9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

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The *International Symposium on Advanced Ovarian Cancer: Optimal Therapy. Update* was founded in 1996 by us, Dr. Andrés Poveda and Prof. Jan B. Vermorken, each edition has also been directed by us.

On March, 1st its ninth 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, GINECO, GOG, NCIC, GCIG or ENGOT. GEICO members are medical oncologists, gynecologists 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).

The meeting is held under the auspices of the Spanish Society of Medical Oncology (SEOM), the Gynecologic CancerIntergroup (GCIG), and the European Society for Medical Oncology (ESMO), Educational Committee for its Medical Oncology Recertification Approval (ESMO/MORA) Program.

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), 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, ANZGOG, GINECO, GEICO, JGOG, KGOG, MRC, MITO, MANGO, SWOG, etc.

From the 2nd edition (1999), the entire papers have been published in the "International Journal of Gynecological Cancer" (Blackwell. 2000, vol. 10; supp. 1. 2001, vol. 11; supp. 1. 2003, vol. 13, supp. 2. 2005, vol. 15; supp. 3; 2008,vol. 18, supp. 1; WoltersKluwer Lippincott Williams & Wilkins 2009, vol. 19, supp. 2), and "Annals of Oncology" (Oxford University Press 2011, vol. 22, supp. 8).

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

TABLE OF CONTENTS

SESSION 4 SYSTEMIC THERAPY IN OVARIAN CANCER: RECURRENT

SESSION 5 NEW DEVELOPMENTS

9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

Keynote Lecture: Genomic Analysis

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Ovarian cancer remains a major health problem in the US. In 2012, there are 22,000 cases resulting in 14,500 deaths[1]. Ovarian cancer has the highest case fatality rate among all gynecologic cancers. Due to a lack of an effective early detection assay, ovarian cancer is most frequently diagnosed in the advanced stage when it is difficult to treat. While ovarian cancer is the most chemoresponsive epithelial cancer, most patients suffer relapse and develop chemoresistant disease. While the median survival has been extended to greater than 4 years, overall survival has not changed appreciable over the last 30 years. Patients with an advanced stage ovarian cancer have a broad survival spanning many years with some patients having refractory disease surviving less than a year with others living for greater than 10 years[2]. Given this heterogeneous survival, stratification of patients using prognostic or predictive markers will be necessary to improve the treatment of women suffering from this disease.

The genomic revolution has provided powerful information that can potentially help identify the needed tools. There has been extensive genomic analysis of ovarian cancer over the last 20 years[3-7]. The Cancer Genome Atlas project has genomically characterized 480 high-grade serous cancers for mutations, copy number variation, expression patterns and methylation[8]. These tumors demonstrate low mutation rates in genes except p53 and BRCA1/2. In contrast, extensive DNA gains and losses can be seen through the genome of these cancers. Losses and gains are both focal and broad with deletions and amplification involving many genes. Gene expression and methylation patterns were identified but did not strongly correlate with clinical outcome. This genomic pattern reflects a tumor with a profound abnormality in DNA repair. Given these results and the genomic instability, it has been proposed that serous ovarian cancer is not targetable with drugs or predictable. The challenge will be to utilize this plethora of genomic data to develop clinically useful tools.

We have taken several approaches to address this challenge. First, we have conducted a systematic evaluation of published prognostic signatures for advanced stage ovarian cancer. Many of these signatures are not reproducible or have minimal prognostic value. We created a database of over 1600 publically available microarrays of advanced stage ovarian cancer and used it to generate a prognostic signature, which outperformed published signatures known. The genes in this survival signature identify several key biochemical pathways. We anticipate that these pathways will allow for therapeutic intervention. Further, we utilize this database to generate a predictive gene expression signature for the ability to be optimally debulked. This signature identifies activated pathways in EMT and TGF-beta. Using real time PCR we have validated this signature using real-time PCR and IHC. The validated signature is able to predict patient who will not be optimally debulked more effectively than any published predictor.

Second we have begun to systematically analyze the genomic aberrations in these tumors in order to better identify key genes. There are two general approaches to translate genomic data into clinically relevant endpoints. First, simplification of the complexity of the sample analysis using technical approaches such as micro dissection allows for more accurate generation of survival related genes. We have generated a gene signature for survival for patient with advanced stage ovarian cancer[5]. This signature was validated using qRT-PCR. Genes in the signature included several novel genes with strong cox scores strongly related to overall poor survival. Analysis of the genes within the signature reveals both important activated pathways and novel genes. The gene with the highest cox score is MAGP2. MAGP2 is a secreted protein with a RGD domain for binding to alpha V beta 3 integrin receptor. MAGP2 is amplified and over expressed in ovarian cancers and those patients with these tumors have a significantly shorter survival. Mechanistic *in vitro* studies demonstrate that MAGP2 can stimulate the migration and invasion of ovarian cancer cells. *In vivo* studies demonstrate MAGP2 stimulates tumor growth. Of note, MAGP2 binds the integrin receptor and therefore promotes the survival and proliferation of endothelial cells. This implies one mechanism by which MAGP2 stimulates tumor growth is by pro angiogenesis process. Based upon this data, we have demonstrated a direct correlation of MAGP2 expression and microvessel density in patient specimens. This detailed analysis has identified a gene amplified and over expressed in ovarian cancer which based upon mechanistic studies may be an ideal therapeutic target.

