Ovarian Cancer Research Review™

Making Education Easy

Issue 30 - 2023

In this issue:

- INF activating therapy may synergise with chemotherapy in PTEN-deficient HGSOC
- WEE1 inhibition promising for *CCNE1*-amplified EOC
- Senaparib has anti-tumour activity in ovarian cancer
- VIPER: NACT hinders visual evaluation of peritoneal disease
- Adjuvant chemotherapy no benefit in stage 1A OCCC
- Patient perspectives on RRSDO for ovarian cancer risk-reduction
- Completeness of surgery vital in ovarian sex cord-stromal tumours
- Inferior outcomes in older women with EOC treated with chemotherapy

Abbreviations used in this issue:

CCNE1 = cyclin E1; **CI** = confidence interval; **EOC** = epithelial ovarian cancer; **HGSOC** = high-grade serous ovarian cancer; **HR** = hazard ratio; **INF-1** = type I interferon; **NACT** = neoadjuvant chemotherapy; **OCCC** = ovarian clear cell carcinoma; **ORR** = objective response rate; **PARP** = poly(ADP-ribose) polymerase; **PFS** = progression-free survival; **RRSDO** = risk-reducing salpingectomy with delayed oophorectomy; **STING** = stimulator of interferon genes; **TIME** = tumour immune microenvironment.

Welcome to the latest issue of Ovarian Cancer Research Review.

We begin this review with results from a preclinical study that evaluates the relationship between tumour genotype, tumour immune microenvironment and prognosis. This is followed by a phase 2 trial of the WEE1 inhibitor adavosertib that reports a promising preliminary antitumour activity in refractory epithelial ovarian cancer (EOC) with cyclin E1 (*CCNE1*) gene amplification, suggesting that further evaluation of this agent as a monotherapy or as part of combination regimens is warranted. Next, an Australian first-in-human study of the novel selective poly(ADP-ribose) polymerase (PARP) inhibitor senaparib reports preliminary anti-tumour activity in advanced ovarian cancer with a signal for improved efficacy in *BRCA* mutated tumours. In other research, the Italian retrospective VIPER study investigates the accuracy of visual peritoneal evaluation of residual disease after neoadjuvant chemotherapy compared to a histopathological reference in advanced ovarian cancer; and patient perspectives on risk-reducing salpingectomy with delayed oophorectomy (RRSDO) in women at increased risk for ovarian cancer are reported by a systematic review. Finally, the efficacy of perioperative chemotherapy is investigated in ovarian clear cell carcinoma, a rare histological subtype of EOC, and in malignant ovarian sex cord-stromal tumours in studies published in *Cancer Medicine* and *Gynecologic Oncology*, respectively. Commentary for this issue has been provided by Associate Professor Yoland Antill, a Medical Oncologist and Cancer Genetics Specialist with expertise in gynaecologic cancers.

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

Kind Regards,

Dr Janette Tenne
janette.tenne@researchreview.com.au

Cancer cell genotype associated tumour immune microenvironment exhibits differential response to therapeutic STING pathway activation in high-grade serous ovarian cancer

Authors: Shakfa N et al.

Summary: This preclinical study from a Canadian research group investigated the relationship between tumour genotype with respect to tumour suppressor loss, stimulator of interferon genes (STING) pathway activation treatment and immune microenvironment in HGSOC. The study employed multiplex immunofluorescence staining to characterise the tumour immune microenvironment in chemotherapy naïve tumour samples from patients (n=110) and in murine models of ovarian cancer harbouring *PTEN* or *BRCA1* gene deletions, both in the context of concomitant *TRP53* knockout. The researchers found that PTEN protein deficient tumours from both patients and murine models were distinguished by a T cell non-infiltrated state that impaired the T cell-mediated immune response with M2-like macrophage dominance and resulted in an unfavourable disease-specific survival in patients and an aggressive pathology in murine models. Finally, exogenous STING activation enhanced chemotherapy response in PTEN deficient tumours *in vivo* by rescuing CD8+ cytotoxic T cell activation and pro inflammatory responses by converting M1-like macrophages to the M2-like phenotype. Interferon activating therapies in combination with chemotherapy may be a novel therapeutic approach in PTEN-deficient HGSOC.

