Ovarian Cancer Research Review™

Making Education Easy

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Abbreviations used in this review:

AC = cyclophosphamide, doxorubicin;
BEP = bleomycin, etoposide and cisplatin;
BOT = borderline ovarian tumours;
FIGO = The International Federation of Gynecologists and Obstetricians;
OS = overall survival; **PAC** = cisplatin, doxorubicin, cyclophosphamide;
PARP = poly (ADP-ribose) polymerase; **PFS** = progression-free;
TCGA = The Cancer Genome Atlas;
VEGF = vascular endothelial growth factor

Welcome to the third issue of Ovarian Cancer Research Review.

We lead this issue with a large study of patients with malignant germ cell tumours identified from the SEER Database that provides very encouraging news regarding the outcome for these patients in the era of modern chemotherapy. A retrospective review of patients with borderline ovarian tumours found that patients treated conservatively are at significant risk of recurrence. A second German study presented in this review confirms these results.

We also review a number of articles with a focus on targeted therapies. One study assessed the addition of the anti-angiogenesis agent trebananib to single-agent weekly paclitaxel in patients with recurrent epithelial ovarian cancer. The authors conclude there was a clinically meaningful prolongation in progression-free survival. This was a very poor prognostic group, and a genuinely meaningful survival benefit may be found if this drug were to be tested in a better prognostic group. A pilot study investigated the biologic processes affecting candidate pathways associated with chemoresponse with the aim of creating a robust gene signature for follow-up studies. Two specific molecular clusters were identified and validated using five independent ovarian cancer gene-expression experiments. These studies demonstrate the progress that has been made in molecular research and indicate how molecular markers will increasingly guide clinical decision making in the future.

We hope you find the selection for this month's edition useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards,

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Prognostic factors in malignant ovarian germ cell tumours (The Surveillance, Epidemiology and End Results experience 1978-2010)

Authors: Solheim O et al

Summary: This is a large study of 2541 patients with malignant germ cell tumours, identified from the SEER Database from 1978 to 2010. It provides very encouraging news regarding the outcome for these patients in the era of modern chemotherapy. The 5-year cancer specific survival for patients with dysgerminomas was 97%, and for non-dysgerminomas it was 92%. Not surprisingly, survival was worse in the presence of metastatic disease. It was also worse in women > 40 years of age, but these tumours are rarely seen in that age group. A sobering finding was that second cancers were diagnosed in 10% of 10 year survivors who underwent radiotherapy, compared to 2% of those who underwent non-radiotherapy treatment. The latter would be mainly surgery and chemotherapy, but often, particularly for dysgerminomas, surgery alone.

Comment: Prior to the 1970s, radiotherapy was commonly used to treat these tumours, because they were very radio sensitive. The main immediate disadvantage of radiotherapy was loss of fertility, so extrapolating from the results of treatment for the more common testicular germ cell tumours, chemotherapy was introduced as the standard of care in the 1970s. Various chemo therapeutic regimens have been used, but the most common regimen used today is bleomycin, etoposide and cisplatin (BEP). Etoposide has been associated with the development of treatment-related leukemia, but the incidence is dose related, and the risk is very low when the cumulative dose is kept below 2000mg/m^2. As these tumours are very chemo sensitive, very few patients require more than 3 or 4 cycles of treatment, which keeps the total dose of etoposide within this range.

Reference: Eur J Cancer 2014 Jul;50(11):1942-50
http://www.ejcancer.com/article/S0959-8049(14)00573-5/abstract

Anti-angiopoietun therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo controlled phase 3 trial

Authors: Monk BJ et al

Summary: This was a randomised, double-blinded phase III trial of weekly paclitaxel (80mg/m²) plus either weekly masked intravenous placebo or trebananib (15mg/kg). Eligible patients had been treated with 3 or fewer previous regimens, and had a platinum free interval of less than 12 months. A total of 919 patients from 32 countries were enrolled from November 2010 to November 2012. There were 461 patients randomised to the trebananib arm and 458 to the placebo group. Median progression-free survival was 7.2 months in the trebananib arm and 5.4 months in the placebo arm (p<0.0001) Trebananib was associated with more adverse-event related treatment discontinuation than was placebo (17% vs 6% respectively), and a higher incidence of oedema (64% vs 28% respectively). There was a difference of 2% or less in class-specific adverse events associated with anti-vascular endothelial growth factor (VEGF) therapy (hypertension, proteinuria, wound-healing complications, thrombotic events, gastrointestinal perforations).