The second approach is a more systematic integrated analysis of genomic abnormalities in order to determine the key genes which are involve on ovarian cancer development have clinical importance. To do this we integrated the CNV results including gene amplifications with gene expression data to identify key “drivers” in this disease. We have identified an amplicon on chromosome 5q31 that conferred a strongly negative prognostic impact in patients[4]. Analysis of this amplicon revealed it contained multiple genes. Overlaying the gene expression data onto the copy number differences identified a smaller group of genes whose over expression would support an important role in ovarian cancer. Of note were two genes included the FGF pathway including FGFR4 and FGF18. We demonstrated FGF18 is up regulated in serous ovarian tumor compared with normal ovarian surface epithelium by qRT-PCR and immunohistochemical (IHC) staining. In addition, FGF18 mRNA and protein expression is strongly associated with poor survival in patients. Ectopic

expression and knockdown experiments demonstrate pronounced oncogenic influence of FGF18 on tumor growth and metastasis. Further analysis reveals that the effect of FGF18 induces angiogenesis and attracts tumor-associated macrophages (TAM) *in vitro* and *in vivo*. To validate these results, FGF18 expression is significantly correlated with increased tumor microvessel density and TAM infiltration in samples from serous ovarian cancer patients. FGF18 plays an important role in promoting the progression of serous ovarian cancer by modulating both tumor cells and tumor microenvironment and is a potential therapeutic target.

In summary, these bioinformatic and molecular efforts will help translate the plethora of genomic data we have for epithelial ovarian cancer into clinically useful approaches. The defect in DNA repair makes ovarian cancer unique and particularly challenging. With minimal gene mutations and the shifting molecular genotype, specific structure function analysis will be necessary to determine the precise role for each amplified or lost gene in these cancers. This will ultimately allow for a more tailored and individualize treatment which is likely to be more successful.■

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9th International Symposium

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SESSION 1 PATHOGENESIS: FROM MORPHOLOGY TO MOLECULAR DIAGNOSIS

Molecular Pathogenesis

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A new paradigm for the pathogenesis of ovarian cancer based on a dualistic model and the recognition that the majority of ‘‘ovarian’’ carcinomas originate outside the ovary assist in organizing this complex group of neoplasms and facilitates the development of new and novel approaches to prevention, screening, and treatment. One group of tumors (type I) is generally indolent, presents in stage I (tumor confined to the ovary) and develops from well-established precursors, so-called borderline tumors. These tumors are characterized by specific mutations, including KRAS, BRAF, ERBB2, CTNNB1, PTEN and PIK3CA, but rarely TP53. They are relatively genetically stable. The other group (type II) is composed of tumors that are aggressive, present in advanced stage, and develop from intraepithelial carcinomas in the fallopian tube. They have a very high frequency of TP53 mutations but rarely harbor the mutations detected in type I tumors. They are genetically highly unstable.

This proposed model is intended to serve as a framework for studying ovarian cancer. It is not complete and does not resolve all issues. For example, clear cell carcinoma is classified as a type I tumor based on having a characteristic PIK3CA mutation, relative genetic stability, frequent presentation in stage I, and association with endometriosis, a well-established precursor lesion. But unlike other type I tumors, clear cell carcinoma is high-grade at presentation.

Recent studies on the origin of ovarian cancer have directed attention to a putative precursor lesion in the fallopian tube that morphologically and molecularly resembles high-grade ovarian serous carcinoma, and that has been designated ‘‘serous intraepithelial tubal carcinoma (STIC)’’. Thus, rather than developing de novo from the ovary, as earlier proposed, the majority of type II tumors seem to arise from a STIC in the fimbriated end of the fallopian tube that spreads to the ovary. Another possible mechanism for the development of ‘‘ovarian’’ carcinoma is dislodgement of normal tubal epithelium from the fimbria, which implants on the site of rupture where ovulation occurred resulting in the formation of an inclusion cyst that may then undergo malignant transformation. Thus, serous tumors may develop from inclusion cysts, as has been thought, but by a process of implantation of tubal (mullerian-type) tissue rather than by a process of metaplasia from ovarian surface epithelium (mesothelial). Endometrioid and clear cell carcinomas may also originate from nonovarian, mullerian-type tissue, as it is widely accepted that these tumors develop from endometriosis that is thought to develop as a result of retrograde menstruation. The origin of mucinous and transitional cell (Brenner) tumors is still not well established, although recent data suggest a possible origin from transitional epithelial nests located in paraovarian locations. Thus, there is mounting evidence that type I and type II ovarian tumors develop independently along different molecular pathways, and that both types develop outside the ovary and involve it secondarily. This explains why current screening strategies designed to detect ovarian cancer, when it is confined to the ovary, are ineffective in accomplishing this goal.

Given the obstacles in early detection (screening) and the significant but relatively limited success in treatment, attention should be directed to primary prevention. This takes on particular relevance with the recognition that the majority of ovarian carcinomas are derived from cells in the fallopian tube or from passage of the endometrial tissue through the fallopian tubes and the important role of ovulation in ovarian carcinogenesis. Salpingectomy alone may be sufficient to accomplish this, as removal of the fallopian tubes would reduce the risk of ovarian cancer while preserving ovarian function. Ovarian conservation seems to be particularly important for a woman’s health, as it has been shown that oophorectomy is associated with increased overall mortality and a higher frequency of nonfatal coronary heart disease. Other approaches should also be explored, for example the use of oral contraceptives that presumably by preventing ovulation reduces the risk of ovarian cancer. In any case, new diagnostic, prevention and therapeutic approaches must be developed on the basis of our evolving understanding of ovarian carcinogenesis.■

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SESSION 1 PATHOGENESIS: FROM MORPHOLOGY TO MOLECULAR DIAGNOSIS

Clinical Implications

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Common embryonic precursor tissues ultimate diverge to yield the several major organs of the female genital tract, each with a separate constellation of recognized malignancies. In the now closing era of morphologic diagnostics, any epithelial tumor on or involving the ovaries was presumed to come from and be strictly of ovarian origin, absent the rare but clearly metastatic tumors. Thus, many women who might have had small fallopian tube primary cancers that rapidly extended onto or into the ovary were deemed to have ovarian cancer. Was that actually the case and did it matter clinically? Since we recognize similarities in those cancers and their response to chemotherapies, we were neither misleading our patients nor mistaking their care. Now, as we begin to better understand and reorganize our categorization of the different types of cancers of nonuterine Müllerian origin, we may have to revisit how we apply data gleaned from clinical trials, biomarker studies, and epidemiology from the morphologic diagnosis era. For ease of reading, these will be called tubo-ovarian cancers herein.