Comment: HGSOC largely remains resistant to immune checkpoint inhibition. It is also well recognised that as a tumour type there is significant genetic heterogeneity. In this study, genotype is assessed against tumour immune microenvironment (TIME) and prognosis. Evidence suggests that alterations in tumour suppressor function involved in type I interferon (INF-1) regulation can drive the evolution of the TIME and downstream responses. While *BRCA* mutated tumours have increased platinum sensitivity, those with co-existent PTEN loss are more likely chemoresistant, with both genes having regulatory function in the IFN-1 activation - *BRCA* through the STING pathway and *PTEN* through interferon regulation factor. STING activation is thought to enhance the TIME with recruitment of CD8+ T cells, whereas PTEN loss results in a more immune cell deplete TIME. This study adds to the body of evidence that *BRCA1* deficiency is associated with an active TIME but adds that those with PTEN loss have deplete TIME enriched for M2-like macrophages with immune suppressive activity including poor antigen presenting. Importantly however, the study describes a reversal of this pathway of immune suppression with the introduction of agents aimed at STING activation. This reprogramming of the TIME also resulted in an improved platinum response. There are currently a number of clinical trials evaluating the effect of STING agonists in combination with immune checkpoint inhibitors, but this study demonstrates the importance of understanding the potential value of genomic alterations that may be of particular value to the mechanism of action of these agents.

Reference: J Immunother Cancer 2023;11(4):e006170

Abstract

Multicentre phase II trial of the WEE1 inhibitor adavosertib in refractory solid tumours harbouring *CCNE1* amplification

Authors: Fu S et al.

Summary: Inhibition of the WEE1 kinase may be a novel therapeutic option for women with *CCNE1*-amplified EOC, with results from a multicentre US trial demonstrating preliminary antitumour activity. A total of 30 patients with a pretreated, histologically advanced solid tumour refractory to standard-of-care therapies with at least seven copies of *CCNE1* and a good performance status were accrued to the trial and administered continuous 21-day cycles of 300 mg adavosertib monotherapy on days 1-5 and 8-12. Ten different primary malignancies were included in the trial population, most commonly EOC (n=14), followed by breast cancer (n=3) and uterine cancer (n=3). Patients were heavily pretreated with a median of three prior systemic therapies (range, 1-7). Antitumour activity was detected in the overall trial population with an objective response rate (ORR) of 27% at a median follow-up of 9.9 months, with the best response attained a partial response and increased activity in the EOC cohort (ORR, 36%). Stable disease maintained for at least six months was achieved by a further three patients, all with EOC, for disease-control rates of 37% and 57% in the overall study population and the EOC cohort, respectively. The median duration of response, progression-free survival (PFS) and overall survival in the EOC cohort were 6.3, 6.3 and 14.9 months, respectively. Sixty percent of patients experienced a treatment-related adverse event, most commonly haematological (anaemia, neutropenia and thrombocytopenia), gastrointestinal (diarrhoea, nausea) or fatigue. There were no treatment-related deaths. The study authors concluded that further evaluation of adavosertib as a monotherapy or as part of a combination regimen is warranted in EOC.

Comment: The prognosis for patients with platinum resistant ovarian cancer remains poor with limited opportunity for chemotherapy response, and even more limited options for targeted therapeutic options. *CCNE1* amplification is seen in approximately 10%-15% of high-grade serous ovarian cancer (HGSOC) cases and is associated with chemotherapy resistance, the use of homologous proficient repair pathways (and therefore PARP inhibitor resistant). CCNE1 is integrally involved in cell cycle regulation and those with *CCNE1* amplified tumours are likely to be particularly reliant on the effect of WEE1 checkpoints to allow for DNA repair, in turn, it is hypothesised that those tumours amplified for *CCNE1* may be particularly vulnerable to the inhibition of WEE1, with replication stress, accumulation of genomic instability and resultant apoptosis rather than continued mitotic cell division. Adavosertib is an oral WEE1 inhibitor. In this small phase 2 trial of patients with *CCNE1* amplification, 14 had platinum-resistant HGSOC. Among the participants with HGSOC the ORR was 36%, with five patients achieving a partial response and three attaining stable disease for six months or more. Importantly though is whether *CCNE1* over expression can also be utilised as a marker of WEE1 inhibitor sensitivity, with recent reports from the IGNITE trial where Au Yeung et al reported an ORR of 53% in cyclin E1 overexpression but non-amplified platinum-resistant HGSOC. This would extend the potential therapeutic opportunity to a second group of cancers, representing around 35%-45% of early HGSOCs. These early phase trials suggest that WEE1 inhibition is worthy of pursuit in tumours associated with both cyclin E amplification and overexpression. The toxicities associated with this agent are significant, predominantly haematological and therefore manageable, and to a lesser degree gastrointestinal (diarrhoea, nausea and vomiting).