Comment: We are seeing more and more studies of various targeted therapies in gynaecological cancer in general, and ovarian cancer in particular. Trenananib is a non-VEGF anti angiogenesis agent that works by inhibiting the binding of angiopoietins 1 and 2 to the Tie2 receptor. The authors conclude that there was a clinically meaningful prolongation in progression-free survival. Quality of life and symptom improvement should be the major concerns in these end-stage women, so it is difficult to accept that 1.8 months is clinically meaningful when 17% of patients had their treatment stopped because of adverse events. This was a very poor prognostic group, and a genuinely meaningful survival benefit may be found if this drug were to be tested in a better prognostic group.

Reference: Lancet Oncol 2014 Jul;15(8):799-808
http://tinyurl.com/kwrvac6

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial

Authors: Ledermann J et al

Summary: This paper presents data from a retrospective, preplanned interim analysis by BRCA mutation status from a randomised, double-blind phase 2 study that assessed maintenance treatment with the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib, 400mg twice daily, versus placebo in patients with platinum sensitive recurrent serous ovarian cancer. The patients must have received two or more platinum-based regimens and had a partial or complete response to their most recent platinum-based regimen. Between August 2008 and February 2010, 136 patients were assigned to olaparib and 129 to placebo. Patients with a BRCA mutation had a significantly longer median progression-free survival than the placebo group (11.2 vs 4.3 months; p<0.0001), while patients with wild-type BRCA also had a significant but smaller prolongation of PFS (7.4 vs 5.5 months; p=0.0075). At this second interim analysis, overall survival was not significantly different for either group. The main grade 3 adverse event was fatigue (7% in the olaparib group vs 3% in the placebo group).

Comment: PARP inhibitors are a new class of targeted therapy predominantly for patients with germ line BRCA mutations. They may also benefit patients with somatic BRCA mutations as well as a subset who have methylation of the gene or impairment of homologous DNA repair, so-called BRCA-ness. This explains why patients with wild-type BRCA also derived a significant, though smaller benefit in terms of progression-free survival (1.9 vs 6.9 months). BRCA mutations are found in about 20% of patients with high-grade serous ovarian cancer. The BRCA mutation renders these tumours more platinum sensitive, and the fact that there is now a specific type of targeted therapy that can benefit these patients makes it important to test all patients with high-grade serous cancers for BRCA mutations who are 70 years of age or younger, regardless of the family history.

Reference: Lancet Oncol 2014 Jul;15(8):852-61
http://tinyurl.com/kce6zy3

Influence of histological subtype on the risk of an invasive recurrence in a large series of stage I borderline ovarian tumor including 191 conservative treatments

Authors: Uzan C et al

Summary: This was a retrospective review of 254 patients with stage I borderline ovarian tumours seen between 2000 and 2010. There were 140 mucinous tumours (55.1%) and 114 serous tumours (44.9%). Conservative management had been used for 191 patients (75.2%). After a median follow-up of 45 months, recurrences had developed in 43 patients (17.1%; 31 borderline and 12 invasive). Risk of recurrence was found to be increased in patients treated conservatively, particularly by cystectomy, in patients with stage 1B disease and in those incompletely staged. A micropapillary subtype and mucinous histology were risk factors for progression to invasive cancer.