There are now numerous studies evaluating tubo-ovarian cancers of Müllerian origin at various molecular levels. The clear message is that there are different molecular types of cancers originating in the Müllerian tract, a group of which fall into what we have known as ovarian and tubal cancers. There are common somatic and germ line molecular threads that are evolving and allowing logical reorganization using histologic and molecular information. These new categories, soon to be recognized as “types” of tubo-ovarian cancers may originate from epithelium of the ovary, tube and/or uterus. The new knowledge is driving the building of a structure-function type relationship that is generating novel clinically-applicable hypotheses for testing.

Clinical implications of using molecular descriptors in characterizing nonuterine Müllerian tubo-ovarian cancers are broad. Clinical opportunities begin with improvements in diagnosis. The molecular knowledge has added value to classical pathologic diagnosis through providing reliable biomarkers that can be included in surgical pathology diagnosis. For example, an endometrioid tumor that does not appear to come from the endometrium and has positive WT1 staining is likely in the high grade endometrioid tubo-ovarian cancer category. Second, this dichotomization allows different prognostication. High and low grade subsets of serous and endometrioid tubo-ovarian cancers have different therapy responsiveness and overall survival outcomes. Lastly, this differentiation appears to lead to more homogeneous treatment-related groups. High grade serous and endometrioid cancers are more sensitive to standard therapies of DNA damaging agents, such as platinums and the taxane microtubule stabilizers. They behave more homogeneously leading to results that could be more confidently applied to similar patients. Within the context of the high grade serous cancers is the subset of women with BRCA1/2 mutation and those who have BRCA-like molecular features. We now know that the mutation carriers have susceptibility to the new class of PARP inhibitor agents, both as single agents and in combinations. About half of high grade serous cancer patients are BRCA-like and this group of patients also appear to be both platinum- and PARP inhibitor sensitive. Somatic mutational findings have also led to recognition that another, more rare subset, the true mucinous tubo-ovarian cancers, are nearly all KRAS mutant with a third or more also having amplification of HER2. The latter finding clearly has therapeutic implications for the inclusion of anti-HER2 therapy such as trastuzumab and lapatinib, now under clinical investigation.

Application of a new morphomolecular characterization also brings clinical challenges. “Re”-writing classifications, clinical trial eligibility and strata, and clinical interventions will mean starting with a new, blank slate. We will have to redefine baselines of clinical responses to therapy, progression-free and overall survivals, and relationships between clinical parameters, treatments, and outcomes. Tubo-ovarian cancers are relatively rare cancers worldwide when considered as a single entity. Recategorizing these cancers using morphomolecular designations will create even smaller patient subsets but perhaps with cleaner, more focused and readily testable hypotheses. Success will require greater national involvement of patients and international collaboration in order to make clinical progress in a reasonable timeframe. It is likely to lead to more reliable and reproducible findings, especially where targeted agents are involved. Overall, incorporation of this broad new knowledge into diagnosis, dichotomization, and treatment tubo-ovarian cancers should translate into improved diagnostic and therapeutic directions for patients, lead to development and validation of new and reliable biomarkers, and hopefully, bring us to early diagnosis, a critical need that has eluded us to date.■

"Old" morphologic diagnosis`	"Old" organ site	"New" morphomolecular diagnosis	"New" organ site	Molecular characteristics
Serous papillary	Ovary	High grade serous/ papillary	Fallopian tube	- BRCA1/2 mutation or HRD* - $WT1^{+}$ - p53 mutant - additional subtypes
		Low grade serous/ papillary	Ovary	KRAS/BRAF mutation
Endometrioid	Ovary	High grade endometrioid	? Ovary ? Fallopian tube	?HRD/?HNPCC PTEN $WT1^{+}$
		Low grade endometrioid	Uterus (endometriosis) ? Ovary with metaplasia	PTEN, ARID1A, CTTNB1 mutations
Clear cell	Ovary	Clear cell	Uterus (endometriosis) ? Ovary with metaplasia	IL6/JAK2/STAT3 pathway ARID1A
Mucinous	Ovary	Mucinous	r/o appendix/GI sites Ovary, if stage I	KRAS ~30^{+}% HER2 amp (3^{+})

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SESSION 2 SURGERY IN OVARIAN CANCER

State of the Art of Surgery in Advanced Ovarian Cancer

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Historical Evolution

The first person to quantitate the importance of cytoreductive surgery for patients with advanced epithelial ovarian cancer was Griffiths in 1975[1]. In a single institution, retrospective study of 102 patients who underwent primary cytoreductive surgery, Griffiths reported improved survival if all tumor nodules > 1.5 cm in diameter could be removed. He coined the term "optimal" for this cytoreductive outcome. Griffiths reported that the extent of metastatic disease was not of prognostic significance.