Reference: J Clin Oncol 2023;41(9):1725-34
Abstract

A phase 1 dose-escalation study of the poly(ADP-ribose) polymerase inhibitor senaparib in Australian patients with advanced solid tumours

Authors: Gao B et al.

Summary: Gao et al report results from a first-in-human study of the novel selective PARP inhibitor senaparib in patients with advanced solid tumours. A total of 39 patients with a progressive incurable solid malignancy (ovarian cancer, n=11; prostate cancer, n=10; breast cancer, n=3) after at least one prior systemic therapy who had exhausted all standard therapies were enrolled from three Australian sites and received up to 12 months of single-agent oral senaparib at doses ranging from 2 mg to 150 mg once daily in three-week cycles. A favourable safety profile and good tolerability was reported with treatment-emergent adverse events predominantly mild or moderate and the most common treatment-related adverse events nausea and fatigue. There was one treatment-related fatality due to bone marrow failure after the end of study treatment. No dose-limiting toxicity was found and the recommended phase 2 dose was determined to be 100 mg/day. Preliminary evaluation of antitumour response in 22 patients evaluable for efficacy found three partial responses (ORR, 13.6%), all in patients with ovarian cancer with response durations of 1.4, 2.8 and 22.1 months. Increased activity was reported in the *BRCA* mutated versus *BRCA* wild-type cohorts (ORRs 33.3% [n=2/6] vs 6.3% [n=1/16]), although absolute numbers were very small. The authors hypothesised that senaparib may provide a more tolerable option to olaparib for use in combination regimens.

Comment: Senaparib is an oral selective inhibitor of PARP1 and PARP2 with 20-fold higher in vivo activity than olaparib. This was a first-in-human trial conducted in three Australian sites, using a standard incremental dosing to determine the maximum tolerated dose. The primary endpoints of the study were the incidence and nature of dose-limiting toxicities with exploratory endpoints ORR, disease-control rate, duration of response, PFS and where applicable, prostate-specific antigen and cancer antigen (CA)-125 concentrations. Thirty-nine participants were enrolled (8 with known germline *BRCA* pathogenic variants) including ovarian, breast, prostate as the most common tumour types. The treatment-emergent adverse events were similar to those experienced with PARP1 inhibitors but did include one grade 5 event of bone marrow failure without evidence of myelodysplasia thought to be related to senaparib. Of the 22 participants evaluable for tumour response, responses were seen more commonly in *BRCA* carriers than non-carriers but stable disease was just as likely in carriers and non-carriers. Disappointingly, it is not reported whether any of the participants had prior PARP inhibitor exposure. The dose going forward and recommended by authors was 100 mg daily, with anti-tumour activity seen and the treatment-emergent adverse events largely grade 1/2 (9% grade ≥ 3). Interestingly, the gastrointestinal toxicities were less prevalent than reported with other PARP inhibitors. PARP inhibitors are the first targeted therapies to exploit the synthetic lethality in *BRCA1/2* associated tumours, and have proven additional benefit in tumours associated with preservation of homologous recombination deficiency. Trapping of PARP varies between the current commercially available PARP inhibitors - talazoparib the most potent and the weakest being veliparib. They also have differing allosteric effects with release of PARP1 from DNA prevented by olaparib and talazoparib but promoted by niraparib, rucaparib and veliparib. The more potent PARP trappers, in general, are required to be given in lower doses - in this study, the maximum tolerated dose was not reached suggesting support for PARP potency. Potency in itself does not seem to impact the development of PARP inhibitor resistance, in particular for reversion mutations and therefore senaparib may represent an alternate option in a recognised class with a more tolerable side effect profile rather than a novel agent with options targeting resistance mechanisms. Being an inhibitor of both PARP1 and 2 haematological toxicities and long-term issues with myelodysplasia remain more likely than with the inhibitors of PARP1 alone.

