would be a strong association between CRS 3 after neoadjuvant therapy and *BRCA* mutational status (germline/somatic) due to increased platinum sensitivity the findings are conflicting. This is one of the larger studies reported to date and included 69 patients (40%) with *BRCA* mutations as well as 103 with *BRCA* wild-type. Almost 44% of patients with a *BRCA* mutation had a CRS 3 compared to 29% in *BRCA* wild-type. It is a pity we don't know what proportion of these are HRD versus HRP. A total of 14 (8.1%) patients had a complete pathological response, which was evenly split with 6 (43%) patients with *BRCA* mutated and 8 (57%) *BRCA* wild-type patients. The CRS was prognostic in patients with *BRCA* wild-type only, and did not correlate with PFS in carriers of *BRCA* mutations. It is difficult to draw conclusions regarding prognosis given that 65% of *BRCA* mutated received a PARP inhibitor; 30% of all patients had hyperthermic intraperitoneal chemotherapy. We need data on the correlation between HRD status and CRS and whether this could be used as a surrogate for HRD testing.

Reference: Int J Gynecol Cancer 2022;32(5):639-45
Abstract

End-of-life care for patients with advanced ovarian cancer in the Netherlands: A retrospective registry-based analysis

Authors: Broekman K et al.

Summary: This Dutch nationwide study reports lower rates of aggressive end of life inpatient palliative care in patients with advanced ovarian cancer compared to published rates from other European countries and the US. Data on medical care use in the last six months of life were extracted from the Vektis insurance database for all patients that died over a two-year period (2016 & 2017; n=1,775). Five domains of intense inpatient care were analysed - administration of chemotherapy, emergency room visits, surgical procedures, hospital and intensive care unit (ICU) admissions. The end-of-life rate of hospitalisation was ~50%, 12% of patients received chemotherapy in the last month and few patients underwent surgery or were admitted to the ICU (<10%).

Comment: ASCO identified that avoiding chemotherapy at end of life was one of the top five practices that could improve patient care and also reduce costs. Multiple studies in the USA have reported high rates of medical care in the last few weeks to months of life in patients with ovarian cancer including administration of chemotherapy, ICU admissions, hospital admissions and visits to the emergency department. For example, in a large SEER study of patients with ovarian cancer, in the 90 days prior to death, 65% of patients had an inpatient admission, 54% received chemotherapy and 19% had a palliative procedure. We don't have similar data in Australia that I am aware of. This study from the Netherlands, where there is ready access to palliative and supportive care provided mainly by GP's and community nurses, reported findings very different to the USA experience. Over 50% of patients received chemotherapy in the final six months of life and I expect that this is lower than in Australia, but probably more importantly, only 12% received chemotherapy in the last month of life and surgery was performed in only 4% of patients in the last two months. The decision to discontinue systemic therapy is challenging and difficult for both clinicians and patients. It is important to ensure that patients with platinum-resistant/refractory ovarian cancer with poor prognostic features understand that not having systemic therapy doesn't mean that they will not have ongoing supportive care to address symptoms which is likely to keep them out of hospital in the final months of life. Access to palliative care appears to reduce futile treatment towards the end of life.

Reference: Gynecol Oncol 2022;166(1):148-53
Abstract