In a report from the University of California, Los Angeles (UCLA) in 1983, Hacker et al. demonstrated that cytoreduction to residual nodules 5mm or less carried an even better prognosis, but also demonstrated for the first time that tumor biology had independent prognostic significance. Within the "optimal" group, patients having >1000cc ascites or metastatic nodules >10cm in diameter prior to cytoreduction had a significantly poorer survival[2].

In a 1992 retrospective review of the surgical reports from GOG Protocol 52, (a chemotherapy study in patients with residual disease 1cm or less in diameter), Hoskins et al. confirmed the importance of tumor biology. They demonstrated that the extent of metastatic disease prior to cytoreduction and the number of small residual nodules were both of prognostic significance[3]. They stated "This study failed to prove the hypothesis that initial cytoreductive surgery would allow a patient presenting with large-volume ovarian cancer to have the same chance for survival as a patient found to have small volume disease (ab initio)".

The importance of complete cytoreduction

The first person to suggest that "complete" rather than "optimal" cytoreduction should be the objective of primary surgery for advanced ovarian cancer was Eisenkop in 1998[4]. Between 1990 and 1996, his team operated on 163 consecutive patients with stage IIIC and IV epithelial ovarian cancer. All visible tumor was resected in 139 patients (85.3%). In order to achieve complete resection, 85 (52.1%) had an en bloc recto-sigmoid resection, 66 (40.5%) had diaphragmatic stripping or resection, 145 (89%) had peritoneal implant ablation with the Argon Beam Coagulator or Cavitron Ultrasonic Aspirator, and 31 (19%) had miscellaneous operations, such as splenectomy, liver resection or distal pancreatectomy. Patients having complete cytoreduction had a median survival of 62.1 months, compared to 20 months for patients with any residual disease (p=0.001).

The importance of complete cytoreduction was further examined by du Bois et al. in a retrospective review of 3126 patients with stages IIB-IV epithelial ovarian cancer entered onto three prospective randomized trials of chemotherapy (AGO-OVAR 3, 5 and 7)[5]. Approximately one third each fulfilled criteria for complete resection, Group A (1046 patients), optimal cytoreduction, (1-10mm), Group B (975 patients), and suboptimal cytoreduction, (>10mm), Group C (1105 patients). Multivariate analysis showed improved progression-free and overall survival for group A (p <0.0001). Further independent prognostic factors for overall survival were age, performance status, histologic grade, FIGO stage, and histologic type (ie, mucinous worst).

The group from the Mayo Clinic examined the relative impact of disease status, patient status, and the aggressiveness of the surgeon on the resectability of advanced ovarian cancer[6]. In multivariate analysis, only ASA score, presence of carcinomatosis, and surgery by an aggressive surgeon were independently associated with optimal residual disease status (defined as nodules less than 1 cm).

The role of lymphadenectomy

Only one randomized controlled trial has examined the role of lymphadenectomy in patients with advanced epithelial ovarian cancer[7]. Patients who had residual nodules 1 cm or less in the peritoneal cavity were randomized between systematic pelvic and paraaortic lymphadenectomy (N=216) versus resection of bulky nodes only (N=211). There was a six month benefit in progression-free survival (p=0.02) in the lymphadenectomy arm, but no difference in overall survival.

Thoracic involvement

The first person to undertake thoracoscopy to determine the extent of intrathoracic disease and the feasibility of intrathoracic cytoreduction was also Eisenkop, in 2002[8]. He used mainly a transdiaphragmatic approach, after observing

a significant increase in operating time associated with thoracoscopy through the chest wall. Small pleural implants were ablated with the Argon Beam Coagulator, while larger implants were excised with long Metzenbaum scissors and the bases ablated. He concluded that thoracoscopy improved the ability to achieve complete cytoreduction in some cases, and allowed modification of the intraabdominal cytoreduction in cases with unresectable intrathoracic disease.

A recent paper evaluated the role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in the staging of patients with advanced ovarian cancer[9]. In 20 of 30 patients (67%), FDG PET/CT detected supradiaphragmatic lymph node metastasis, compared to 10 of 30 (33%) for conventional CT scan. The location of the positive nodes was parasternal in 14 (70%), cardiophrenic in 14 (70%), other mediastinal in 8 (40%), axillary in 6 (30%), and subclavian in 1 (5%). The authors felt that the clinical relevance of their findings was currently unclear, and that any change in treatment strategies should await further studies.

The use of neoadjuvant chemotherapy

For the past decade, most of the debate has revolved around the indications for neoadjuvant chemotherapy for patients with advanced ovarian cancer.

In 2008, Vergote presented the results of a randomized EORTC-NCIC study of primary debulking surgery versus 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery in patients with stages IIIC-IV ovarian, fallopian tube and peritoneal cancer at the 2008 meeting of the IGCS in Bangkok. The results were published in 2010[10]. There were 718 patients enrolled and 670 were randomized. Perioperative morbidity and mortality tended to be higher in the group having primary surgery, but overall and progression-free survival were similar in both groups. The median overall survival was 29 months after primary surgery and 30 months after neoadjuvant chemotherapy, and the median progression-free survival was 12 months in each group. Complete resection of all macroscopic disease was the strongest independent predictor of overall survival in both groups.