Reference: Cancer 2023;129(7):1041-50
Abstract

Visual peritoneal evaluation of residual disease after neoadjuvant chemotherapy in advanced ovarian cancer patients: The VIPER study

Authors: Costantini B et al.

Summary: Data from the Italian retrospective VIPER (Visual Peritoneal Evaluation of Residual disease) study indicate that intraoperative assessment of abdominal disease dissemination in patients with ovarian cancer is substantially hindered by chemotherapy induced fibrotic changes, rendering laparoscopic visual evaluation inaccurate. Analysis was based on 155 patients with advanced ovarian cancer who underwent diaphragmatic peritonectomy at the time of interval debulking surgery after neoadjuvant chemotherapy (NACT) in a three-year period spanning 2016 to 2019. Compared to the reference standard of formalin-fixed histopathological examination, the accuracy of intraoperative laparoscopic visual evaluation of the diaphragmatic peritoneum was 67.1% (specificity 100%, sensitivity 64.3%).

Comment: In recent times, an increasing number of teams are electing to use an approach to the management of advanced ovarian cancer with NACT followed by interval debulking and further adjuvant chemotherapy ± maintenance treatment. Resection to R0 remains a prognostically significant marker of risk of recurrence and determinant of those likely to benefit from maintenance bevacizumab. The use of NACT aims to induce cellular apoptosis and resulting fibrosis in the tumour area that visually may be more difficult to differentiate from viable tumour. Complication rates are likely increased with more extensive surgery and diaphragmatic stripping and so a desirable assessment of the benefit of the extensive resection is warranted. In 155 patients who were laparoscopically deemed unresectable with stages 3/4 EOC, with visually involved diaphragmatic peritoneal disease, the primary aim of this study was to establish the sensitivity, specificity and accuracy of intraoperative laparoscopic visual evaluation of the diaphragmatic peritoneum compared with histopathological examination during interval debulking surgery. Additional assessments included the accuracy of frozen section analysis compared with final histology, rates of postoperative complications and the longer-term impact of residual diaphragmatic micrometastasis or macrometastasis on disease-free survival in patients with no gross residual disease. All patients had a diaphragmatic peritonectomy or resection. Those with any visually flat lesion, apparently devoid of three-dimensional architecture were defined as "visually dubious peritoneum." The accuracy of visual evaluation had an accuracy rate of 67.1% with respect to final histopathological report, with 100% accuracy in patients with "visually pathologic" areas but in only 81% in those with a "visually dubious" peritoneum. Frozen section analysis of suspicious areas was accurate in most cases (92.6%) but still had a false negative rate of 28.6%. Median disease-free survival was 18 and 16 months for patients with diaphragmatic micro- and macrometastases, respectively (p=0.037) with the prognostic advantage maintained only when patients debulked to R0. The authors developed an algorithm based on their results indicating diaphragmatic peritonectomy should proceed in those patients with visually pathological diaphragms and those with positive disease on frozen section, but not in those with negative, accepting the false negative rate of frozen section. The difference in disease-free survival in patients with microscopic disease is a hot topic of debate with the LION study indicating no poorer outcomes for those with microscopic disease and the awaited results of the TORPEDO study yet unknown. In the future for patients with residual disease decisions around the use of maintenance therapy is important, but additionally makes an excellent strategic point to assess for benefits in the introduction of novel and potentially more targeted therapies in the adjuvant setting. Finally, in the patients where visually suspicious disease remains, could the utilisation of more effective measures such as fluorescent agents be used for identifying tumour be a more efficient and cost-effective strategy than frozen section?