Comment: This is a large study which confirms earlier studies that patients treated conservatively for borderline ovarian tumours are at significant risk of recurrence, particularly in the contralateral ovary, or in the same ovary if treated by cystectomy. There is about a 20% likelihood that the recurrence will be invasive. If there is a normal contra lateral ovary present, patients found to have a borderline ovarian tumour on permanent histological section should be advised to have a complete laparoscopic salpingo-oophorectomy on the affected side. These tumours occur predominantly in premenopausal women, so fertility preservation is often requested. Two questions arise. Firstly, how should the contralateral ovary be monitored? Our practice is to perform a 6-monthly transvaginal ultrasound, but we have occasionally seen patients develop an interval invasive recurrence. When childbearing has been completed, we recommend laparoscopic removal of the contralateral tube and ovary. Secondly, what constitutes adequate staging? Certainly, these patients should have peritoneal washings for cytology, a careful palpation of all peritoneal surfaces and retro peritoneal lymph nodes, biopsy of anything that is suspicious, and infracolic omentectomy. Systematic pelvic and para aortic lymphadenectomy, as would be required to stage a high grade serous ovarian cancer, is not justified.

Reference: Ann Oncol 2014 Jul;25(7):1312-9
http://annonc.oxfordjournals.org/content/25/7/1312.long

Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study

Authors: Trillsch F et al

Summary: This retrospective study investigated 950 patients with borderline ovarian tumours treated at 24 German centres between 1998 and 2008. Their median age was 49 years (14.1 to 91.5). There were 280 patients (29.5%) under 40 years, and fertility preserving surgery was performed in 149 (53.2%) of these. Compared to the older patients, recurrence was significantly more frequent in patients <40 years (19.0 vs 10.1% 5-year recurrence rate; p<0.001), and the recurrences were usually in ovarian tissue i.e, normal contralateral ovary or affected ovary following cystectomy. Disease-specific overall survival did not differ between the two groups. In the case of recurrent disease, malignant transformation was less frequent in younger women (12.0% vs 66.7%; p<0.001), and most invasive recurrences presented as peritoneal carcinomatosis. Multivariate analysis for patients under 40 years identified advanced FIGO stage and a fertility-sparing approach as independent prognostic factors for recurrence.

Comment: This study compliments the previous study of borderline ovarian tumours, and confirms the fact that fertility preservation is a reasonable option for these young women. Careful ultrasonic monitoring is necessary to check the status of any residual ovarian tissue, because this is where most of the recurrences will occur. Although younger women were more likely to develop recurrent disease, presumably because of fertility preserving surgery, the good news from the study is that recurrences in the younger women were much more likely to be borderline than in the older group. Nevertheless, 12 percent of these younger women still developed an invasive recurrence, so informed consent is very important when counselling these patients about fertility-sparing management. Mucinous borderline tumours in particular can occasionally behave aggressively after fertility preserving surgery, and removal of the remaining tube and ovary is usually recommended when childbearing has been completed for any borderline tumour. Oral contraceptives should be offered if conception is not an immediate option.

Reference: Ann Oncol 2014 Jul;25(7):1320-7
http://annonc.oxfordjournals.org/content/25/7/1320.abstract

Ovarian Cancer Research Review™

Independent commentary by Professor Neville F Hacker, AM is Director of the Gynaecological Cancer Centre at the Royal Hospital for Women in Sydney, and Professor of Gynaecological Oncology, Conjoint, at the University of NSW.

He is a former President of the International Gynaecological Cancer Society, and a current Member of the FIGO Cancer Committee. He has received many honours, including the inaugural Jeanne Ferris Award from Cancer Australia, and the inaugural Robert Sutherland AO "Making a difference" Award from the NSW Cancer Institute, both in 2013. He has written over 170 peer reviewed a rticles, over 30 book chapters, and edited two textbooks, both in their 5th editions.

Analysis of chemotherapeutic response in ovarian cancers using publicly available high-throughput data

Authors: Bosquet JG et al

Summary: This pilot study used the The Cancer Genome Atlas (TCGA) data set for serous ovarian cancer to look for molecular markers of chemo sensitivity. They were able to identify different copy number alterations, mutations, DNA methylation and miRNA expression between patients who responded to standard treatment and those who did not, or who recurred prematurely. They correlated these significant parameters with gene expression to create a signature of 422 genes associated with what they called chemo response. Two specific molecular clusters were identified, and they were able to validate their findings using five independent ovarian cancer gene-expression experiments.