This study has been criticized by the German and Austrian Gynecologic Oncology Groups[11]. The major points of criticism were as follows: (i) better prognosis stage 3 patients were excluded, (ii) 72.3% of patients in the primary surgical arm received platinum and a taxene, compared to 84.7% in the neoadjuvant chemotherapy arm, (iii) the surgical outcome was heterogeneous, with complete resection rates after primary surgery ranging from 3.9% in the Netherlands to 62.9% in Belgium. (iv) there was also heterogeneity with respect to outcome for different postoperative residuals. There was an advantage for primary surgery in patients with no residual disease (median survival 45 vs 38 months) or residual disease up to 1 cm (32 vs 27 months). Only the cohort with residual disease greater than 1 cm showed no difference between the two arms, and this was the largest cohort in the primary surgical arm, (v) in subgroup analysis, patients with metastatic disease up to 5 cm had a better survival after primary surgery ($p < 0.05$).

Postoperative morbidity and mortality

The Nationwide Inpatient Sample was used by Wright et al to identify 28,651 women who underwent surgery for ovarian cancer in the United States from 1998 to 2007[12]. The postoperative complication rate increased with age, from 17.1% in those under 50 years, to 29.7% in those 70-79, and 31.5% in those 80 years or older ($p < 0.05$). Complication rates also increased from 20.4% for patients having no extended procedures to 34% for those having one, and 44% for those having two or more ($p < 0.0001$).

The same authors examined the effect of radical cytoreductive surgery and its associated perioperative morbidity on the omission and delay of chemotherapy[13]. The occurrence of more than two perioperative complications and initiation of chemotherapy more than 12 weeks after surgery were associated with decreased survival.

Interpretation of current literature on cytoreduction for advanced epithelial ovarian cancer

The EORTC/NCIC study of neoadjuvant chemotherapy versus primary surgery demonstrated that neoadjuvant chemotherapy does not improve survival, in spite of increasing the incidence of complete tumor resection. This is not surprising, as small tumor nodules on the peritoneal surfaces will disappear after neoadjuvant chemotherapy if the disease is chemosensitive, so the two patient groups are not comparable.

The EORTC/NCIC study demonstrated less morbidity in the neoadjuvant chemotherapy arm. Patients who are likely to experience postoperative morbidity are older (75 plus years), have comorbidities, or have a poor nutritional (low albumen levels), and/or performance status[14]. Such patients often have a large volume of ascites or a moderate to large pleural effusion, and if they have chemosensitive tumors, their effusions will dry up after two or three treatment cycles.

In view of the above, it is the author's view that the gold standard for patients with advanced ovarian, fallopian tube, or peritoneal cancer should be primary cytoreductive surgery, with the aim of complete tumor resection. Neoadjuvant chemotherapy and interval debulking should be reserved for a subgroup of patients with significant comorbidities, particularly if they are elderly, or for patients with large volume ascites or a moderate to large pleural effusion. The value of resecting disease above the diaphragm is yet to be proven, and there is no proven benefit to systematic pelvic and paraaortic lymphadenectomy.■

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9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

SESSION 2 SURGERY IN OVARIAN CANCER

Surgical Intervention in Relapsed Ovarian Cancer is Beneficial. In Favor

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Despite improvements in surgery and chemotherapy many patients with advanced ovarian cancer relapse and require further therapy[1,2]. Standard of care in this clinical scenario is chemotherapy[3,4,5]. The choice of chemotherapy depends on treatment free interval, prior therapy, expected toxicity and patient wish[6]. So far, reports on cytoreductive surgery for patients with relapse within 6 months have not shown a meaningful benefit and therefore, surgery for patients with early relapse is not recommended. In contrast, several authors reported promising results in secondary cytoreductive surgery in patients with platinum sensitive relapse[7,8]. A meta-analysis has shown an increase of 3 months in overall survival per 10% additional complete resection rate in the series[9]. Up to the available evidence, the 4th Ovarian Cancer Consensus Meeting in Vancouver stated the aim of this type of surgery is complete resection[10]. Nevertheless, some series reported a survival benefit in patients with residual disease of 1 cm or more[11,12]. However, these findings were not significant or had other limitations like case mix including early relapse, surgery for palliative care, or remarkably low survival rates in patients with 1 cm and more residual disease. Furthermore, it was already shown that pre-operative factors like peritoneal carcinomatosis might be a negative predictor for complete resection, but this is not a prognostic factor if complete resection can still be reached[13].

Therefore, selection of eligible patients is important to avoid unnecessary surgical risks in patients in whom complete resection of the tumor could not be achieved. The DESKTOP I study evaluated the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score which could help to identify patients in whom complete resection is possible. Patients with complete resection at first surgery (if unknown, alternatively stage I/II), good performance status (PS) and absence of ascites were categorized as AGO score positive, and all others were scored negatively[14]. A subsequent prospective trial validated the AGO score successfully showing that a positive score could help to identify the possibility of complete resection in patients with platinum sensitive relapse in 76% of the patients[15]. However, survival advantages of additional surgery were still not shown in a randomized trial. But the results seem to favor surgery in addition to chemotherapy in eligible patients. The median survival of completely debulked patients ranges from 16 to 100 months. In contrast, the above mentioned chemotherapy studies did rarely report overall survival of 30 months or more.

Depending on the experiences and surgical capabilities, postoperative morbidity and mortality rates are varying, but complication rates in surgery for recurrent ovarian cancer are not significantly higher, compared to primary debulking surgery. The morbidity rate in a meta-analyses of surgery in recurrent ovarian cancer ranged between 0 and 88.8% with a weighted mean of 19.2%[9]. Thirty-three percent of patients had at least one complication in the postoperative period. In the DESKTOP II trial, the peri-operative mortality was 0.8%. Nevertheless, these data are most prone to be affected by selection and publication bias, since there is neither strict definition for morbidity, nor for the observed time after surgery.