Reference: Ann Surg Oncol 2023;30(4):2319-28
Abstract

Patients with stage IA ovarian clear cell carcinoma do not require chemotherapy following surgery

Authors: Shuqing L & Zhiling Z

Summary: In order to explicate the efficacy of adjuvant chemotherapy in early resectable ovarian clear cell carcinoma (OCCC) in an absence of clinical trial data a retrospective analysis of data from the Surveillance, Epidemiology and End Results database was undertaken. Data on 1,038 women who underwent cytoreductive surgery for stage 1A OCCC ± adjuvant platinum-based chemotherapy between 2004 and 2015 were extracted and included in the study. Propensity score-matched analysis in 692 patients found no difference in five-year survival between cohorts who received/did not receive post-operative chemotherapy (54.6% vs 55.8%; p=0.760) and Cox proportional hazards models did not find chemotherapy to be an independent factor associated with survival (hazard ratio [HR], 0.934; 95% confidence interval [CI], 0.764-1.142; p=0.524). Factors identified as associating with inferior survival included older age and tumour size larger than 2 cm.

Comment: OCCC is a rarer subtype of EOC with unique genomic drivers that differs from the most common HGSOC and rarer endometrioid and ultra rare mucinous subtypes. It is more commonly associated with endometriosis and is more common in Asian populations (up to 20% of all EOC), compared to Caucasians. Platinum-based combinations remain the backbone of adjuvant chemotherapy for EOC utilising the susceptibility of homologous recombination deficient DNA repair pathways most commonly seen in non-mucinous EOC. OCCC is recognised to have increased platinum insensitivity and resistance, likely reflecting alternate genomic drivers and repair pathways. *BRCA* and other genes associated with the homologous recombination deficiency pathway are less frequent in OCCC, and even when they co-exist there are reports of increased platinum and PARP inhibitor resistance. Risks of recurrence are high for OCCC even when diagnosed at early stages and therefore, there is a high desire to provide adjuvant therapy with the aim of improving outcomes. This paper reports on the outcomes of chemotherapy compared with no chemotherapy in stage 1A OCCCs utilising retrospective data from the SEER database. The limitations of this study reflect the retrospective design with the details around treatments poor. The authors make a likely assumption that chemotherapy used would be platinum. Additionally, subgroup analysis is limited and there is no capacity for molecular analysis. Overall, they report no benefit for the use of chemotherapy in this earliest-stage cohort. Poorer outcomes were reported for older patients. While there may have been a small benefit in the patients < 50 years of age, statistical modelling would suggest this is spurious and nonsignificant. This paper adds to a number of other studies reporting a failure of benefit for platinum-based therapies in this ovarian cancer subgroup. It is well recognised that traditional chemotherapy protocols used for EOC were of no benefit to mucinous ovarian cancers, likely reflecting a different molecular landscape in these tumours. The importance of understanding drivers and susceptibilities in tumours whereby tailoring therapies is increasingly recognised and adopted in many tumour types. In recent years, immunotherapy has made a significant impact to many tumours but has had very limited success in EOC. Intriguingly however, there is a suggestion of a potential increased sensitivity to immune checkpoint inhibitors in the OCCC tumours, particularly when coupled with other agents such as VEGF inhibitors, with a number of trials now assessing for potential benefit in the recurrent and platinum-resistant setting. How this will impact adjuvant recommendations remains to be seen.

Reference: Cancer Med 2023;12(6):6668-74
Abstract

Patient perspectives on risk-reducing salpingectomy with delayed oophorectomy for ovarian cancer risk-reduction

Authors: Perez L et al.

Summary: A systematic review of the literature aimed to shed light on the factors prioritised by patients at increased risk for ovarian cancer when considering risk-reducing salpingectomy with delayed oophorectomy (RRSDO) or salpingo-oophorectomy in light of the evidence suggesting that *BRCA1/2* mutated cancers originate in the fallopian tube prior to ovary involvement and the substantial deleterious health- and quality-of-life impacts of salpingo-oophorectomy. A search of MEDLINE, EMBASE and Cochrane Library online databases identified six articles published after 2014 that reported the factors that patients with a genetic predisposition for ovarian cancer considered when deciding between surgeries and the uptake of each option. The studies included predominantly White women with a median age range of 35 to 45 years from the UK, USA and the Netherlands. Overall, the acceptance rate for RRSDO ranged from one-third to just over 70%. Avoidance of surgical menopause, fertility preservation, concerns about sexual dysfunction, family history of breast cancer and avoidance of hormone replacement therapy were the main considerations that swayed patient preferences towards RRSDO while concerns about oncologic safety, surgical timing and surgical complications were the biggest deterrents for this approach.

