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The International Symposium on Advanced Ovarian Cancer: Optimal Therapy. Update was founded by Dr. Andrés Poveda and Prof. Jan B. Vermorken and each edition has been directed by them.

On March, 6th its tenth edition is being held. This symposium is organized every other year by GEICO (Grupo Español de Investigación de Cáncer de Ovario, Spanish Ovarian Cancer Group), and, since 2009, together with ESMO (European Society for Medical Oncology).

GEICO (Grupo Español de Investigación de Cáncer de Ovario, Spanish Ovarian Cancer Group), was founded in June, 1999 and from its beginning has developed its own studies as well as collaborated with international groups involved in the Research on ovarian cancer such as EORTC, NSGO, AGO, GOG, GINECO, NCIC and other GCIG groups. GEICO members are medical oncologists, gynecologist and molecular biologists especially interested in the study and research of gynecological tumors. They belong to different hospitals all over Spain. GEICO is part of the GCIG (Gynecologic Cancer InterGroup) and ENGOT (European Network for Gynecological Oncological Trial).

The meeting is held under the auspices of the Spanish Society of Medical Oncology (SEOM), the Gynecologic Cancer Intergroup (GCIG), and the European Society for Medical Oncology (ESMO), Educational Committee for its Medical Oncology Recertification Approval (ESMO/MORA) Program. It is also accredited by the European Accreditation Council for Continuing Medical Education (EACCME).

One hundred and fifty people attended the symposium’s first edition, held in 1996. Since then, the interest in this meeting has increased. Last edition (2011), more than five hundred people coming not only from Spain but also from Europe, North and Latin America, Asia and Australia were present in the symposium. This is a great challenge for us.

Some important international cooperative groups, from Europe, America and Australia collaborate with this symposium such as GOG, NCIC, AGO, EORTC, ANZILOG, GINECO, GEICO, JGOG, KOGG, MRC, MITO, MANGO, GOTIC, etc.


Our meeting has the category of a classic educational activity where many people come to teach, to learn, and also to discuss the value of how standard as well as new approaches are being incorporated into the management of ovarian cancer. In this symposium, held in one day, we cover all hot topics concerning diagnosis, biology and therapy of ovarian cancer.

WELCOME!

Andrés Poveda and Jan B. Vermorken

Directors
KEYNOTE LECTURE:
Progress in the treatment of ovarian cancer.
Lessons from homologous recombination deficiency. The first 10 years
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In April 2005, two papers appeared in the journal Nature, describing the exquisite in vitro sensitivity of BRCA mutated cells to treatment with a selective inhibitor of the enzyme poly (ADP) ribose polymerase (PARP) (1, 2). The concept of tumour selective synthetic lethality was born, and this heralded the beginning of an eventful decade, culminating in the approval by regulatory authorities both in Europe and in the USA of the first oral PARP inhibitor – olaparib – for the treatment of BRCA-mutated (BRCAm) ovarian cancer patients. Since BRCA mutations are a regular feature of high grade serous ovarian cancer (approximately 20% considering both germ-line and somatic mutations), the impact of this development in treatment is likely to be considerable. This lecture will review the events of the past 10 years describing some lessons to be learnt and pointing to key issues for the future of this exciting aspect of ovarian cancer therapy.

Within two months of that initial dual publication, the first clinical trial of the oral PARP inhibitor KU559436 (subsequently acquired by AstraZeneca and renamed olaparib) was initiated. PARP inhibitors had been subject to clinical trials in oncology previously but the initial focus had been as a combination partner for chemotherapy, (subsequently acquired by AstraZeneca and renamed olaparib) was initiated. PARP inhibitors had been subject to clinical trials in oncology previously but the initial focus had been as a combination partner for chemotherapy, aimed at circumventing drug resistance (3). The first clinical trial with olaparib as a single agent was reported in 2009 (4), with the data from the expansion cohort published in 2020 (5). These demonstrated that the drug was well-tolerated, safe and active in patients with BRCAm ovarian cancer, particularly but not exclusively in those with platinum-sensitive disease. The overall response rate was 46% (23 of 50 patients) with a median response duration of 8 months and activity was later confirmed in a separate international Phase II trial conducted at 2 dose levels (400mg and 100mg bd) (6), with the higher dose level appearing to be more active.

In a subsequent randomised Phase II study, the higher dose of 400mg bd again appeared to be more active (than 200mg bd), although this small 3-armed trial (in patients with BRCAm relapsed ovarian cancer with a zero to 12 month platinum-free interval) was powered primarily to compare olaparib (pooled data from the two dose levels) with the control arm of conventional chemotherapy – caelyx (7). For the first time it became clear in this study that in patients with BRCA m ovarian cancer, caelyx had a higher level of efficacy than in unselected cases, and this was supported by data from other studies (8). To an extent, this led to a misinterpretation of the trial results. At the higher dose of 400mg bd olaparib, the response rate and PFS were numerically superior to caelyx, but the differences were not significant for the reasons stated. Some observers considered this to demonstrate a failure of olaparib to meet expectations, despite having a response rate of 59% and median PFS of 8.5 months, in BRCAm patients with advanced recurrent disease. Indeed, 4 years then elapsed before the drug was eventually approved by FDA for this specific indication (9) without the need for further randomised trial data, but with the support of further data from a separate study in 193 patients with platinum resistant BRCA m ovarian cancer, treated with single agent olaparib and showing a 31% response rate and median PFS of 7 months (10). At present, and in contrast to the USA, olaparib is not approved in Europe for the treatment of advanced recurrent disease.

In the meantime two lines of clinical development were actively pursued. The first examined the concept that PARP inhibition in ovarian cancer might have utility extending beyond those cases associated with BRCA mutations. The key property predicting efficacy is homologous recombination deficiency (HRD), and in 2011, Levine’s work within the Cancer Genomic Atlas framework indicated that up to 50% of cases of high grade serous ovarian cancer might be candidates for PARP inhibition, based on a range of genetic defects in addition to BRCA 1/2 germ line and somatic mutations (which constitute 15%-20%) (11). The clinical relevance of the observations was assessed in a clinical trial published in 2011, which demonstrated efficacy of olaparib in a series of patients with sporadic BRCA wild-type ovarian cancer, albeit at a slightly lower level (24%) and confined mainly to patients with platinum-sensitive disease (12).

The second line of investigation, which led directly to the approval of olaparib by regulatory authorities in Europe, examined the use of the drug as a form of maintenance therapy and approval is specifically for that indication. The key randomised trial involved patients with platinum-sensitive relapsed disease (n=265) who received single agent olaparib or placebo following platinum-based treatment. The median progression-free survival increased from 4.8 months to 5.4 months (HR = 0.35) and overall treatment was well-tolerated. The trial had not selected for patients with BRCA mutations, and mutation status was initially unknown in the majority of cases (64%) (13). However, retrospective analysis (of both germ line and somatic BRCA mutation status) indicated that 136 patients (51%) were positive for BRCA 1 or 2, and the treatment benefit in this subgroup was even more marked (median PFS increasing to 11.2 months (HR = 0.17)) (14). Other notable features in
this retrospective analysis included the positive benefit in patients with BRCA wild-type disease and in those with somatic BRCA mutations and both these observations will be taken forward in subsequent trials involving olaparib as well as 2 other PARP inhibitors (niraparib and rucaparib, both of which have shown comparable levels of efficacy and tolerability to olaparib in BRCA germ line mutation positive and wild type patients)(15,16).

Looking forward, a number of key issues regarding the clinical utility of PARP inhibitors come to mind. As the use of this treatment expands, further relapse and resistance to PARP inhibitors will become increasingly recognised. Current data indicate that resistance is likely to be multi-factorial; mechanisms including the development of secondary BRCA mutation, enhanced drug efflux relating to P-glycoprotein and changes in other repair proteins such as 53BP1 may all be involved(17). The collection of tumour tissue in relapsing patients should be extremely informative in this context, with tumour heterogeneity likely to emerge as a key issue. Importantly, the clinical data suggest that cross-resistance between PARP inhibitors and platinum-based treatment is likely to be only partial(18). Indeed one of the main differences between these forms of therapy is the evidence that some patients (even with platinum-resistant disease) can enjoy a prolonged disease-remission with a PARP inhibitor. An example of a patient with platinum-resistant disease on olaparib treatment for 7½ years will be shown.

Returning to the issue of potential PARPi efficacy in BRCA – wild type cancer, other future developments are likely to include the establishment of a laboratory assay which accurately assesses HRD in ovarian cancer samples. A number of lines of investigation have pursued this, including functional and immunochemical assays, but the most promising appear to be genomic DNA-based assays which may reflect HRD and predict PARPi sensitivity irrespective of its cause(19).

Finally combination strategies involving PARP inhibitors are likely to receive increasing attention in the coming months and years. The utility of PARP inhibitors combined with cytotoxic chemotherapy is of doubtful value, because of enhanced toxicity of this combination, and because of data from a randomised trial indicating that the main benefit (of olaparib) was as maintenance treatment as a single agent rather than in combination concurrently with chemotherapy (carboplatin/paclitaxel)(20). More promising strategies include the use of PARP inhibitors together with antiangiogenic agents, or with inhibitors of the P13K/AKT pathway. Both take advantage of preclinical observations indicating that it is possible to increase PARPi sensitivity with a concurrent targeting agent(21,22), and clinical studies are already underway. The relevance of this, particularly in respect of antiangiogenic agents is particularly clear when one considers the potential treatment options for a patient with BRCA mutation positive platinum-sensitive relapsed ovarian cancer. Bevacizumab presents one such option, based on the clear evidence of benefit in the OCEANS trial(23), while olaparib presents another – as described above. The intriguing notion is that the combination of the 2 approaches would be more successful than either alone, and combinations of olaparib together with the VEGFR TKI cediranib and with bevacizumab are being taken forward with this in mind(24,25).

In summary the first 10 years of the HRD story has been extraordinarily productive and a new treatment for patients with BRCA mutation positive ovarian cancer (and hopefully others) has emerged. This is not the end of the story, and careful clinical development taking account of lessons learnt in the past 10 years is likely to lead to further major improvements in the management of this disease in the next decade.
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CRITICAL ISSUES FOR FURTHER DEVELOPMENT IN OVARIAN CANCER

Immunology

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Ovarian cancer is the most common cause of gynecological cancer-associated death amongst women with approximately 239,000 new cases to be diagnosed in the world in 2014[1]. Cytoreductive surgery and platinum based chemotherapy has remained the backbone of ovarian cancer treatment yet as the disease is discovered at an advanced stage, the prognosis is poor with a 5-year survival rate of 38%[2]. There is a vital need for alternative treatments to increase the response rate and survival. Recent scientific evidence demonstrated that ovarian cancer is an immunogenic tumor that can be recognized by the host immune system[3]. Spontaneous antitumor immune response of tumor-reactive T-cells and antibodies can be detected in peripheral blood, tumors and ascites of ovarian cancer patients with advanced disease[4-6]. Ovarian cancers also express a variety of tumor-associated antigens including HER-2/neu; p53; amino enhancer of split protein; the folate binding protein; sialylated TN (sTN), a mucin antigen; MUC-1; MUC-16/CA-125; NY-ESO-1, a testis differentiation antigen; and mesothelin. Universal antigens are also expressed by a variety of ovarian cancers including the human telomerase reverse transcriptase (hTERT), cytochrome P450 CYP1B1; and survivin. A variety of somatic mutations which are rarely shared among different tumors and exhibit an extreme degree of heterogeneity with an average of 60 private, non-synonymous mutations per tumor are also present in ovarian cancer patients[7].