A recent Cochrane Analysis investigated the value of cytoreductive surgery in addition to chemotherapy in patients with recurrent ovarian cancer. The authors did not identify eligible studies to answer this question[16]. Two prospective randomized trials evaluating the role of cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer are ongoing (AGO DESKTOP III, GOG 213).

Support of these studies is urgently needed to define the role of secondary cytoreductive surgery in patients with recurrent ovarian cancer.■

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9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

SESSION 2 SURGERY IN OVARIAN CANCER

Surgical Intervention in Relapsed Ovarian Cancer is Beneficial. Contra

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It is understandably difficult to argue against *belief*, and that is what the question posed in this debate is all about. Somehow, it is simply *known*, in the absence of evidence-based randomized 3 trial data that both primary and secondary surgical resection of ovarian cancer is beneficial. After all, that is what gynecologic oncologists have been trained to do, that is what they are taught, and that is the conclusion drawn from examinations of multiple reports dealing with *retrospective data*.

So, the question is what is wrong with this picture, and specifically in the setting of relapsed ovarian cancer?

As demonstrated by the landmark international neoadjuvant chemotherapy trial revealing the equivalence (with less highly clinically-relevant morbidity) of the neoadjuvant approach when examined in an *evidence-based trial* compared to primary surgical cytoreduction in advanced ovarian cancer, *retrospective data simply and unequivocally do not substitute for the conduct of such studies*[1]. As a result, all of the retrospective data in the world with their major inherent biases (discussed below) cannot compare to the results of one (or several) well-designed, conducted, analyzed, and reported phase 3 trial[2].

Further, an alternative hypothesis for any theorized benefits associated with *aggressive secondary surgical cytoreduction* undertaken by superbly trained and impressively technically skilled gynecologic oncologists can be provided by considering one (or more) of the following[3]:

1. *Selection bias* (Patients selected for such aggressive surgery have recognized or unrecognized favorable clinical factors, including less co-morbidity compared to patients unable to undergo such surgery.)

2. *More favorable biology* (Cancers able to be cytoreduced to microscopic residual or very small volume macroscopic cancer have an inherent biology that both permits the successful completion of such surgery and also identifies malignancies responsive to subsequently delivered anti-neoplastic drug therapy.)

3. *"Traditional" benefits associated with surgical removal/bypass of tumor masses* (Patients may simply benefit from the relief of bowel obstruction permitting improved nutrition while they undergo subsequent cytotoxic chemotherapy. However, in this specific situation the surgery is performed in well-defined clinical situations (e.g., bowel obstruction) and is not undertaken in all patients for the purpose of somehow favorably impacting survival independent this very direct effect).

Of course, all of this being said, it is theoretically possible that secondary surgical cytoreduction may favorably impact outcome in epithelial ovarian cancer *but* the definitive data are simply not currently available to prove this point. Further, it is also possible (perhaps "equally" so) that the phase 3 trials designed to address this question will reveal only limited (if any) benefit associated with such surgery in this clinical setting.■

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9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

SESSION 3 SYSTEMIC THERAPY IN OVARIAN CANCER: 1st LINE

Do We Have a New Standard in Suboptimal Debulked Disease?

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At present, newly diagnosed patients with advanced-stage high-grade serous cancers of ovarian, fallopian, or primary peritoneal origin are routinely evaluated for primary treatment, which incorporates cytoreductive surgery and chemotherapy using a combination of carboplatin and paclitaxel. Surgical stage remains the most important prognostic factor, and over 80% of newly-diagnosed patients will have FIGO Stage III-C or IV tumors. The second most important prognostic factor is the extent of residual disease after cytoreductive surgery, with the greatest difference between optimal microscopic disease (no visible residual) compared to optimal macroscopic or suboptimal residual disease. Among patients who undergo initial cytoreductive surgery, approximately 80% achieve optimal cytoreduction, including about 25% within the most favorable subgroup, microscopic residual. This leaves about 20% of patients with suboptimal residual disease.

However, with better imaging techniques, and the increased utilization of neoadjuvant chemotherapy (NACT) with interval cytoreductive surgery (ICS), the population of patients selected for primary cytoreductive surgery (PCS) has become more restricted, favoring patients with younger age, limited disease, small-volume ascites, and absence of comorbidities. As a result, older-age patients with more extensive disease, high-volume ascites, and medical comorbidities are more likely to receive NACT-ICS. In addition, there has been a trend for selection of patients to undergo more aggressive primary surgery, including upper abdominal procedures, such as resection of multiple hepatic, splenic and gastrointestinal metastases.

Taken together, these evolving clinical practices will tend to increase the rate of optimal cytoreduction in patients who are selected for primary surgery, leaving even fewer patients with suboptimal disease following primary surgery. Therefore, this presentation will focus on patients managed with NACT-ICS, as well as those with suboptimal disease after primary surgery.

Standards evolve as data from ongoing trials mature. The following considerations will be discussed from the perspective of existing data, clinical consensus, and biased recommendations:

- *Goals of treatment.* This is a population with extremely high-risk for recurrence, regardless of the outcomes of primary chemotherapy and cytoreductive surgery. As such, the goals of treatment are largely palliative, to improve disease-associated symptoms, delay recurrence, and maximize quality of life. From that perspective, it is important to minimize the risks associated with primary therapy, as there is no realistic chance of cure with currently available treatment options.

- *Selection of patients for PCS and NACT- ICS*. The target population for this presentation is similar, but not identical, to the patients enrolled on the EORTC randomized phase III trial that addressed the role of NACT. Due to the advanced disease status among patients enrolled on the EORTC trial, the median PFS and OS was poor, but with similar long-term outcomes on both treatment arms. Therefore, it is reasonable to consider both treatment approaches for patients with advanced-stage disease, including bulky tumor deposits, large-volume ascites, advanced physiologic age, and other comorbidities. Advantages associated with NACT include a potential reduction in perioperative morbidity related to venous thromboembolism, infection, transfusions, and wound healing, which are appealing in this population.