Comment: With no effective means of screening or early detection for tubo-ovarian cancer, carriers of germline pathogenic variants in genes associated with an increased risk for the same have limited options for management of cancer risk. Risk-reducing salpingo-oophorectomy is recommended for carriers as young as 35 years for *BRCA1* carriers and in general prior to the onset of natural menopause for most other genes. The impacts for women are therefore potentially considerable. This systematic review of patient preferences provides insights into many factors and may provide the clinician with a guide to discussions around risk-reducing salpingo-oophorectomy. Increasingly, women are raising the concept of RRSDO to minimise impacts associated with the surgery, despite the lack of supportive data for the same as several trials addressing this important question continue to recruit and mature. The reported studies indicate strong preferences for this strategy, with the majority of premenopausal women indicating a preference for participating in a study offering the same or indicating preference or intent to undergo RRSDO outside a trial. Factors influencing these preferences include delaying menopause, fertility preservation, concerns about sexual dysfunction, personal and family history of breast cancer and avoiding hormone replacement therapy. Factors influencing hesitancy around RRSDO include oncologic safety, surgical timing and potential complications. For participants who had already undergone risk-reducing salpingo-oophorectomy, there were strong preferences for RRSDO if this had been an option. Concerns and ambivalence around the use of hormone replacement therapy is prevalent in all studies and one of the strong drivers for preference for RRSDO. Family history of ovarian cancer and personal history of breast cancer were both associated with preference for risk-reducing salpingo-oophorectomy over RRSDO. With no studies open in Australia offering RRSDO this review offers clinicians insights into the factors influencing preferences in premenopausal women together with reflections from those who have already undergone risk-reducing salpingo-oophorectomy. Importantly, most of the participants across all studies reflect a well-educated and Caucasian ethnicity. With the increase in germline testing for hereditary breast and ovarian cancer syndrome women from a non-Caucasian background and those of lower socio-economic status and education will face decision making. They may have a limited capacity for a two-step process for risk management, and factors influencing preferences that have not been reflected in these studies.

Reference: Gynecol Oncol 2023;173:106-13
Abstract

Impact of surgery and chemotherapy in ovarian sex cord-stromal tumours from the multicentric Salomé study including 469 patients. A TMRG and GINECO group study

Authors: Hanvic B et al.

Summary: Ovarian sex cord-stromal tumours are not overly chemosensitive and completeness of surgery is critical for disease control, according to results from a retrospective study in a French network dedicated to rare gynaecological cancers diagnosis and management. The study included data from 469 women with a malignant ovarian sex cord-stromal tumour, including mostly adult Granulosa cell tumours, who underwent upfront surgery with/without adjuvant chemotherapy at a Tumeurs Malignes Rares Gynécologiques (TMRG) network centre in a just over four-year period up to July 2015. The incidence of first recurrence, two recurrences and three recurrences with a median follow-up of 6.4 years were 33%, 17% and 10%, respectively. Fifteen percent of patients received front-line post-operative chemotherapy, and 58.5% of patients were administered adjuvant chemotherapy at initial relapse. No significant PFS benefit to adjuvant chemotherapy was found in either the front-line for early-stage disease or relapsed settings. Younger age and earlier stage disease associated with favourable PFS in the front-line treatment setting and complete surgical resection correlated with extended PFS in any line of therapy.

Comment: For the clinician faced with managing extremely rare cancers, decision making often requires tertiary or quaternary consultation to ensure consensus opinion and adherence to guidelines. The establishment of the rare malignant gynaecological tumour network in France allows clinicians to consent patients to provide deidentified cancer and treatment-related parameters in return for tumour board access. In turn, the data is now able to be utilised for review of these rare tumours in a meaningful way to provide greater understanding of prognostic outcomes and therefore, guiding treatment needs. This analysis assesses the outcomes of women with all subtypes of sex cord-stromal tumours. With a cut-off for enrolment in 2015 for this study, a median of 77 months of follow-up for PFS, overall survival, initial adjuvant treatments and at relapse are reviewed for 469 adult patients with early-stage through to advanced-stage at diagnosis. The importance of complete surgical resection is highlighted for prognostic improvements in both PFS and overall survival. Chemotherapy had no benefit for those with early-stage disease. While the BEP regimen (bleomycin/etoposide/cisplatin) continues to be utilised in patients younger than 50 years of age, there was no difference in PFS with less toxic regimes. In addition, it raises the importance of the recognition of rare genetic risk associated with Leydig Sertoli Cell tumours. While this is a nonrandomised study, there could be bias in the indication for chemotherapy, which would depend on the treating physician and the patient's overall health. Randomised trials for these rare tumours are scarce, and well-conducted retrospective studies often provide support for our clinical practices.