Despite the expression of TAA by ovarian cancer, spontaneous antitumor immune response has only been demonstrated in a approximately 55% of patients with ovarian cancer in the form of intraepithelial tumor-infiltrating lymphocytes (TILs) [8]. Coukos and others reported that patients whose tumors had TILs experienced longer progression-free and overall survival[9,10]. On the contrary, immune evasion mechanisms in this patient population correlated with poor survival such as CD4+CD25+FoxP3+ T-regulatory (Treg) cells[10,11] and programmed death ligand 1 (PD-L1 or B7-H1), a ligand for the immunosuppressive T-cell receptor PD1[12]. The association of TILs with prolonged survival, as well as the association of immune escape mechanisms with poor survival suggest that ovarian cancer patients could respond to the same immunotherapy approaches such as interleukin-2 (IL-2), cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or PD-1 antibodies or adoptive transfer of ex vivo expanded TIL, similarly to patients with other immunogenic tumors such as melanoma[12]. These types of immunomodulatory agents are promising as standard chemotherapeutic agents and radiotherapy approaches which also have immunomodulatory properties. The mechanisms for immunomodulation in ovarian cancer include activation of professional antigen presenting cells (APCs) by engaging co-stimulatory receptors (such as CD40), activation of effector T lymphocytes by immunomodulatory monoclonal antibodies (mAB) and finally depletion of regulatory T-cells or immunosuppressive machineries. Finally cellular immunotherapeutics such as vaccines, and adoptive T-cell therapy can be used in treating patients with ovarian cancer.

Consistent with experience in other immunogenic tumors[13,14], vaccines have shown limited efficacy as monotherapy in patients with advanced recurent disease but the results are notable and provide basis for further optimization. In a retrospective analysis of 20 patients treated in the adjuvant setting after response, Sabbatini and colleagues demonstrated that patients vaccinated with monovalent or heptavalent vaccines against carbohydrate epitopes experienced significantly longer time to progression and higher progression-free survival rates relative to controls treated with alternative consolidation therapies[15]. Various phase I studies where patients with advanced ovarian cancer patients were vaccinated with different vaccines including anti-idotype ACA-125, an analogue of CA-125[16], CEA-MUC-1-TRICOM poxviral-based vaccine[17], HER2 vaccine[18] and p53 peptide antigen vaccine[19,20] have resulted in improved survival and the induction of antigen-specific T-cell and humoral immunity. Ouende used recombinant poxviruses (vaccinia and fowlpox) expressing tumor-associated antigens (NY-ESO-1) as cancer vaccines to induce tumor-specific immune response in 22 EOC patients with advanced disease[21] with a median PFS of 21 months (95% CI, 16-29 months), and median OS of 48 months. An alternative approach to vaccines directed towards specific antigens is whole tumor antigen vaccines created using tumor cells, autologous tumor lysate, or tumor-derived RNA[22,23]. We and others have also shown objective responses in recurrent advanced ovarian cancer patients when vaccinated with DC-based whole tumor vaccination[24]., or viral oncolysate vaccine generated from ovarian cancer cell lines infected with influenza-A virus[25,26] or with autologous tumor cells infected with Newcastle disease virus[27]. A major limitation of cancer vaccines stems from the inability to elicit a rapid and overwhelming T-cell response, which is required to reject established tumors. This problem is magnified in ovarian cancer by the paucity of well-characterized rejection antigens and by the significant molecular heterogeneity of the disease[28]. Even when a defined target is available, and vaccination successfully induces an immune response, the long-term benefit can be limited by tumor evolution. Recent advances in immunotherapy suggest that “personalized”, private antigens (that arise from mutations) could also be expected to induce rapid and strong secondary immune responses (reviewed by)[23,27].
SESSION 1  CRITICAL ISSUES FOR FURTHER DEVELOPMENT IN OVARIAN CANCER

We conducted a pilot clinical trial testing an autologous oxidized whole tumor cell lysate dendritic cell based vaccine injected intranodally, alone or in combination with bevacizumab with or without low-dose IV cyclophosphamide and/or oral aspirin in advanced recurrent ovarian cancer patients. Patients were treated every 2-3 weeks, till exhaustion of vaccine or progression. The majority of patients were platinum-resistant and heavily pretreated. To date, 35 patients have received over 392 vaccine doses. Immune response to autologous antigen was seen mainly in cohorts, which received low-dose cyclophosphamide. A significant increase in the frequency of T cells recognizing known tumor associated antigens observed post-vaccine. Moreover we were able to demonstrate for the first time that vaccination with whole tumor lysate-loaded DCs elicited a CD8 T cell response against mutated peptides derived from private non-synonymous somatic tumor mutations. Few patients achieved a partial response or were disease-free at end of treatment. Estimated PFS at 6 months was 70% for the cohort receiving vaccine plus bevacizumab with cyclophosph and only 31% in a historic cohort of 16 patients from our institution who received Bevacizumab and Cyclophosphamide (without vaccine). Additionally, Overall Survival at 20 months was 100% for the cohort receiving vaccine plus bevacizumab with cyclophosphamide and 61% for the historic cohort. Clinical benefit was demonstrated only in patients who exhibited an immune response against whole tumor lysate or autologous tumor.

Another approach is adoptive T cell therapy. In an early pilot T cell transfer trial where autologous tumor infiltrating lymphocytes (TILs) were administered after surgical resection and cisplatin chemotherapy, the disease-free survival and overall survival was found to be prolonged in ovarian cancer patients [23]. In another study, administration of TILs (alone or in combination with chemotherapy) was shown to induce objective cancer regressions [24]. We have also recently reported a Phase I study of a combinatorial approach encompassing DC based autologous whole tumor vaccination and anti-angiogenesis therapy, followed by the adoptive transfer of autologous vaccine-primed CD3/CD28-co-diminished lymphocytes [25]. Three patients with residual measurable disease who have been previously vaccinated with a whole tumor lysate vaccine received outpatient lymphodepletion and adoptive T cell transfer, which was well tolerated and resulted in a durable reduction of circulating regulatory T cells and in increased CD8+ lymphocyte counts. The vaccine-induced restoration of antitumor immunity was achieved in two subjects, who also demonstrated clinical benefits, including one complete response.

Adoptive T cell therapy can become more effective and powerful by genetically engineering patients' lymphocytes endowing them with more tumor specificity. Genes used to modify T cells include those encoding T cell receptors (TCRs) and chimeric antigen receptors (CARs). TCR-based engineering represents a compelling strategy for ovarian cancer therapy as TCRs that recognize HLA-A2 restricted epitopes from known ovarian cancer antigens such as NY-ESO-1, p53 and others [26]. Engineering T cells with redirected specificity to recognize antigens in an MHC-unrestricted fashion can be achieved through the use of CARs. In this case T cells are transduced with fusion genes encoding an extracellular domain that specifically binds to tumor epitopes through a single chain variable fragment (scFv) antibody, linked to intracellular signaling modules that mediate T cell activation [27]. Some of the generated CARs, which have been investigated in vitro and in vivo and are relevant to ovarian cancer are the oncosialate receptor-alpha, MUC-16, HER-2 and mesothelin [28,29]. One study of adoptive transfer of CARs in ovarian cancer, demonstrated safety but showed no clinical response because of low expression of the transgenic CAR and poor persistence of the transferred T cells [30]. Improved success of CARs in the clinic requires a panel of bioengineered T cells with different specificities, custom-made for each individual, which is technically and economically challenging.

In the past decades, we have seen a dramatic increase in the number of immunotherapy clinical trials to enhance antitumor immune response and cancer vaccine efficacy. Sufficient evidence indicates that ovarian cancers are indeed, immunogenic tumors and excellent candidates for immunotherapy. Both passive, as well as active immunotherapeutic modalities have shown potential clinical benefit in at least a subset of these patients. Future challenge for immunotherapy against ovarian cancer is to use a combinatorial approach to test rational immunomodulatory combinations that can induce efficient anti-tumor immunity that may achieve prolonged patient survival. The other major challenge for cellular immunotherapeutics is the development of manufacturing technologies that are less costly and do not require a very complex infrastructure so therapy can be accessible by the masses.
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REFERENCES


INNOVATIONS IN THE APPROACH TO BORDERLINE TUMORS AND EPITHELIAL OVARIAN CANCER

Molecular pathology of borderline tumors

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The relevance of molecular studies in ovarian serous borderline tumors (OSBTs) can be summarized in three interconnected areas, as delineated below:

PATHOGENESIS

Kras and Braf mutations have been found in both OSBT and ovarian low grade serous carcinoma (OLGSCa). In OSBT, Kras mutations have been reported to range from 17% to 39% while Braf mutations have been found to range from 23% to 46%. In OLGSCa, the incidence of Kras mutations has been reported to range from 19% to 35%, while the incidence of Braf mutations has been found to range from 0% to 33%. It seems that benign ovarian serous tumors can progress to OSBT due to a Braf mutation, but they do not tend to progress to OLGSCa. OSBT with Braf mutation is associated with cellular senescence and up-regulation of tumor suppressor genes. In contrast, OSBT without a Braf mutation may progress to low grade serous carcinoma due to Kras mutation or some other genetic alteration. ERBB2 mutations have been found in 6% of OSBTs.

PROGNOSIS

Braf mutations appear to be more common in OSBT and early stage OLGSCa, but rare in late stage OLGSCa. This mutation was also more frequently detected in OSBT that did not recur, which indicates a protective role of this mutation against progression to LGSCa. Our group has reported that Kras mutations are commonly seen in recurrent LGSCa (>70%). In addition, it has been found that the Kras mutated cells can be present in a very small number in the primary OSBT and their identification depends on the use of elaborate techniques such as full COLD (coamplification at lower denaturation temperature)-PCR and deep sequencing rather than the use of more common methods such as conventional PCR and Sanger sequencing. Nevertheless, recurrent LGSCa can originate from OSBT with or without detectable Kras mutations. Of interest, one study showed that patients with Kras G12v mutation had a shorter survival time from the time of the initial OSBT diagnosis than patients without this mutation. This association could indicate an association between Kras G12v mutation and a more aggressive phenotype of OSBT that recurred as LGSCa. The latter finding contrasts with the results of a small cohort of cases studied by our group in that the overall survival for patients with de novo advanced stage low grade serous carcinoma without Braf/Kras mutations was shorter than the overall survival for patients with tumors with Braf/Kras mutations (47.3 months vs. 77.9 months; p=0.28).

TREATMENT

There is limited data about the impact of Kras mutation on the treatment of OSBT. Cancer cell lines with Kras G12v mutation are more sensitive to AZD6244 (selumetinib) than cell lines with wild-type Kras. In addition, a study including only 8 patients with LGSCa treated with AZD6244 at MDACC found that 2 patients with tumors containing Kras G12v mutation were both responders to this therapeutic agent. Other aspects to be considered while assessing the role of these mutations include: 1) the need to determine the true concordance of Braf or Kras mutations between primary tumors and recurrent or metastatic disease and 2) the impact of tumor heterogeneity.
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SESSION - 2

INNOVATIONS IN THE APPROACH TO BORDERLINE TUMORS AND EPITHELIAL OVARIAN CANCER

Optimal approach to borderline tumors

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Since the 1970s the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) classify borderline ovarian tumors (BOT) as a stand alone group of ovarian epithelial tumors\(^1,2\). They are characterized by nuclear abnormalities, increased mitotic activity but in contrast to ovarian cancer they do not exert infiltrative destructive growth or stromal invasion\(^3\). BOT represent 10 to 20\% of all ovarian epithelial tumors\(^6\) and their epidemiology: One third of patients with BOT are younger than 40 years\(^5,6\). Therefore, preservation of the childbearing potential plays a very important role and is a central issue of counseling patients with BOT. Fortunately, BOT present more frequently as a disease limited to the ovaries compared to invasive carcinoma; du Bois et al. have recently shown in a systematic review of 6362 cases that 78.9\% of the patients with BOT are diagnosed at FIGO stage I\(^7\). Extended disease spread within the pelvis or beyond (FIGO stage II-III) is rarely seen at time of diagnosis, disease beyond the abdomen (FIGO stage IV) represents an exception\(^3\). In accordance to ovarian cancer, every surface epithelial cell type (serous, mucinous, endometrioid, clear cell, transitional cell and mixed epithelial cell) has been reported to be origin for BOT\(^8\). However, serous (S-BOT, 53.3\%) and mucinous (M-BOT, 42.5\%) borderline ovarian tumors are the most common by far\(^7\).