- *Utilization of intravenous (IV) or intraperitoneal (IP) chemotherapy*. Prior randomized studies have reported improved outcomes with IP chemotherapy in patients with optimal residual disease. While IP therapy is feasible in patients with suboptimal residual disease, data are awaited from ongoing randomized trials to determine if IP therapy has any advantage in this setting. At this point, IV chemotherapy would be standard for patients with suboptimal disease, but patients might also be considered for IP therapy after completion of NACT-ICS with small-volume residual disease, which is similar to the approach currently utilized in the ongoing NCI-CTG OV21 trial.

- *Incorporation of bevacizumab*. Results from ICON7 and GOG0218 suggest that incorporation of bevacizumab will improve PFS, particularly in patients with bulky high-risk disease. While ICON7 also suggests an improvement in median survival within the high-risk population, a survival advantage has not been observed on GOG0218, even though the majority of patients were enrolled with high-risk disease. A potential explanation for this apparent discordance between the two phase III trials includesnon-protocol crossover to commercial bevacizumab post-progression on the GOG trial (estimated at 30%), compared to essentially no crossover on ICON7. In addition, while bevacizumab was generally well-tolerated, all agents contribute to toxicity in this setting, and there was increased toxicity associated with concurrent chemotherapy and bevacizumab, compared to the extended monotherapy component. Finally, randomized phase III trials in the setting of platinum-sensitive and platinum-resistant recurrent

disease have also documented improved PFS with incorporation of bevacizumab. Taken together, it would be reasonable to plan primary therapy to consist of surgery and chemotherapy without bevacizumab, with utilization of bevacizumab in the setting of recurrent disease, when the benefit-risk ratio is maximized.

- *Choice of chemotherapy regimen*. All patients would begin with intravenous carboplatin and paclitaxel, as there is no regimen with demonstrated superiority. Dose-dense weekly paclitaxel is a strong consideration, based on the JGOG trial, and studies in recurrent breast and ovarian cancer also favor a weekly schedule of drug administration. However, utilization of 80 mg/m^2/week is associated with frequent dose reductions and delays, due to hematologic toxicity, and there is also a risk of cumulative neurotoxicity. Existing data do not support a dose-response relationship with either platinum agents or taxanes, within clinically-relevant dose ranges. Therefore, a dose of 60 mg/m^2/week might be preferred, but this has not been validated in a phase III trial.

- *Adjustment for physiologic age and comorbidities.* Most clinical trials of primary therapy have not enrolled a high proportion of older patients (above age 75), or patients with poor performance status and comorbidities. However, GOG and other groups have been exploring feasibility and optimized dosing for older patients with and without comorbidities. While single-agent therapy with carboplatin might be a consideration, there is a platelet-sparing effect from incorporation of paclitaxel, and this tends to minimize treatment delays due to thrombocytopenia. As a result, it would seem preferable to utilize both drugs. Until guidelines from ongoing trials are available, it is reasonable to utilize conservative dosing, such as carboplatin AUC=5 (adjusted for renal function) and paclitaxel 135 mg/m^2 every 3 weeks, or paclitaxel 60 mg/m^2/week.

- *Alternatives to standard platinum-based chemotherapy.* This is an important consideration for patients with high-risk disease, and requires further development in the context of clinical trials. Studies would be facilitated by collection of serial tumor specimens to define molecular patterns of treatment resistance, and utilization of functional imaging (CT, MRI, or PET) to provide an early indication of tumor response, to permit transition to alternative non-platinum chemotherapy regimens.

- *Novel clinical trial design*. Exploration of new treatment regimens would also be facilitated by the availability of an early biomarker that correlates with long-term clinical outcomes, such as the finding of pathologic complete remission during NACT of locally-advanced breast cancer. Currently, pathologic remission of advanced-stage high-risk ovarian cancer is very uncommon, and it would seem preferable to identify other markers during NACT, including functional imaging, CA-125 normalization, or findings at ICS.

In summary, with advances in selection of patients for cytoreductive surgery, and more aggressive surgical effort, there are fewer patients with suboptimal disease, and more patients with high-risk diseasethat are being considered for NACT-ICS. Standard therapy for this population is a biased recommendation, but should be NACT-ICS with weekly paclitaxel, using doses that are individualized, based on age, performance status, and comorbidities.■