Comment: This study demonstrates the type of progress that has been made in molecular research since the completion of the Human Genome Project in 2003, and indicates how molecular markers will guide clinical decision making increasingly in the future. Instead of giving a generic chemo therapeutic regimen and monitoring the patient for response, it should be possible to predict responsiveness on the basis of the molecular signature of the tumour.

It is difficult for the practicing clinician to keep abreast of the advances in molecular biology. TCGA, created by the National Cancer Institute in the United States, with significant contributions from our own Australian Ovarian Cancer database, has been a tremendous resource for molecular research, and rapid advances in technology for sequencing genes and analysing the data (bioinformatics) have seen cancer research progressing at an unprecedented pace.

Reference: Cancer Res 2014 Jul 15;74(14):3902-12
http://cancerres.aacrjournals.org/content/74/14/3902.abstract

Prognostic role of bowel involvement in optimally cytoreduced advanced ovarian cancer: a retrospective study

Authors: Giorda G et al

Summary: This study looks at the importance of bowel involvement in patients undergoing aggressive cytoreductive surgery for advanced ovarian cancer. Between 1997 and 2004, 301 patients underwent surgery. Optimal debulking (defined as residual disease < 0.5 cm) was achieved in 244 patients (81%), and no residual disease in 209 (69.4%). Bowel resection was performed in 116 patients (38.5%), mainly rectosigmoid resection alone (69.8%). Pelvic peritonectomy was performed in 202 patients (67.1%), and upper abdominal procedures in 82 (27.2%). As expected, progression-free (PFS) and overall survival (OS) were better in patients with residual disease <0.5 cm, but for this group, bowel involvement was associated with a decreased PFS and OS in grade 1-2 patients, whereas in grade 3 patients, only OS was adversely affected. These same findings were true for patients with no residual disease.

Comment: These findings are not entirely surprising. It is well known that the residual disease status at the start of chemotherapy is the single most important prognostic factor, and patients who have no residual disease after primary cytoreductive surgery have the best prognosis of all. The extent of metastatic disease prior to cytoreduction is also an important prognostic factor, and patients having disease that necessitates bowel resection in order to get most or all of the disease resected usually have more extensive metastatic disease to start with, and will have a worse prognosis even if optimally debulked. This is a biological fact, and no intervention such as chemotherapy can change it. If by resecting the bowel, the patient will be left with minimal or no residual disease, the prognosis will be the best possible in the circumstances. If resecting the bowel will not optimally debulk the disease, the only indication to do the bowel resection would be to relieve a bowel obstruction, because bowel resection in such circumstances will only increase morbidity, without improving survival.

Reference: J Ovarian Res 2014; 7: 72
http://www.ovarianresearch.com/content/7/1/72

A phase II non- randomised study of oxaliplatin and doxorubicin combination therapy in the treatment of recurrent ovarian cancer

Authors: Pokataev I et al

Summary: This was a small study of doxorubicin 50 mg/m^2 IV and oxaliplatin 130 mg/m^2 IV on day 1 every three weeks in patients with recurrent platinum sensitive and platinum resistant ovarian cancer. The platinum-free interval was set to be less than 24 months. There were 33 patients entered, including 21 with platinum-resistant and 12 with platinum-sensitive disease. Response rate was 54.9% in the platinum sensitive patients and 33.4% in the platinum resistant group (p= 0.59). Progression-free survival in platinum resistant patients was 6.7 months, compared to 10.8 months in the platinum sensitive group (p=0.14). The authors concluded that this was an active regimen in patients with platinum-sensitive and platinum-resistant recurrent ovarian cancer.

Comment: Patients with platinum-sensitive disease usually receive further carboplatin, combined with paclitaxel/liposomal doxorubicin/gemcitabine on relapse, but patients with platinum-resistant disease do not have a lot of good options. A response rate of 33.4% and a PFS of 6.7 months for this poor prognostic group warrants further investigation in a larger study. Oxaliplatin is usually used to treat colorectal cancer, typically combined with folinic acid and 5-fluorouracil in a combination called FOLFOX. Neurotoxicity can be a dose limiting toxicity. Doxorubicin, trade name Adriamycin, was used in the early trials of combination chemotherapy for epithelial ovarian cancer, initially in combination with cyclophosphamide (AC), and then with the addition of cisplatin in the early 1980s (PAC). Both were active combinations, and the latter was the standard of care until replaced by carboplatin and taxol in the 1990s. Doxorubicin causes hair loss, myelosupression, nausea, vomiting and diarrhoea, but it can also sometimes cause cardiotoxicity and radiation recall.