As a consequence of the epidemiology with many patients still in the reproductive age, there is considerable interest for conservative management preserving the childbearing ability. For this reason gynecologists require objective and reliable prognostic parameters for a thorough consultation. To establish informed consent, patients not opting for radical surgery need to be able to understand their risk for relapse. However, most of the relapses are BOT again and thus a second chance for cure exists - in contrast to invasive ovarian carcinoma.

Similar to ovarian cancer, the FIGO stage at time of diagnosis is one of the strongest prognostic factors\(^4,9,10\). While only 5\% of patients initially diagnosed in FIGO stage I are confronted with relapse of the disease, patients with extended disease are faced by recurrence in up to 25\% of cases\(^4,7,10\).

A histopathological feature possibly linked to a worse prognosis is the presence of microinvasion\(^10-12\). However, this has not been confirmed in large meta-analyses\(^12,14\) so that further investigations are warranted. For peritoneal implants, especially invasive implants, prognostic significance has been reported in several studies\(^12,12-15\). It has been postulated that the presence of invasive implants represent the most important risk factor besides the initial FIGO stage\(^12\), so that these patients have to be followed very closely. Invasive implants share many features with cancer and they may already mark the transformation to invasive carcinoma. Consequently, they are recognized as low grade ovarian cancer in the latest WHO classification of tumours of the reproductive tract\(^19\).

Comprehensive surgical treatment of BOT includes the complete removal of all macroscopic tumor lesions within the abdomen as well as a complete staging\(^20\). Similar surgical procedures for ovarian cancer are applied to BOT, however, this might cause overtreatment in some patients. According to the FIGO requirements staging includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washing with cytology, resection of peritoneal lesions, systematic peritoneal biopsies in all areas of the abdomen as well as pelvic and paraaortic lymphadenectomy\(^21,22\). The requirement of systematic lymph node dissection has been controversially discussed over the past years. Despite lymph node involvement in 21-29\% of cases, occasionally leading to an upgrade in FIGO stage\(^23,24\), recurrence and survival rates for patients with affected or not affected lymph nodes remain similar\(^25,26,27\). Different investigators concluded from these results that systematic lymphadenectomy can be omitted as part of the initial treatment for BOT\(^7,9,28,29\).

Appendectomy should be performed in M-BOT to exclude the possibility of ovarian metastasis of mucinous tumors of the appendix\(^28,30\). In consideration of significantly younger patients compared to invasive ovarian cancer, fertility preserving surgery is a very important topic and preservation of the uterus and at least one ovary has to be discussed.
with the patients and should be regarded as an acceptable standard of care although available data suggests that in general the rate of recurrence is higher after conservative management (10% to 20% vs. approximately 5% for radical surgery)\(^4,10,30,31,32,33\). However, the higher recurrence rate did not result in a higher mortality rate in the so far largest series, the German ROBOT study\(^34\).

Laparoscopy seems to be the most attractive approach to BOT surgery. The ROBOT study did not show any disadvantage for laparoscopy compared to laparotomy as initial or final surgical approach with respect to both relapse rate and overall survival\(^34\). In a retrospective French multicenter study of 358 patients from 2004, Fauvet and colleagues confirmed that cyst rupture (33.9% vs. 12.4%) and incomplete staging occurred significantly more frequent in the laparoscopy group. However, this had also no influence on the relapse rate\(^35\). The potentially higher risk for relapse and the possible need for repeated surgery in this case – but commonly without survival difference have to be discussed with the patient when balancing cosmesis and surgical burden.

To date, there is no proven benefit from any adjuvant therapy (chemotherapy or radiotherapy), even in advanced stage disease and with the presence of invasive implants\(^30,31\). In 1993 Tropé and colleagues performed a meta-analysis of 4 prospective studies conducted in Norway for BOT in FIGO stage III. They revealed that survival rates were higher in patients without adjuvant therapy (99%) than in patients who received adjuvant therapy (radio-/chemotherapy, 94%)\(^29\). In 2005 Longacre et al. published a survey of 276 patients with BOT treated at Stanford University Hospital between 1956 and 1998\(^32\). All patients had a follow up of more than 5 years. Of 113 patients with advanced S-BOT 52 received adjuvant therapy (34 chemotherapy, 8 radiation, 10 combined chemotherapy and radiation) while 61 patients did not receive any further treatment. 71% of the patients in the adjuvant group were still alive after a median follow up of 126.5 months. In contrast 87% of the patients without adjuvant therapy survived after 93 months of median follow up\(^33\). Therefore current guidelines do not recommend adjuvant treatment for patients even with advanced BOT\(^29,30\).

For patients who received fertility preserving surgery, the question will arise whether the remaining ovary and uterus should be resected once the family planning is completed. As discussed before, the risk for recurrence is significantly higher although most recurrences remain BOT. For this reason it appears acceptable to wait until recurrence develops\(^30,32\). Nevertheless, for some patients the psychological impact of waiting for relapse may be considerable, and removal of the remaining ovary might be an option because the majority of relapses occur in the remaining ovary. In any case, the low (but not nil) risk for the development of invasive ovarian cancer should be discussed against a general recommendation towards completion surgery.

Overall recurrence rates are estimated between 3% and 10\(^4,9,37,38\). A systematic review\(^7\) showed that 37% of recurrences are diagnosed during the first two years, 31% in year 2-5, and 32% of patients experience relapse later than 5 years after diagnosis, including 10% occurring after more than 10 years\(^5\). Such long intervals open the question arises whether these tumors possibly developed “de novo” instead of really being relapses\(^4,48\).

Malignant transformation describes the situation in which patients with BOT develop recurrent disease in form of invasive ovarian cancer. Usually, these malignant tumors represent as low grade carcinoma and can even occur after several years\(^4,5\). 20% of patients diagnosed with recurrence will have invasive ovarian cancer so that several investigators tried to identify the molecular changes being responsible for this transformation\(^4,49\). It has been reported that the expression profile of BOT and low grade carcinoma is pretty similar. Both frequently present with K-ras, B-raf mutations and high expression levels of c-Fos in contrast to high grade carcinoma\(^4,46\). They are slowly developing from benign lesions and characterized by a relative chemoresistance\(^4,48\).

In clinical surveys the rates of recurrence and malignant transformation are seemingly biased and underestimated due to lack of long-term follow up. This has to be considered when probability of relapse and death are discussed with the patients. Future studies will have to account for this large time frame.
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INNOVATIONS IN THE APPROACH TO BORDERLINE TUMORS AND EPITHELIAL OVARIAN CANCER

Molecular imaging in invasive ovarian carcinoma

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Ovarian cancer has the highest mortality of all gynecological cancers. Despite extensive research in the past decades, only few therapies with proven clinical benefit have been added to the therapeutic arsenal. In contrast to the situation in many other tumor types, molecular markers to target therapeutic decisions are scarce. Currently, drugs targeting the vascular endothelial growth factor (VEGF), hormonal treatment and poly ADP ribose polymerase inhibitors (PARPi) are the targeted therapies registered for the treatment of a subpopulation of patients with epithelial ovarian cancer. Besides BRCA mutations for PARPi, no predictive markers of response have been identified. It is becoming increasingly clear that characteristics in tumor cells can vary over time and across tumor lesions within patients. Molecular imaging may be of value for personalized treatment of ovarian cancer by visualizing the expression of potential drug targets and by intra-operative tumor visualization. Additionally, molecular changes after therapy initiation may serve as early predictor of response.

MOLECULAR IMAGING

Conventional imaging techniques such as computed tomography (CT) provide anatomical information. In ovarian cancer these techniques have limitations, such as limited sensitivity to detect small peritoneal lesions. Molecular imaging is defined as “the visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems”. Techniques for molecular imaging include radionuclide imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET), magnetic resonance imaging (MRI), and optical imaging.

Most knowledge in the clinic is available for SPECT and PET imaging. Relevant molecules can be labeled using radioactive nuclides for SPECT or PET. Molecular PET imaging can visualize general tumor processes, such as glucose metabolism using $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) and DNA synthesis using $^{18}$F-fluorodeoxythymidine ($^{18}$F-FLT). In addition, an increasing number of more specific targets, such as hormone- and growth factor receptors, can be evaluated using labeled ligands specific for these targets. PET imaging provides a whole body image in a non-invasive manner, allowing assessment of heterogeneity between and within lesions as well as repeat scanning to monitor treatment response. Optical imaging can be performed using fluorescent dyes, where light instead of radioactivity allows direct visualization of the labeled target tissue.

MOLECULAR IMAGING IN OVARIAN CANCER

**Fluorodeoxyglucose PET:** Various studies have investigated the use of $^{18}$F-FDG PET in the diagnosis of primary and recurrent ovarian cancer. The additional value of $^{18}$F-FDG PET in ovarian cancer patients is limited, and therefore has not been implemented in the routine work up of these patients. One study investigated $^{18}$F-FDG PET as an early response marker in the setting of neo-adjuvant chemotherapy. Patients with normalization of the maximum standardized uptake value after three courses of therapy were found to have a higher likelihood of benefiting from three additional courses in order to obtain pathological complete response or minimal residual disease and receive optimal surgery.

**Estrogen receptor imaging:** In phase 2 studies, endocrine therapy resulted in objective responses in up to 19% and clinical benefit in up to 51% of patients with ovarian cancer. Given the relatively low response rates, predictive biomarkers are required to select patients most likely to benefit. In breast cancer, the estrogen receptor (ER-) is a good predictor for response to endocrine agents. Although the ERs is expressed in ~70% of the epithelial ovarian cancer patients, it is unknown whether tumor ERs expression is predictive for treatment response in ovarian cancer.
Whole-body imaging of breast cancer ER with the PET-tracer 16α-18F-fluoro-17β-estradiol (18F-FES) has a sensitivity of 84% and specificity of 98% to detect ER positive tumor lesions. Interestingly, a high level of heterogeneity was found: approximately half of the patients had discordant ER expression across lesions. In this study, low tumor 18F-FES uptake in metastases in patients with ER positive primary breast cancer predicted hormonal therapy failure.

A study in ovarian cancer showed that 18F-FES PET uptake was in accordance with histology at debulking surgery but not at primary diagnosis of ovarian cancer, indicating that 18F-FES PET can provide reliable information about current tumor ERα status. Evaluation of the predictive value of 18F-FES uptake for success of endocrine therapy in ovarian cancer is warranted.

VEGF Imaging: Bevacizumab and pazopanib have demonstrated clinical activity in women with epithelial ovarian cancer. However, improvements in overall survival have not been demonstrated and progression-free survival benefit is limited. Biomarkers that identify patients most likely to benefit from anti-angiogenic therapies are essential to maximize patient survival while minimizing unnecessary toxicity and costs. Dynamic contrast-enhanced (DCE) MRI to detect changes in vascular function and measurement of tumor hypoxia using PET-labeled nitroimidazole compounds are of interest, but have not been validated in ovarian cancer.

Bevacizumab can be radiolabeled in order to visualize and quantify VEGF in vivo using SPECT and PET imaging. 89Zirconium labeled bevacizumab demonstrated tumor specific uptake in a xenograft model of ovarian cancer. 82Zr-bevacizumab showed lowering of VEGF-A expression following treatment with an HSP90 inhibitor or the mTOR inhibitor everolimus in ovarian cancer xenografts. In patients, 82Zr-bevacizumab uptake in primary breast tumors correlated with tumor VEGF-A levels. 82Zr-bevacizumab tumor uptake clearly decreased after treatment with bevacizumab in renal cell cancer patients and after treatment with everolimus in patients with neuroendocrine tumors. 82Zr-bevacizumab has not been tested in ovarian cancer patients, but may be of interest as an upfront or early predictive biomarker for bevacizumab efficacy.