Reference: Gynecol Oncol 2023;174:190-99
Abstract

Ovarian Cancer Research Review™

Independent commentary by Associate Professor Yoland Antill

Yoland is a Medical Oncologist and Cancer Genetics Specialist based in Melbourne, working in both the public and private sectors. She is an active clinical trialist and researcher, in particular in the field of gynaecologic cancers. She is the current deputy chair of the Australian and New Zealand Gynaecology Oncology Group's Research Advisory Board. She has an honorary academic appointment with Monash University.

The effect of older age on treatment outcomes in women with advanced ovarian cancer receiving chemotherapy

Authors: Sia T et al.

Summary: An NRG-Oncology/Gynaecologic Oncology Group (GOG-0182-ICON5) ancillary study reports the impact of age on outcomes in patients with advanced ovarian cancer treated with peri-operative chemotherapy. The study cohort included 3,686 women with stage 3/4 EOC who underwent upfront or interval cytoreductive surgery plus perioperative chemotherapy with one of five combination regimens (paclitaxel and carboplatin ± gemcitabine, doxorubicin HCl liposome, or topotecan; or gemcitabine plus carboplatin). The patient population was dichotomised into older and younger age cohorts with a threshold of 70 years. Analysis found that the 16.8% of older women aged at least 70 years had inferior clinical outcomes than younger women with a significantly elevated risk of mortality – both cancer-specific and noncancer-related – and disease progression. The only toxicity found to differentially impact age cohorts was grade 2 peripheral neuropathy that was almost twice as prevalent in the older cohort treated with carboplatin/paclitaxel versus the younger cohort.

Comment: With our aging population comes an increased number of patients with a cancer diagnosis. The median age of ovarian cancer is 62 years currently but increasingly, women over 70 years are referred for treatment in the setting of advanced ovarian cancer. Increased frailty and number of comorbid conditions are likely factors impacting treatment decisions. From participants from the GOG0182-ICON5 trial, outcomes are presented to assess for differences in overall survival according to age group (< 70 and > 70 years) from 3,686 patients with 620 in the older age group (89%, 70–79 years; 11%, 80–89 years). This is one of the largest chemotherapy studies in advanced ovarian cancer, with the overall trial results showing no benefit for the investigational arms over carboplatin and paclitaxel, but is ideal to look at other questions relating to chemotherapy use. Secondary endpoints included the effect of age on baseline characteristics, treatment compliance, toxicities, PFS, time interval from surgery to initiation of chemotherapy, and rates of optimal cytoreduction. For all arms, median overall survival was 37.2 months in older patients compared to 45.0 months in younger patients (HR, 1.21; 95% CI, 1.09–1.34; $p<0.001$). Older patients had increased all-cause mortality together with increased risks of dying of both cancer and non-cancer related causes compared with younger women. In general patients > 70 years had poorer performance status and poorer tumour characteristics. Among other differences, grade 3-4 toxicities were also greater, the proportion of women progressing to interval debulking surgery lower, and optimal cytoreduction surgery less in the older age group. An assessment of functional capacity and the potential interaction of comorbid conditions is essential in all patients but in particular those older, and potentially more vulnerable, patients. These assessments and planning apply not only to systemic chemotherapy but also around the surgical management of these patients with increased perioperative complications and increased length of stay also seen more commonly in the older age group. The temptation to use more simple regimens such as single carboplatin has been assessed in the EWOC-1 trial with the carboplatin arm having significantly worse outcomes than the taxane combination arms. Several frailty scores have been developed and can be used to gauge the likely risk of overwhelming toxicity associated with chemotherapy use and should be considered given the higher risks associated with both disease and treatment related impacts. Importantly, the participants from this trial were still of sufficient wellbeing to consider trial participation and therefore may under reflect the true impacts of both disease and treatments in the clinical setting.

Reference: Gynecol Oncol 2023;173:130-37
Abstract