Reference: Clinical Ovarian & Other Gynecologic Cancer 2014 Jul 7
http://tinyurl.com/p6klmmm

Improving referral for genetic risk assessment in ovarian cancer using an electronic medical record system

Authors: Petzel SV et al

Summary: These authors introduced a form summarising referral for genetic counselling for women with ovarian cancer into the electronic medical record, thereby allowing gynaecological oncologists to electronically submit a request for genetic services. They then compared patient and provider characteristics for women newly diagnosed with ovarian, fallopian tube and primary peritoneal cancer referred one year before and one year after introducing the form. There were 86 new referrals with ovarian cancer seen before, and 83 after the introduction of the electronic referral form. Post-intervention referral rates increased from 17% to 30% (p=0.053). Sixty percent of referred patients participated in counseling.

Comment: Hereditary Cancer physicians are a relatively new sub specialty of medicine, and Hereditary Cancer Clinics have been established in all major cancer centres. Of the gynaecological cancers, ovarian and endometrial are most likely to require referral for counselling, and the indications for referral keep expanding. It is difficult for a practicing gynaecological oncologist to keep abreast of these indications, and for this reason, we have had one of the hereditary cancer physicians attend our weekly Tumour Board meeting for the past 3 years. Any family history of cancer is noted on the patient information sheet, but we now know that about 40% of patients with high grade serous cancers who have a BRCA mutation have no family history of breast or ovarian cancer. The presence of the hereditary cancer specialist at the Tumour Board ensures that all relevant patients are identified and referred, and it also continually updates all members of the team regarding the ever changing guidelines for referral. In addition, it often allows country patients to receive their first consultation in hospital prior to discharge. Although electronic referral would no doubt be helpful, I believe the most important way to improve referral rates is to have the hereditary cancer specialist present at the weekly Tumour Board meeting.

Reference: Int J Gynecol Cancer 2014 Jul;24(6):1003-9
http://tinyurl.com/ljd83nj

Symptom burden and outcomes of patients with platinum resistant/refractory recurrent ovarian cancer: a reality check: results of stage 1 of the gynecologic cancer intergroup symptom benefit study

Authors: Friedlander ML et al

Summary: The authors identified 126 patients with "terminal" ovarian cancer, who were receiving palliative chemotherapy. All patients completed 5 validated health-related questionnaires before starting chemotherapy, and before each treatment. They also reported their expected and perceived benefits from treatment. Physicians also documented the reasons for treatment, adverse effects, and estimated the number of cycles of treatment that patients would receive. All patients were symptomatic, but had high expectations of benefit from treatment. Only 41% of patients received the predicted number of cycles, and although RECIST response rates were only 8.5%, almost 50% of patients reported symptom improvement. There was discordance between patient report and physician grading of toxicity.

Comment: When ovarian cancer is first diagnosed, hopes of a cure are high among patients, and virtually all are keen to commence their chemotherapy, albeit often with much apprehension. However, when several chemo therapeutic drugs have failed, decisions regarding further treatment options are much more difficult. The disease is usually disseminated around the peritoneal cavity, and bowel symptoms, pain and ascites are all common problems. Palliative care physicians can offer advice regarding symptom control, but most patients remain keen to pursue further chemo therapeutic options, in spite of counselling that the likelihood of benefit in terms of prolongation of life is negligible. It is important for patients to retain some hope, and further treatment also allows them to maintain a viable connection with the team that has been caring for them for the past several years. It is encouraging that about half of these patients did receive some symptomatic benefit, but many others progressed rapidly and died. The aim of this group is to develop prognostic models to better select patients for treatment, and this would clearly be highly desirable.

Reference: Int J Gynecol Cancer 2014 Jun;24(5):857-64
http://tinyurl.com/oe24nep