Molecular imaging in clinical drug development: 82Zr-bevacizumab labeling and potential use as an early biomarker of effect has demonstrated proof-of-concept that labeling of antibodies can be used early in drug development to help select patient for early phase studies and as an early response marker.

Human epidermal growth factor receptor 2 (HER2) is amplified in up to 35% of the mucinous ovarian cancers. Disappointingly, early clinical trials using anti-HER2 agents have not demonstrated effectivity in this patient group, despite selection for patients with HER2 overexpression and/or amplification in the biopsy. One of the reasons could be heterogeneity in expression. 82Zr-trastuzumab PET scanning already showed substantial imaging heterogeneity between breast cancer patients considered to be HER2 positive. Although PET imaging using labeled HER2-antibodies is used in clinical trials in breast cancer, clinical data are not yet available in ovarian cancer patients. Interestingly, in mouse HER2-expressing ovarian xenograft studies, 82Zr-trastuzumab tumor uptake clearly increased after treatment with bevacizumab or an HSP90 inhibitor, that down regulates the expression of HER2.

HER 3 can play a critical role in tumor growth, proliferation and progression and monoclonal antibodies targeting HER3 are of interest in ovarian cancer. The glycoengineered humanized monoclonal HER3 targeting antibody RG-7116 was labeled with 89Zr. In xenograft models, 89Zr-RG-7116 specifically accumulated in HER3 expressing tumors providing information regarding antibody distribution, tumor targeting and tumor HER3 expression levels. In a phase 1 clinical trial 89Zr-RG-7116 helped to determine antibody biodistribution and showed tumor specific uptake in HER3 positive cancers.

The tumor antigen mesothelin is frequently overexpressed in ovarian cancer and there is little expression in normal tissue making it an attractive therapeutic target. MMOT0530A, an anti-mesothelin antibody, was labeled with 64Cu. This radiolabeled naked antibody was used in a phase 1 clinical trial in which patients received the mesothelin antibody-drug conjugate (DMOT4039A). PET scanning illustrated antibody uptake in both primary and metastatic tumor lesions.
Further results from these early trials will provide indications of utility of these PET-tracers in the further clinical development of these drugs.

OPTICAL MOLECULAR IMAGING TO IMPROVE SURGERY

Surgery is the mainstay of therapy in ovarian cancer. The degree of debulking is one of the most important prognostic factors besides tumor grade and stage. In clinical reality, complete debulking is not always feasible and methods to identify patients who will benefit from surgery as well as methods to help achieve complete debulking are of interest. Peroperative guided surgery, using fluorescent molecular tracers that can be visualized directly, is of interest both to improve surgical outcome and guide post-operative therapeutic decisions. Numerous tracers with potential for use in ovarian cancer are being developed.

The folate receptor is overexpressed in 90-95% of epithelial ovarian cancers. Excitingly, folate conjugated to fluorescein isothiocyanate (folate-FITC) could be detected in 3 out of 3 folate expressing ovarian tumors in patients, but not in 1 non-folate expressing tumor, 1 serous borderline tumor and 5 benign tumors (11). The hepatocyte growth factor receptor c-MET is a receptor tyrosine kinase that is a prognostic factor in ovarian cancer and a potential therapeutic target. In a mouse xenograft model it was possible to detect c-MET expression in submillimeter peritoneal metastases using a fluorescently tagged c-MET targeting peptide injected intravenously and detected using a hand-held probe. The tracer might be of even more relevance when acting in the near infrared (NIR) spectrum. Currently a NIR fluorescence label is available for human use. Labeled antibodies targeting VEGF (IRDye800CW-bevacizumab) and HER2 (IRDye800CW-trastuzumab) enabled intraoperative detection of submillimeter ovarian cancer lesions in a mouse xenograft model of ovarian cancer with high sensitivity and specificity. Targeted tracers are of interest both for per-operative use and for selection of patients for maintenance treatment. The first proof-of-concept studies in human using IRdye800CW-bevacizumab are ongoing in breast and colorectal cancer.

FUTURE PERSPECTIVE IN OVARIAN CANCER

The completeness of the debulking surgery is the benchmark of ovarian cancer treatment. Improving this completeness by optical molecular imaging seems to be a way forward. Whether the use of this technique will result in an improved progression free survival and overall survival has to be established. Furthermore, more than half of the patients with a negative second-look surgery after complete clinical response develop tumor recurrence likely originating from microscopic (chemoresistant) tumor deposits. Identification of molecular targets in these small lesions using optical imaging may provide opportunities for initiating targeted maintenance therapy.

In ovarian cancer, only a few molecular markers to target therapeutic decisions are known. Molecular imaging may help assess which patients will benefit from targeted therapy. Immunotherapy is of current interest in various cancer types, among which ovarian cancer. PD-1 or PDL-1 directed checkpoint inhibitor antibodies are of interest to develop as PET-tracers to determine drug distribution. Moreover, the PET tracer 18F-interleukin 2 is also of interest as it might provide insight into the behavior of activated T-lymphocytes in patients treated with immunotherapy.
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SESSION - 2

INNOVATIONS IN THE APPROACH TO BORDERLINE TUMORS AND EPITHELIAL OVARIAN CANCER

Neoadjuvant chemotherapy in ovarian cancer revisited?

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The standard management of patients with advanced ovarian cancer has been primary cytoreductive surgery followed by chemotherapy for the past decades. While the data in support of optimal cytoreduction are almost all from retrospective analyses, the consistency of the observation of improved patient outcome with more extensive surgical debulking has led to the primary aim of tumor cytoreduction to be no macroscopic visible disease after surgery.

The impact of debulking on patient survival has been shown to be equivalent whether complete debulking is attained with easily resectable disease involving the omentum and ovaries or whether it requires more extensive surgery involving the peritoneal diaphragm, rectosigmoid colon, or paraaortic lymph nodes. Furthermore, contemporary studies have demonstrated that the impact of potentially negative biologic factors such as grade and histology can be overcome by surgical debulking.

An alternative to the standard approach of attempted primary cytoreductive surgery followed by chemotherapy was recently reported by the European Organization for Research and Treatment of Cancer – Gynecologic Cancer Group (EORTC-GCG) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group. In this trial patients with stage IIIC or IV ovarian cancer were randomized to PDS followed by platinum-based chemotherapy or to neoadjuvant platinum-based chemotherapy (NACT) followed by IDS and postoperative platinum-based chemotherapy. After debulking surgery, the rate of complete tumor resection was 19.4% in patients in the PDS arm, and 51.2% in the NACT arm. The PFS and OS was the same between the two arms. Complete resection of all macroscopic disease, at PDS or after NACT, was the strongest independent variable in predicting OS. However, in spite of the reported 51.2% complete cytoreduction rate in the NACT arm, the PFS and OS reported in this trial were low and similar to the survivals reported in previous studies of suboptimally debulked patients.

More recently, a second randomised phase III trial comparing PDS followed by platinum-based chemotherapy with NACT and IDS was reported by the National Cancer Research Institute (NCRI) Gynecological Cancer Studies Group. This trial had a comparable design to the previous study but also included patients with stage IIIB. After debulking surgery, the rates of complete tumor resection were 16% in patients in the PDS arm, and 40% in the NACT arm. Again, PFS and OS were similar between the two arms and very low compared to that of other studies.

Owing to the limitations of these studies, the question whether primary debulking surgery or neoadjuvant therapy with interval debulking should be the standard approach for patients with advanced ovarian cancer cannot be answered. While some gynecologic oncologists feel that the poor survival rates invalidate the findings of the two studies, there are many gynecologic oncologists who are now changing their practice due to these findings and are offering NACT in lieu of attempted primary cytoreduction.

Although progression-free and overall survival for the NACT arm are consistent with those in other neoadjuvant studies in the literature, the survival outcomes in the PDS arm are alarmingly low. These low survival rates could have three potential causes: one, patient selection such that only the sickest and most advanced patients were enrolled; two, surgery was substandard compared with that in other trials; and/or three, surgical cytoreduction, no matter what the residual disease, has no benefit on survival. The last possibility, that the extent of surgery was of insignificant clinical importance, is unlikely to be true given that complete resection of all macroscopic disease was the strongest independent variable in predicting overall survival in both arms. What contribution the other two possibilities made to the poor survival rates in the PDS arm cannot be adequately determined.

Both previous studies have one major problem that potentially invalidates their findings. Since it has been shown by several studies and meta-analyses that complete cytoreduction with no residual disease after surgery is most beneficial for patients with advanced ovarian cancer, the comparison of the approaches upfront surgical debulking versus interval debulking needs to account for this factor. More precisely, the trial needs to compare complete tumor resection at upfront debulking with complete tumor resection at interval...
debubling. The rate of complete gross resection at primary surgery in both trials was very low (19% and 16%), in other words, the factor necessary for the evaluation was only present in less than 20% of the population.

In surgically specialized gynecologic cancer centers, the rate of complete resection in unselected patients with advanced stage ovarian cancer ranges between 50 and 70%\(^{2,30}\). When performing a trial comparing PDS followed by platinum-based chemotherapy with NACT and IDS only in centers fulfilling a minimum requirement of 50% complete resection rate, meaningful results can be expected.
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Antiangiogenic agents

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In the 1990’s platinum/taxane chemotherapy supplanted cisplatin/cyclophosphamide and became the international standard of care for the first-line treatment of advanced epithelial ovarian cancer (EOC). Despite initial chemo-sensitivity to platinum/taxane combinations, most patients with advanced EOC relapse after first-line therapy. Thus, more effective therapies are needed to improve response rates and prolong progression-free survival (PFS) thereby improving both the quality and length of life following the diagnosis of advanced EOC.

Angiogenesis plays a fundamental role in normal ovarian physiology as well as in the pathogenesis of ovarian cancer, promoting tumor growth and progression through ascites formation and metastatic spread. Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are expressed on ovarian cancer cells, and increased VEGF expression has been associated with the development of malignant ascites and tumor progression(1). Bevacizumab (Avastin®, Genentech; South San Francisco, CA, USA), a humanized anti-VEGF monoclonal antibody, is the most widely studied anti-angiogenesis agent both across tumor types and specifically in EOC being approved by the US Food and Drug administration on November 14, 2014. Preclinical data suggest that prolonged administration of bevacizumab as maintenance therapy after cisplatin-based chemotherapy prolongs survival by inhibiting or delaying disease recurrence in a murine ovarian cancer model(2).

In March of 2005, single agent bevacizumab at 15mg/kg (IV) every 3 weeks was first reported to be active in a case of recurrent high-grade serous ovarian cancer after failing eleventh line cytotoxic chemotherapy and radiation. An objective durable response lasting at least 5 months was documented(3). Since then, many case series(4) and phase II trials have confirmed these results. Gynecologic Oncology Group (GOG) protocol 170-D prospectively studied single agent bevacizumab at this dose and schedule among 62 women with recurrent ovarian cancer. Thirteen patients (21.0%) had documented responses (two complete, 11 partial; median response duration, 10 months), and 25 (40.3%) survived progression free for at least 6 months. Median PFS and overall survival (OS) were 4.7 and 17 months, respectively. Prior platinum sensitivity, age, number of prior chemotherapeutic regimens, or performance status were not predictive of clinical activity(5).

Most recently, four randomized phase III trials have been performed adding bevacizumab to either front-line chemotherapy (GOG 218 (6) or ICON7 (7)) or to chemotherapy in “platinum-resistant” (AURELIA Trial (8)) or “platinum-sensitive” (OCEANS Trial(9)) recurrent EOC. Although all four studies met their primary endpoints of prolonging PFS (Table), only two suggested an improvement in OS among unique subsets of patients. In ICON7, among patients at high risk for progression, the benefit of adding bevacizumab was greatest. The estimated median PFS was 10.5 months with standard therapy, as compared with 15.9 months with bevacizumab (hazard ratio for progression or death in the bevacizumab group, 0.68; 95% CI, 0.55 to 0.85; P<0.001). Similarly, there were 188 deaths in the group of women with FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery (109 in the standard-therapy group and 79 in the bevacizumab group) and the median overall survival was increased from 28.8 months in the standard-therapy group to 36.6 months in the bevacizumab group, (hazard ratio for death in the bevacizumab group, 0.64; 95% CI, 0.48 to 0.85; P = 0.002). In GOG 218, the median OS for FIGO stage IV subjects was increased from 32.8 months in arm 1 (placebo containing arm) to 40.6 months in arm 3 with the addition of bevacizumab plus maintenance (HR 0.72, 95% confidence interval 0.53-0.97)(10).

Unfortunately, there has been concern about toxicity especially bowel perforation(11), renal dysfunction and hypertension(12). In addition, the expense and cost effectiveness of bevacizumab has created much controversy(13). In addition, biomarkers and imaging have not consistently been predictive of response(14,15,16) and patient reported outcomes have not shown improvements in quality of life with the addition of bevacizumab(17). Importantly, both AURELIA and ICON7 were not placebo-controlled trials creating a potential bias in evaluating both PRO and PFS. OCEANS had no PROs at all.

Newer antiangiogenics as well as agents like vascular disrupting agents (VDAs) that target existing blood vessels are in development. Angiopoietin-1 (Ang1) and -2 (Ang2) interact with the Tie2 receptor, which is expressed on endothelial cells, to mediate vascular remodeling in a signaling pathway that is distinct from the VEGF axis. Ang1 promotes vessel stabilization by increasing endothelial junctions and pericyte coverage; Ang2 blocks Ang1’s blood vessel stabilizing action, increasing angiogenesis and vascularity in tumors. Trebananib (formerly known as AMG 386; Amgen Inc) is a peptide-Fc fusion protein (or peptibody) that acts by binding...
both Ang 1 and Ang2, thus preventing their interaction with the Tie2 receptor. Trebananib has shown anti-
angiogenesis activity in preclinical models of ovarian cancer, single-agent activity in relapsed ovarian cancer in
phase 1 study as well as a prolongation of PFS in randomized phase 2 and 3 trials in recurrent EOC (18). In contrast
to anti-VEGF agents, trebananib has not been associated with an increase in typical class-related anti-VEGF
toxicities. Its most significant toxicity has been reported to be edema (18). The results of Trebananib in Ovarian
Cancer-1 (TRINOVA-1), a 919 subject randomized placebo-controlled phase III trial investigating the addition of
trebananib to single-agent weekly paclitaxel in relapsed EOC, showed a PFS improvement of 52% (Cox model
HR = 0.66; 95% CI 0.56 - 0.76; P<0.001) from a median of 5.4 (95% CI 4.3 - 5.5) to 7.2 months (95% CI 5.8 - 7.4) (19).

VDAs are distinct from typical antiangiogenics and are ideal candidates to combine with antiangiogenic
agents such as bevacizumab. In contrast to anti-angiogenics agents that target VEGF and angiopoietins,
VDAs target existing tumor vascular rather than preventing neovascularisation. Tumor vessels can be
selectively targeted by VDAs because the newly formed endothelial cells associated with cancer progression
lack smooth muscle and pericyte coverage thereby relying more on intracellular tubulin to maintain their flat
tube-like shape in vessel walls. VDAs that inhibit cancer-associated endothelial cell tubulin cause the affected
endothelial cells to "round up" thereby obstructing tumor-associated blood vessel lumens. This causes vessel
collapse and obstruction. Finally, non-tumor associated blood vessels are relatively resistant to VDAs not only
because of increased amounts of endothelial cell smooth muscle but also because of increased endothelial
pericyte coverage allowing them to maintain their shape when exposed to VDAs.

Interestingly, cells on the periphery of solid tumors are also relatively insensitive to VDA induced vascular
shutdown. This resistant peripheral rim of tumor cells contributes to tumor regeneration, metastasis, and
ongoing progression after VDA exposure. Conceptually, combining VDAs with anti-angiogenesis compounds
such as bevacizumab might overcome this "regrowth" phenomenon.

Combretastatin A4 (CA4) is a VDA originally isolated from the African bush willow (Combretum caffrum).
Fosbretabulin is a water-soluble prodrug of cis-combretastatin A4 (cis-CA4) otherwise known as combretastatin
A4 mono tris phosphate (abbreviated in the literature as CA4P). Fosbretabulin is a small molecule that acts
as a potent and reversible tubulin depolymerizing agent. Preclinical models have shown that fosbretabulin
results in massive acute vascular collapse as early as two hours after administration with recovery as soon as
24 hours providing further rationale for combining with bevacizumab. In a phase 1 study of the combination of
fosbretabulin plus bevacizumab, the dose limiting toxicity appeared to be hypertension with the maximum
tolerated dose of fosbretabulin being 63 mg/m² every other week. Importantly, this study showed dynamic
contrast enhanced diffusion weighted MRI evidence of profound vascular changes associated with
fosbretabulin administration that were only sustained following bevacizumab. In a recent randomized phase II
study in recurrent ovarian cancer, the combination of bevacizumab + fosbretabulin improved PFS compared
to bevacizumab alone (HR = 0.685; 90% 2-sided CI =0.47 - 1.00). The proportion responding to bevacizumab
was 28.2% (90% CI 16.7 - 42.3%) among 39 patients with measurable disease and 35.7% (90% CI 23.5 - 49.5%)
among 42 patients treated with the combination (20). Phase 3 trials of this novel non-cytotoxic chemotherapy
combination are indicated.

Finally, preclinical studies suggest that angiogenics and PARP inhibitors are synergistic. Additionally,
they can be combined at full doses which is unusual for two clinically active agents (21). A recently reported
randomized, open label, phase 2 trial compared the activity of olaparib (oral PARP inhibitor) alone to
combined cediranib (an oral potent inhibitor of VEGF receptor tyrosine kinases) and olaparib in recurrent
platinum-sensitive high-grade serous EOC (NCT 01166486). Median PFS was 9.0 months for cediranib / olaparib (HR 2.9, 95% CI 1.5-5.6, p = 0.001). There were 2 complete responses and 21
partial responses in subjects on olaparib (56% objective response rate) and 3 complete responses and 33
partial responses in patients on cediranib / olaparib (84% ORR, p = 0.008). The overall rate of Grade 3/4 toxicity
was higher for patients on cediranib/olaparib (70%) than on olaparib (7%). Differentially occurring toxicities
included fatigue (27% cediranib / olaparib vs 7% olaparib), diarrhea (23% vs 0%), and hypertension (39% vs
0%) (22). This combination also deserves phase III study but toxicity might be problematic.

In summary, ovarian cancer is a "disease of tissues" where antiangiogenics and VDAs can have dramatic
effects. Combination, duration and biomarker studies are sorely needed.
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SESSION - 3
CLINICAL IMPACT OF TARGETED THERAPIES
PARP inhibitors
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The introduction of platinum-based drugs and paclitaxel were landmark developments in the treatment of ovarian cancer. After a decade without significant improvements in therapy there are now two new strategies that have evolved; the inhibition of angiogenesis and DNA repair pathways. The second is exemplified by inhibitors of PARP (poly ADP ribose polymerase) an important enzyme activated in response to single strand damage of DNA. Inhibition of this pathway in cells that have deficiency in homologous recombination (HRD) repair results in ineffective repair of DNA double strand breaks resulting in gross genetic instability and cell death. There are now several PARP inhibitors (PARPi) undergoing development, but most of the clinical information comes from studies with olaparib. This drug has significant activity, sometimes long-lasting, in women with BRCA mutation positive (BRCAmut) ovarian cancer.

During early development, a number of strategies were pursued. These included a comparison with chemotherapy in BRCAmut ovarian cancer and combination therapy with carboplatin and paclitaxel[6,7]. The strategy of exploring olaparib activity as a maintenance therapy arose from emerging data suggesting that HRD, the key factor making tumours susceptible to PARPi might be present in patients without a BRCAmut. The presence of HRD was thought to be more common in patients with high grade serous tumours, particularly those that were sensitive to platinum-based therapy. Thus, the ‘study 19’ trial was designed to explore the effect of maintenance olaparib in this population. It was a randomized phase II trial that included 265 patients with high grade serous cancer who had achieved a partial or complete response to platinum-based chemotherapy. The main outcome was progression free survival which was significantly increased by olaparib, 400 mg bd [HR 0.35; 0.35 (95% CI, 0.25–0.49);P<0.00001], extending the median time to progression by 3.6 months[8]. An early evaluation of overall survival (38% maturity) showed no difference, and this led to a temporary cessation in the development of olaparib. However, it appeared that there might be a survival benefit in the BRCAmut group of women but BRCA status was only known in about one third of patients. A retrospective analysis of germline and tumour BRCA status followed and data became available for 96% of the patients. Approximately 50% of patients in the trial had a BRCA mutation (136 patients) and 118 were BRCA wild-type. Re-analysis showed that the effect of olaparib in BRCAmut patients was even greater. The median PFS was extended by 6.9 months, from 4.3 to 11.2 months [HR=0.18;95% CI (0.10, 0.31); P<0.00001]. A smaller but significant benefit was still seen in BRCA wild-type patients [HR=0.54; 95% CI (0.34, 0.85); P=0.0075]. Data are still insufficiently mature to know whether survival is increased by olaparib in BRCAmut positive patients. The drug is well tolerated with fatigue, nausea and anaemia being the commonest Adverse Events (AE). There was no detriment to Quality of Life in patients taking olaparib. Drug interruption or dose reduction occurred in only a few patients so that most were able to continue olaparib until disease progression. Only 7 (5%) patients discontinued due to an AE. Indeed, amongst those with a BRCAmut 17% remained on the drug for more than 3 years after completing chemotherapy for recurrent ovarian cancer.

The time from radiological progression to the start of the next line of chemotherapy and the time to the next subsequent line of treatment were studied as exploratory endpoints in the BRCAmut patients. As the trial remained ‘blinded’ following progression, these two endpoints have potentially important clinical relevance. The clinical indication for restarting chemotherapy was prolonged in those on olaparib by a median difference of 9.4 months. Furthermore, the time to the second subsequent treatment, an approximation to PFS2, a regulatory endpoint acknowledged by the EMA, was 23.8 months for those on olaparib compared to 15.2 months on placebo. This demonstrates that benefit of the drug is maintained beyond progression.

Whilst the data from study 19 have been sufficient for licensing by the EMA, the data in study 19 was not found to be acceptable for licensing by the FDA. However, the drug has recently been given accelerated approval by the FDA for patients with BRCAmut ovarian cancer who have received 3 or more prior lines of treatment. A key single arm study and data on file demonstrated response rates to olaparib of 31% in this group of women[9]. A confirmatory trial to study 19 using 300mg bd tablets in BRCAmut positive high grade serous or endometrioid patients (SOLO-2) has been completed. Olaparib has also been studied as maintenance therapy following first-line treatment in this group of women (SOLO-1). The results of these studies will not be available for a few years.
The maintenance strategy is being explored in two other ongoing trials, one with niraparib (NOVA trial: NCT01847274) and the other with rucaparib (ARIEL 3: NCT01968213). Both drugs are active as single agents and the trials, unlike SOLO-2 include patients with BRCA wild-type. Both trials include genomic-based tests to predict HRD.

PARP inhibitors represent a new class of agents for the treatment of ovarian cancer, and they are the first drugs in this disease that are being used on the basis of a predictive marker, currently a BRCA mut, but the indications are likely to be extended into a biologically determined test for HRD. Personalised medicine for the treatment of ovarian cancer has arrived.
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SESSION - 4
DIFFERENTIATED APPROACH TO EPITHELIAL OVARIAN CANCER
Low grade serous
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BACKGROUND

Historically, all women with epithelial ovarian cancer or primary peritoneal cancer, regardless of their tumor's histologic subtype, have been treated similarly within single-institution, investigator-initiated, or cooperative group trials. However, within the past few years, based on our enhanced understanding of the heterogeneity of ovarian or peritoneal cancer related to refinement of pathologic criteria, elucidation of molecular biology, and reports of clinical behavior, separate clinical trials for specific subtypes have been developed and conducted. One of the leaders in this transformation has been the Rare Tumor Committee of the Gynecologic Oncology Group (GOG), which was established in 2005. In 2014, the GOG merged with other cooperative groups to form the new NRG Oncology cooperative group. Since 2005, several clinical trials for rare ovarian/peritoneal cancer subtypes have been activated. The story of the evolution of progress in the study of low-grade serous carcinoma (LGSC) of the ovary/peritoneum really began in the early 1990s when the binary grading system for serous carcinoma was first proposed. After over a decade of experience using this system rather than that of the International Federation of Gynecology and Obstetrics (FIGO), the findings were reported in 2004. This seemingly trivial proposal for replacement of the time-honored 3-tier grading system (Grade 1-3) with the 2-tier system (low grade and high grade) actually galvanized the medical community to seriously study the significant differences between low- and high-grade serous carcinoma in terms of molecular biology and clinical behavior.

PATHOLOGY

The binary grading system for serous carcinoma is based primarily on the assessment of nuclear atypia with the mitotic count used as a secondary criterion. In addition, serous tumor of low malignant potential and LGSC appear to coexist in 60% of cases. Subsequent reports only further strengthened the observation that the FIGO grading system is flawed and the wisdom surrounding dichotomization of the grading system for serous carcinoma. For instance, in the study of Bodurka et al., there was no difference in clinical outcome in patients with grade 2 or 3 tumors in multivariate analysis.

MOLECULAR BIOLOGY

Based on available evidence, we currently believe that LGSC may arise following an initial diagnosis of serous tumor of low malignant potential or de novo. The weight of evidence further suggests that the mitogen-activated protein kinase (MAPK) pathway plays a prominent role in the pathogenesis of both entities. Genomic profiling studies have demonstrated that LGSC segregate from high-grade serous carcinomas but are similar to serous tumors of low malignant potential. Compared with high-grade serous carcinomas, LGSC have a much lower frequency of p53 mutations or p53 expression, greater expression of estrogen receptor (ER) and progesterone receptor (PR), greater expression of PAX2, overexpression of anterior gradient homolog 3 (AGR3), and overexpression of insulin like growth factor 1 (IGF-1). Although germline BRCA mutations occur in a relatively high proportion of women with high-grade serous carcinoma, LGSC do not appear to be part of the hereditary breast-ovarian cancer syndrome. In 2003, Singer et al. reported that KRAS mutations are found in 33% of serous tumors of low malignant potential and in 35% of LGSC, and BRAF mutations in 28% and 33%, respectively. Subsequent reports of LGSC, however, seemed to confirm a 20-40% frequency of KRAS mutations but a much lower frequency of BRAF mutations—2-6%. In fact, the presence of a BRAF mutation in an advanced stage serous tumor of low malignant potential may somehow protect against the development of a subsequent LGSC. In a study of 23 patients with an original diagnosis of serous tumor of low malignant potential who subsequently recurred with LGSC, patients with KRAS G12V mutations had shorter survival times than those with either KRAS G12D, wild-type, or rare KRAS variants. And, although it appears that aberrations of the PI3K/AKT/mTOR pathway are relatively rare in LGSC, there is some evidence that dual blockade of the MAP kinase and PI3K/AKT/mTOR pathways may be associated with enhanced activity compared with MAP kinase pathway blockade alone.
CLINICAL BEHAVIOR

Surgery is a major modality of treatment in LGSC. For most patients, primary surgery, including surgical staging for patients with apparent early-stage disease and cytoreductive surgery for those with metastatic disease, is the initial treatment. Fertility-sparing surgery is an option for selected young patients. For selected women with extensive metastatic disease or significant co-morbidities, neoadjuvant chemotherapy with interval cytoreductive surgery may be recommended. Several predominant themes have emerged from studies of the clinical course of LGSC of the ovary or peritoneum: 1) Residual disease status following primary surgery is significantly associated with overall survival (OS); 2) Patients with CA 125 levels that normalize after 1-3 cycles of chemotherapy are less likely to experience disease progression as compared to those whose CA 125 levels never normalize or normalize after 4 cycles; 3) Obesity is a significant predictor of OS; 4) Patients are relatively young at diagnosis; 5) LGSC is relatively chemoresistant but associated with prolonged OS compared to high-grade serous carcinoma. In addition, hormonal therapy is a reasonable and potentially active treatment for women with metastatic LGSC.

TARGETED THERAPEUTICS:

Based on preclinical research findings, potential genes or pathways for targeting LGSC include the MAPK pathway, IGFR-1, the angiogenesis pathway, and possibly the PI3K/AKT/mTOR pathway. In a landmark GOG phase II trial (GOG 0239), Farley et al. reported a response rate of 15% to selumetinib. Another 65% of patients in the trial had SD. The median PFS was 11.0 months. Mutational analysis, however, revealed no correlation between mutations of BRAF or KRAS and objective response. Three ongoing phase II or III clinical trials have emerged from this experience. Two studies have also indicated promising activity associated with bevacizumab in LGSC. To date, there have been no clinical trials exploring the role of IGFR1 targeted therapy or PI3K/AKT/mTOR monotherapy in women with LGSC.
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DIFFERENTIATED APPROACH TO EPITHELIAL OVARIAN CANCER

Clear cell tumors

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INTRODUCTION

Clear cell carcinoma of the ovary (CCCO) is a distinct entity of epithelial ovarian cancer in terms of clinical, histopathological or genetical features. In this symposium, we will discuss the uniqueness of CCCO, current treatment strategy, and future perspectives.

CLINICAL FEATURE

The incidence of CCCO is unique. There are distinct ethnic differences in the incidence of CCCO. Recent report from the US showed incidences of CCCO were 4.8% in whites, 3.1% in blacks, and 11.1% in Asians. In Asia, incidence of CCCO in Japan has been increasing and it is now more than 25%. Similar incidence of CCCO has been observed in Taiwan and Singapore, but an incidence in Korea is similar to Western countries (Personal Communications). Therefore, CCCO is quite rare tumor in the western country but not so common in Asia.

Most CCCO patients are stage I. In the large scale randomized trial conducted by JGOG, which enrolled stages IA-IV CCCO, 66.4% of the patients were stage I.

CCCO has been known to be resistant to chemotherapy compared with serous adenocarcinoma. Sugiyama et al first reported a retrospective analysis showing the overall survival of patients with stage III CCCO was significantly worse than survival of patients with stage III serous adenocarcinoma. Winter et al reported a retrospective review of demographic, pathologic, treatment, and outcome data from 1,895 patients with stage III ovarian cancer who had undergone primary surgery followed by 6 cycles of intravenous platinum plus paclitaxel. They found patients with clear cell and mucinous histology showed significantly worse PFS (p=0.006) and OS (p<0.001).

HISTOLOGICAL FEATURES

The CCCO has been known to have glycogen-containing cells with abundant clear cytoplasm and hobnail cells. There are tubulocystic, papillary, solid, and mixture patterns.

Typically, a cytokeratin profile for CCCO is CK7 positive and CK20 negative. CCCO is usually negative for estrogen/ progesterone receptor and WT1. Recently, it has been shown that hepatocyte nuclear factor-1 beta is a good marker for CCCO.

Molecular biology and genetics studies have shown that CCCOs are usually negative for p53, BRCA1 and BRCA2 mutations, but positive for ARID1A and PIK3CA mutations.

TREATMENT STRATEGY

Treatment strategy for the CCCO is basically the same as other histological ovarian cancers.

For early stage CCCO, full staging surgery should be performed, including bilateral salpingo-oophorectomy, total hysterectomy, pelvic and paraaortic lymphadenectomy, omentectomy and peritoneal biopsy. Since CCCO is considered to be a high-risk group, adjuvant chemotherapy has been recommended even if the stage is IA. However, it has been questioned whether we have to give adjuvant chemotherapy because we now know that CCCO is chemo resistant.

For advanced disease, maximum debulking effort should be undertaken to achieve the zero residual disease, because there was no difference on the prognosis between patients with residual disease less than 1 cm and greater than 1 cm. Takano et al conducted a large retrospective study showing that complete surgery with no residual macroscopic disease was the only independent prognostic factor.
CLINICAL TRIALS

Based on these findings, we need to establish a new chemotherapy regimen.

First Line Chemotherapy

The first clinical trial conducted specifically for CCCO was JGOG3017, a randomised phase III trial of paclitaxel plus carboplatin (TC) therapy versus irinotecan plus cisplatin (CPT-P) therapy as first line chemotherapy for clear cell carcinoma of the ovary. The result of this trial was presented at the ASCO meeting in 2014. In this trial 666 patients were enrolled in 4 years from 2006. This was a GCIG study including Japan, Korea, France and UK.

The purpose of this trial is to seek the superiority of CPT-P regimen over TC regimen in CCCO. However, there were no differences in PFS or OS between two arms. Subset analysis showed that prognosis of CPT-P arm was worse than TC arm. Therefore, it has been suggested TC therapy remain standard chemotherapy for CCCO.

In the JGOG3016 trial, which showed a significant improvement of PFS and OS by giving dose-dense paclitaxel regimen over every 3-week administration, the subset analysis did not show the improvement in CCCO.

These data strongly suggested that we need to develop new regimen incorporating targeted agents. One of the targets that was of the most interest is the PI3K/AKT/mTOR signaling pathway.

GOG268 is the trial that investigates the role of temsirolimus, mTOR inhibitor, for stage III/IV CCCO. In this trial temsirolimus was combined with TC therapy after cytoreductive surgery followed by temsirolimus maintenance therapy. Primary endpoint of this study is to compare the 12 month progression free survival data of CCCO patients who were enrolled in the previous GOG studies. This is a phase II study enrolling 45 patients from Japan and 45 patients from the US. In this trial translational component was included to investigate the difference of molecular signature between Japanese and non-Japanese. Enrollment of the patients was completed and we are waiting for the results.

European group is planning a randomized phase II trial testing the role of antiangiogenic agent, Nintedanib, in recurrent CCC.

JGOG planned a phase II trial for everolimus, another mTOR inhibitor, for recurrent CCCO, but it was canceled because of financial difficulty.

SUMMARY

In conclusion, because of the uniqueness and rarity of CCCO, it will be important to conduct international collaborative trials with an incorporation of translational research to look for or confirm the right target to be attacked.
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SESSION - 4
DIFFERENTIATED APPROACH TO EPITHELIAL OVARIAN CANCER
Mucinous tumors

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Mucinous tumours of the ovary are a relatively rare subset of ovarian cancers. The historic literature suggests that the incidence of mucinous epithelial ovarian cancer is around 12% as exemplified by a recent population-based study (without pathology review) derived from the SEER database in which 11.9% of 40,571 women diagnosed with epithelial ovarian cancer between 1988 and 2007 were classified as having mucinous carcinoma. More recent series conducted with modern histopathologic techniques, improved specialisation within histopathology, and a better understanding of ovarian cancer biology suggest that the incidence of mucinous ovarian carcinoma is much less common than previously thought. Two recent population-based studies which included central pathology review with modern diagnostic criteria suggest that the true incidence of invasive mucinous carcinoma is closer to 3%\(^\text{1,2}\). When the incidence of mucinous carcinoma is investigated according to FIGO stage, the vast majority of mucinous carcinomas are found in patients with early stage disease (FIGO I & II) where they represent 8% of the total as compared to just 1% in patients with more advanced disease (FIGO III & IV)\(^\text{1,2}\). Areas of specific diagnostic difficulty for pathologists and where there is significant inter-observer variability are in the differentiation between borderline tumour of intestinal type and well differentiated mucinous carcinoma of intestinal type. Differences in classification may account for some of the differences in quoted incidence between centres. Other factors contributing to the apparent fall in prevalence of mucinous ovarian carcinoma include:

- Better understanding by pathologists and clinicians of the methodology to distinguish between primary mucinous ovarian cancer and metastases to the ovary from extra-ovarian sites\(^\text{4-8}\). Image guided biopsy and careful pathological evaluation coupled with expert cross-sectional imaging and multi-disciplinary discussion can prevent unnecessary surgery in many patients with metastatic disease to the ovary\(^\text{9,10}\).
- Recognition that mucinous ovarian neoplasms associated with pseudomyxoma peritonei do in fact arise from appendixal primaries\(^\text{11,12}\).

Historically all patients diagnosed with epithelial ovarian cancer, irrespective of histological subtype have been treated in a uniform fashion and have been enrolled in multicentre clinical trials. For instance the ICON3 trial recruited 148 patients with mucinous histology representing just 7% of the total trial population with no differences demonstrated between the arms\(^\text{13}\); in ICON7 just 34 patients (2% of the trial population) were classified as having mucinous carcinoma.\(^\text{16}^\) With advances in pathology and molecular biology it has become increasingly clear that not all ovarian cancer behaves in the same way and in an analysis of 7 phase 3 randomised GCIG trials Mackay demonstrated that for patients with FIGO stage III & IV disease the prognosis for the 3% of cancers classified as mucinous was substantially worse than for serous carcinomas with median OS of 14.6 months compared with 40.8 months\(^\text{14}\). Similar data from 7 studies have been summarised by Naik et al\(^\text{14}\). Data such as these and data from other phase II trials illustrate the poor prognosis of advanced stage mucinous ovarian cancer but do not provide data as to the response rate of this subtype of ovarian carcinoma to standard platinum based chemotherapy. In an attempt to acquire such data Hess et al performed a retrospective analysis of 27 patients with stage III or IV mucinous ovarian cancer treated at the Royal Marsden Hospital between 1992 and 2001. Two matched controls with non mucinous carcinoma were also identified for each patient. The response rate of cases and controls was 26% and 65% respectively; median PFS and OS for cases and controls were 5.7 months vs 14.1 months and 12 months versus 16.7 months respectively\(^\text{16}\).

Data such as those described above together with emerging molecular data suggest that mucinous ovarian carcinoma is a rare but distinct clinical entity. Shih and Kummar\(^\text{13,12}\) have proposed that ovarian cancer be categorised into Type I and Type II based on molecular and clinicopathologic differences. Type I ovarian cancer which includes mucinous ovarian cancer, low grade serous, endometrioid and clear cell carcinoma tend be lower grade malignancies and have an identifiable stepwise progression from a premalignant lesion through to frank malignancy. Type II ovarian cancer is characterised by genetic instability, and a virtually ubiquitous P53 gene mutation without stepwise progression.

Each of the morphological subtypes of Type I ovarian cancer have been shown to have a distinct pattern of gene mutation which are potentially targetable by current or future targeted molecular therapies. In the case of mucinous ovarian cancer the mutation is in KRAS where a mutation is found in 40 to 50% of patients. KRAS is a small molecule which over activates EGFR which is in turn a potential target for EGFR directed therapy such as cetuximab or panitumumab\(^\text{17}\). The other tumour specific gene abnormality identified in...
mucinous ovarian cancer is HER2 gene amplification in 19% of invasive mucinous ovarian cancers and 6% of mucinous borderline ovarian carcinomas(23). In the same series KRAS mutation was found in 44% of mucinous carcinomas and 79% of mucinous borderline tumours, with KRAS mutation and HER2 amplification being close to mutually exclusive. Either KRAS mutation or HER2 amplification seemed to provide a degree of protection against recurrence or death(23). McAlpine et al treated 3 patients with recurrent HER2 positive mucinous ovarian carcinoma and saw a dramatic response to chemotherapy and trastuzumab in one(24).

To date there have been no successful prospective phase II or III randomised clinical trials conducted specifically in mucinous ovarian carcinoma. The MeOC trial(25) was initiated by the GCIG, and set out to investigate the utility of chemotherapy agents more normally used in GI cancer. Patients with newly diagnosed stage II to IV or recurrent stage I mucinous ovarian cancer were randomised to receive conventional ovarian cancer chemotherapy with carboplatin and paclitaxel or an alternative regimen of oxaliplatin and capecitabine. There was a second non-blinded randomisation to bevacizumab or to control. Regrettably the trial closed 5 years after initiation having recruited just 47 of a proposed 322 patients. Central histology review of the submitted patients revealed that despite a contemporary histology protocol patients with tumours metastatic to the ovary were included within the 47 entered.

Future trials in mucinous ovarian carcinoma will be challenging, will have to be carefully designed, appropriately funded, utilise molecular phenotyping, be of adaptive design and be a truly worldwide effort if we are to make progress against this rare subtype of ovarian cancer.
REFERENCES


SESSION - 5

STANDARD OF CARE OF OVARIAN CANCER IN 2015

Primary disease

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Epithelial ovarian cancer (EOC) remains a serious disease, with high lethality regardless of geographic, technical, or financial resources. We have learned that high-grade serous cancer (HGSC) is associated with uniform functional loss of p53, defective apoptotic signaling, genomic instability, defective DNA repair (including associations with germline mutations in multiple genes), early peritoneal/omental dissemination, hypoxia-driven angiogenic signaling, and rapid emergence of drug resistance. In contrast to these seemingly aggressive features, clinical evidence of deep invasion and spread to extra-peritoneal sites is uncommon, except in the setting of clear cell carcinoma (hematogenous dissemination) and carcinosarcoma, attributed to epithelial-mesenchymal transition (EMT). These observations have prompted renewed examination of the relationship between tumor cells and their microenvironment, including omental adipocytes and the peritoneal cavity. In addition, several retrospective studies have documented the prognostic significance of the host immune response, with particular attention to intra-epithelial T lymphocyte populations, and we are seeing the advent of novel immunoregulatory interventions, vaccines, and adoptive therapy. Finally, it has also become clear that high-grade “ovarian” and “peritoneal” cancers can originate from the fallopian epithelium, sites of endometriosis within the peritoneal cavity, and the endometrium, with similar molecular and clinical features.

In spite of these dramatic advances in biology, the core elements of primary therapy, including cytoreductive surgery and platinum-based chemotherapy, remain largely unchanged over the last 20+ years. Independent of treatment, a trend toward reduced incidence and mortality has been observed, perhaps related to preventive measures, such as the more frequent utilization of oral contraceptives. Better clinical management has improved median progression-free and overall survival. However, there has not been any discernible change in disease-related case-fatality ratios for women diagnosed with advanced-stage disease.

There is no doubt that the incorporation of molecular-targeted treatment interventions, such as inhibition of tumor-mediated angiogenesis, modulation of intracellular signal transduction, targeted delivery of therapeutics based on tumor-associated antigens, immune response modifiers, and inhibitors of poly-ADP-ribose polymerase (PARP) will improve outcomes for many women. However, with the possible exception of immune response activation, these interventions are unlikely to have curative potential in the setting of advanced-stage disease. Reductions in mortality will likely require more ambitious strategies to restore defective apoptotic signaling (due to p53 loss), overcome drug resistance, and target tumor stem-like populations.

With that background, and subject to interpretive bias, the standard of care for primary therapy in 2015 should incorporate the following elements:

**Prevention.** Increased prevalence of genomic screening for deleterious mutations in BRCA1/2 and other genes (with lower hazard ratios) will facilitate decisions regarding early interventions (oral contraceptives, dietary changes, lifestyle modifications) and prophylactic surgery (oophorectomy and/or salpingectomy). All pre-menopausal women should consider at least 6 months of oral contraceptive use.

**Adjuvant therapy of early-stage disease.** The accuracy of initial surgical staging has improved, and could be further enhanced with high-resolution functional imaging and/or intra-operative molecular probes capable of finding microscopic disease and guiding selective surgical interventions. However, HGSC is associated with early peritoneal dissemination, and HGSC is therefore responsible for the majority of recurrences in patients with early-stage disease. As such, all patients with invasive HGSC should receive adjuvant chemotherapy.

**Cytoreductive surgery.** With increased disease awareness, improved diagnostics, and high-resolution functional imaging, there will be a modest shift toward reduced-volume advanced-stage disease at diagnosis. In addition, with enhanced surgical capabilities and intra-operative imaging, the majority of patients will achieve optimal cytoreductive surgery without macroscopic residual disease. The role of aggressive cytoreduction remains controversial, based largely on retrospective studies with inherent selection bias. While primary surgery is favored for the majority of patients, an increasing number of patients with high-volume disease, surgical risk factors, and other comorbidities will generally receive neoadjuvant chemotherapy with evaluation for interval cytoreductive surgery.
Molecular profiling. Germline and somatic mutations in BRCA1/2 and other genes associated with homologous recombination DNA repair should be determined at diagnosis, due to the impact of these mutations on prognosis, prediction of benefit from specific treatment interventions, and understanding family risk. While many other molecular changes have been identified, including elements of the host immune response, these observations have not yet led to changes in treatment or patient management, and are best evaluated in the context of clinical research.

Primary chemotherapy. Standard-dose carboplatin and paclitaxel remains a well-tolerated and effective treatment intervention. There is no evidence that higher dose-intensity, or incorporation of additional cytotoxic agents, or substitution of cytotoxic agents, will improve outcomes for patients with HGSC. Weekly paclitaxel appears superior to three-weekly paclitaxel in the management of recurrent disease, and weekly paclitaxel has been associated with improved outcomes when incorporated in primary platinum-based chemotherapy. As such, this should be considered as the primary treatment regimen for most patients.

Intraperitoneal (IP) chemotherapy. Randomized trials, with some caveats, have documented improved long-term clinical outcomes associated with IP chemotherapy. However, over the last 20 years, we have collectively failed to understand the mechanisms involved. While “dose-intensity” is frequently cited as the rationale for IP therapy, there are many reasons related to the biology of tumor implantation that might prevent drugs from entering a tumor nodule. The relationship between tumor implants, the omentum, and the peritoneal cavity appears highly specialized, and it is likely that IP drug administration has an impact on the peritoneal microenvironment, regardless of any direct impact on the tumor. The increased utilization of weekly paclitaxel and other agents (such as bevacizumab), as well as newer targeted interventions, are likely to negate much of the advantage previously ascribed to IP therapy, and we await results from the NRG-GOG0252 (NCT00951496) as well as the JGOG iPocc (NCT01506856) trials.

Maintenance chemotherapy. There is no convincing evidence that extended therapy with cytotoxic agents will improve long-term outcomes, and this should not be considered as a standard-of-care component.

Incorporation of anti-VEGF Interventions. While this remains an area of controversy, with international differences in regulatory approval and drug utilization, the weight of evidence favors treatment in the setting of recurrent disease. It is not necessary to incorporate anti-VEGF interventions (such as bevacizumab or tyrosine kinase inhibitors) with primary chemotherapy, particularly when using weekly paclitaxel.

Clinical research. Efficient screening of new targeted agents remains a high-priority, and it would be advantageous to enroll patients receiving NACT in randomized phase II trials to obtain pre- and post-therapy biospecimens. Several proposals are moving forward within national groups, and in collaboration with the pharmaceutical industry, with a focus on tumor stem-cell populations and immunoregulatory checkpoint inhibition. Promising regimens can be expanded as phase II trials, using an adaptive design framework. In addition, the incorporation of early functional imaging (such as perfusion CT, diffusion MRI, or PET-CT) could identify patients with treatment-resistant disease to further explore alternative regimens during primary chemotherapy.

Summary. The accelerated pace of molecular diagnostics and drug development has not yet translated into wide-scale success for patients with advanced-stage EOC, although a number of promising interventions are under development. Standard-of-care recommendations reflect our current knowledge and interpretation of existing clinical data, but must also consider opportunities for innovative research, as well as the fiscal burdens of health care, particularly in low-resource settings. The next few years will witness a concerted effort to address high-priority clinical, scientific, regulatory, information-based, and financial goals. Taken together, these advances will further improve patient outcomes, and start to reduce the mortality associated with this disease.
SESSION - 5

STANDARD OF CARE OF OVARIAN CANCER IN 2015

Recurrent disease

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Although significant progress has been made in the treatment of OC, the majority of patients experience disease recurrence and receive second-line and more and more frequently several lines of treatment. Here the options available for the treatment of recurrent disease, including the recent development of molecular targeted therapy will be discussed.

PLATINUM-FREE INTERVAL (PFI): A STILL STANDING, BUT FLAKING STATUE

PFI definition has been specified at the last Ovarian Cancer Consensus Conference in 2010 as the interval between the last dose of platinum and relapse. PFI is considered as the major criterion predicting chemotherapy success in ovarian cancer relapse treatment and has allowed to develop distinct therapeutic strategies according to the PFI length. Disease is considered as platinum-refractory when the relapse occurs during platinum-based chemotherapy, platinum resistant when PFI is < 6 months, partially platinum-sensitive when between 6 and 12 months and fully platinum-sensitive when > 12 months.

However, the date of disease progression is somewhat variable according to the method chosen to determine progression (imaging, CA125 level increase or clinical deterioration), introducing some flexibility in the interpretation of PFI and the definition of platinum sensitivity. In addition, PFI has been described in the early 90’s to predict platinum-based chemotherapy retreatment. The interval from the last platinum chemotherapy may not be a valuable criteria for the new molecular targeted therapy. For instance, there some hint that bevacizumab may be more active in patients with larger burden of disease independently of the platinum-free interval. And for anti-PARP therapy, it remains to be demonstrated that PFI is a more potent predictor of efficacy than Homologous Repair deficiency, including the presence of a BRCA mutation.

In conclusion, the PFI categorisation above still continues in clinical practice and trials, but a significant evolution in the concepts is expected in the next future years.

SECONDARY SURGERY WAITING FOR THE DATA

The role of secondary surgery in the management of relapsed ovarian cancer remains uncertain. The AGO has proposed a score combining 3 criteria (complete resection at first surgery, ECOG performance status score of 0 and absence of ascites) which predicts a higher chance to achieve a surgical complete remission, mainly in platinum-sensitive disease. However, the impact of secondary surgery on patient PFS or OS remains unclear and is currently evaluated in 2 randomized trials (AGO DESKTOP and GOG213).

The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in recurrent ovarian cancer is debated. Three randomized trials (CHIPOR, HORSE/MITO 18, and MSKCC) will answer to the question whether HIPEC has any role in relapsing OC patients treatment.

CHEMOTHERAPY: STILL A FUTURE?

Platinum resistance eventually occurs in virtually all patients with recurrent OC. Single agent with a non-platinum compound is considered standard. Four drugs are most often used sequentially. These are pegylated liposomal doxorubicin (PLD), weekly paclitaxel, gemcitabine and topotecan with similar response rates (range 10-15%), PFS (3-4 months) and OS (about 12 months).

The treatment of platinum-sensitive disease with chemotherapy alone is also now well established with combination chemotherapy being considered standard. As stated in the 2010 Vancouver Ovarian Cancer Consensus Conference, platinum-based combination is recommended in relapse when PFI is over 12 months. Non-platinum combination (trabectedin- PLD) may be also an option in the intermediate setting when relapse occurs between 6 and 12 months.

However, the clock may be running for chemotherapy in relapsing OC. In the future, combination of molecular targeted therapy may be even more active than chemotherapy in specific subsets of OC patients. This is suggested by the impressive efficacy data recently reported with olaparib plus cediranib in a small randomized trial of high grade serous OC with platinum-sensitive disease[6].
TARGETED THERAPY: GLOBALIZATION DOES NOT MEAN HARMONIZATION

Bevacizumab (Avastin™) and olaparib (Lynparza™) are the 2 molecular targeted therapies approved in recurrent OC in EU and US. These are the leaders of 2 different classes of drugs, namely anti-angiogenics and anti-PARPs, and several others compounds of the same classes are currently under active development.

Bevacizumab combined with chemotherapy followed by maintenance has been shown in phase III trials to prolong PFS in both platinum-sensitive and platinum-resistant disease (and to improve patient-reported outcome in this last setting).

These trials have modified the preferred chemotherapy regimen used in both settings. In platinum-sensitive disease, bevacizumab has been developed with the carboplatin-gemcitabine regimen (OCEANS) instead of the favorite carboplatin-PLD combination (CALYPSO)\(^1\). A randomized trial from the AGO is currently comparing the OCEANS regimen with the CALYPSO + bevacizumab regimen. In resistant relapse, the AURELIA trial results\(^2\) give some hint that weekly paclitaxel and bevacizumab may have the best synergistic effect over topotecan or even PLD, the previous preferred single drug in this setting.

Olaparib is indicated for BRCA mutated patients in relapse. This oral drug has demonstrated in randomized phase II trials to dramatically prolong PFS in post-chemotherapy maintenance for platinum-sensitive disease\(^3\) and to offer high response rates in heavily pre-treated BRCA mutated patients\(^4\). Phase III trials in platinum-sensitive disease together with first-line are on-going.

It is to note that AURELIA is the only trial registered on both sides of the Atlantic (EU and US). Bevacizumab and olaparib are approved in platinum-sensitive disease in EU, but not in US nor in Asia. Olaparib is approved in heavily pre-treated patients in US, but not in EU.

CONCLUSION

The landscape of recurrent relapse treatment has recently moved. The chemotherapy era has allowed in the past to significantly extend the overall survival of recurrent OC patients thanks to the variety of drugs approved in this setting.

Several molecular targeted drugs have now shown activity in relapsing OC. These include drugs which target the tumor vasculature as well as those that inhibit DNA repair processes. Identifying markers that are predictive of a response is a paradigm for optimizing OC patient care.

However, in this infrequent disease, an harmonization of the OC molecular targeted therapy labels across countries is urgently needed to allow prompt and coordinated development of future drugs.
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SESSION - 5
STANDARD OF CARE OF OVARIAN CANCER IN 2015
Patient reported outcomes in ovarian cancer clinical trials.
Missed opportunities
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The primary endpoint in ovarian cancer clinical trials is commonly progression free survival (PFS) or overall survival (OS) while health related quality of life (HRQOL) and adverse events are usually secondary endpoints. By default, PFS has become the most common primary endpoint in ovarian cancer clinical trials, in both the 1st line and recurrent disease setting as there are many additional therapies available after progression that may impact on overall survival.

PFS is based on disease progression criteria initially developed for use in phase 2 trials that used response as an endpoint. The response and progression definitions were developed in an attempt to standardise reporting of clinical trials and describe what happens to tumours during therapy(2). These changes in tumour size may not necessarily infer a meaningful benefit to patients or be associated with symptom improvement, but over time the RECIST response and progression criteria have led to PFS becoming an important primary endpoint in phase 3 trials, and prolongation of PFS is assumed to confer benefit to patients. It is pertinent that the lead author of the RECIST 1.1 guidelines recognises the limitations of the RECIST definitions and has recently written that “it seems unlikely that there would be substantial difference in an individual patient state if he/she experiences a 19% versus 21% increase in disease or a 29% versus 31% decrease in disease”. A greater than 20% increase of the sum of the target lesions would be recorded as progressive disease. In a clinical trial, this would determine PFS and most likely to lead to the patient coming off the trial.

The assumption underlying RECIST is that tumour measurements can be reliably performed by different readers and are accurate and reproducible. However, the reliability and reproducibility of RECIST 1.1 in ovarian cancer is unknown. Recurrent ovarian cancer can be very difficult to “measure” on a CT scan and it has been estimated that over 50% of patients with recurrent disease do not have measurable disease using RECIST(3).

These intrinsic problems with RECIST and the definitions of progression underscore the importance of also including patient reported outcomes (PROs) as an outcome measure in clinical trials in addition to standard measures such as PFS. PROs provide valuable information and insights that complements clinical and survival outcome data, and enhances the interpretation of trial results. Importantly, their inclusion acknowledges the centrality of the patient perceptions of treatment benefit and adverse effects associated with treatment. For example, we still don’t understand what a prolongation in PFS actually means to a patient and what price she pays for the increase in PFS or what is the impact on the patient of diagnosing RECIST progression when she is well and asymptomatic. Although HRQOL has commonly included as a secondary endpoint in ovarian cancer clinical trials, PRO measures have seldom been applied with the same rigour as other trial endpoints. Few trial protocols have included a detailed statistical analysis plan to generate meaningful patient-centred outcomes data based on pre-specified PRO hypotheses and appropriate sample size calculations.

However, the importance of PROs in clinical trials is becoming increasingly recognised as critical to the interpretation of the results of the trial. The Centre for Medical Technology Policy (CMPT) as well as the Food and Drug Administration (FDA) have developed guidance documents for the use and collection of high-quality PROs in clinical trials to support labelling claims. The FDA PRO Guidance describes design principles and protocol content recommended for optimal administration of PRO measures in clinical trials(4).

The content of trial protocols is now receiving increased attention in the literature. The SPIRIT statement for standardised content of trial protocols was published in 2013(5) and a PRO-extension is now in development, in collaboration with the International Society for Quality of Life Research (ISOQOL)(6). This work follows the recent development of PRO-specific reporting guidelines published by ISOQOL(7), which informed the CONSORT-PRO extension(8). The essence of all the recommendations is that PROs should be assessed with the same attention to detail as other trial outcomes and that PROs receive adequate attention and coverage in the trial protocol. Furthermore, PRO endpoints should be explicitly stated as a specific clinical trial objective and should reflect the specific aims and the objectives of the study. It is important that pre-specified PRO
hypotheses are carefully considered a priori as they will impact on the selection of instrument/s and the timing of PRO assessments. There should be detailed elaboration in the statistical analysis plan, including sample size calculations and pre-specified procedures with how to deal with missing data.

These recommendations are an encouraging move forward, but compliance with the guidelines remains a lofty ideal rather than a reality in most clinical trials. This has resulted in missed opportunities to explore the impact of interventions on patients’ symptoms, functioning and HRQOL and limited interpretation of trial findings.

Recent reviews of the quality of reporting of PRO endpoints have revealed a startling number of trials fail to report essential details of the PRO study, including HRQOL hypotheses, proportions and statistical approaches for dealing with missing data. These omissions make it difficult to interpret the PRO findings and suggest a widespread systemic problem.

The “missed opportunities” in selected ovarian clinical trials will be reviewed and discussed. The intention is to learn from them and thereby try and avoid past mistakes and improve the design of future trials. With the benefit of hindsight, it is clear that we could have learned so much more from many clinical trials if there had been closer attention to PROs and PRO endpoints. To paraphrase George Santany: “Those who cannot learn from past mistakes are doomed to repeat them”.

Patient reported outcomes in ovarian cancer clinical trials. Missed opportunities

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