9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

SESSION 3 SYSTEMIC THERAPY IN OVARIAN CANCER: 1st LINE

Current Situation and New Developments in IP Chemotherapy

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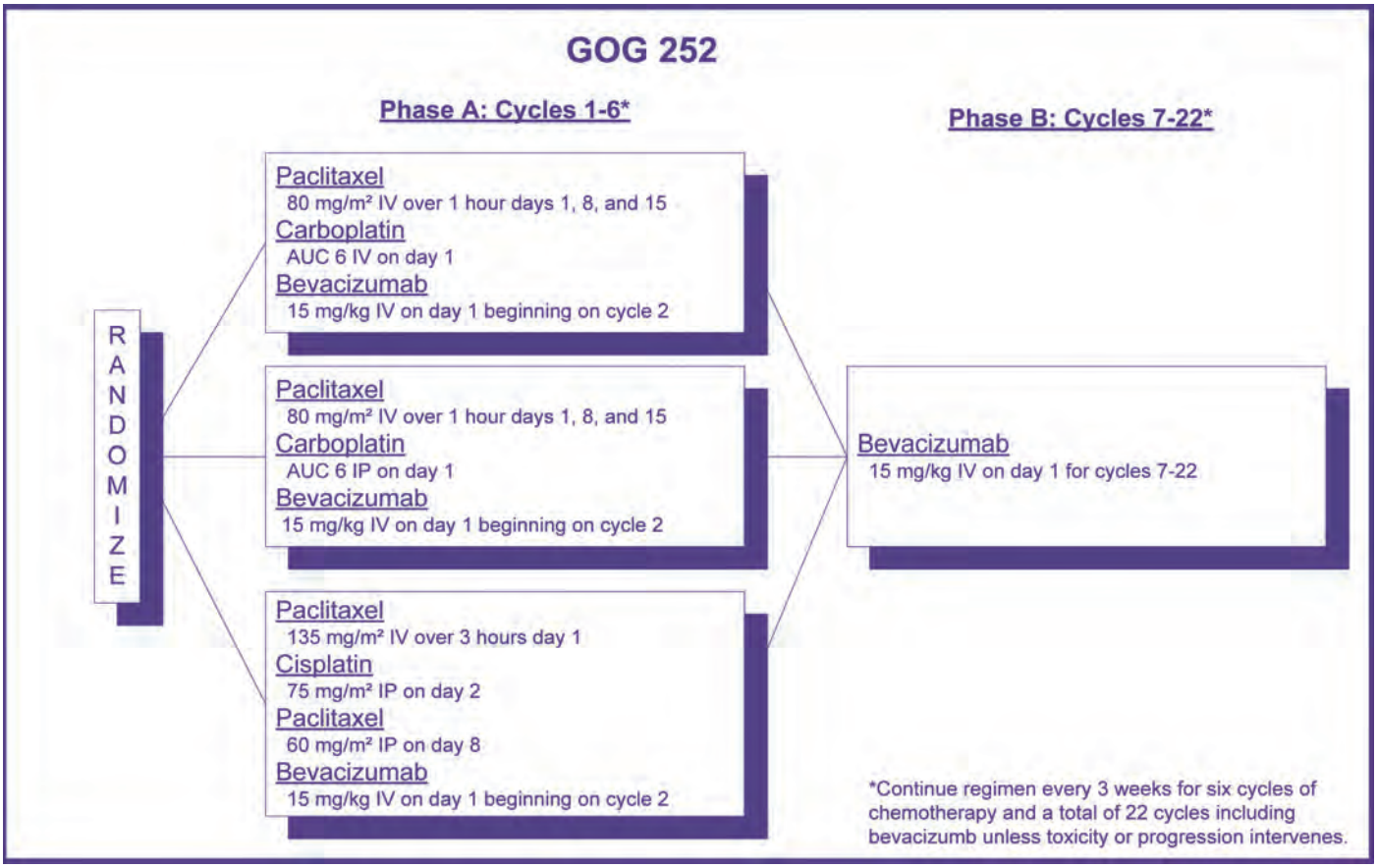
On January 5, 2006, the National Cancer Institute (NCI) released a clinical announcement concerning recommended treatment for advanced ovarian cancer. Based on the results of eight phase III clinical trials, the NCI encouraged the combination of intravenous (by vein) and intraperitoneal (directly into the abdomen) chemotherapy. The combined approach, though more toxic, extends overall survival for women with advanced ovarian cancer by about a year compared to intravenous delivery alone. The best survival reported was achieved with GOG 172 paclitaxel 135 mg/m2 IV with 24 hour infusion day 1, cisplatin 100 mg/m2 IP day 2, and paclitaxel 60 mg/m2 IP day 8 delivered on a 21 day cycle for six cycles. The IP arm overall survival was 65.6 months vs 49.7 months for the IV arm.

Further analysis IP chemotherapy was undertaken by Dr. Landrum and presented at the March 2012 Society of Gynecologic Oncology meeting in Austin Texas. She combined the data from GOG 114 and 172 both using cisplatin 100 mg/m2 in optimally resected Stage III epithelial ovarian cancer. For all IP patients median PFS was 24.9 months (95% CI, 23.0-29.2); the median OS was 61.8 (95% CI, 55.5-69.8). Significant predictors for PFS were identified as histology, surgical stage and size of residual disease. For all IP patients with no residual disease after cytoreductive surgery, median PFS was 43.2 months (95% CI, 32.5 -60.4) and median OS was 110 months (95% CI, 60.0-161.3). For GOG 114 and 172, IP patients with no residual disease had median PFS of 41.1 months (95% CI 24.2-54.6) and 60.4 months (95% CI 36.9- N/A) and median OS of 83.8 months (95% CI 60.1-161.3) and 127.6 months (95% CI, 84.7-N/A), respectively. Interestingly, the patients who did not have lymphadenectomy had a worse survival than either the women with negative or positive nodes. Recurrence in the abdomen was less likely in the IP arm. Age, histology, and size of residual disease were identified as important predictors of OS.

Following the establishment of IP chemotherapy as providing the best overall survival in optimally resected ovarian cancer, there have been two important clinical trial outcomes influencing treatment choices. GOG 218 studied the addition of bevacizumab to intravenous carboplatin and paclitaxel in suboptimally resected and stage IV patients, and demonstrated this addition during chemotherapy and continuing as consolidation for a total of 22 cycles decreased the onset of progression by approximately 6 months, with a hazard ratio of 0.71.

Another advance was reported by the Japanese GOG demonstrating improved progression free survival with paclitaxel IV weekly at 80 mg/m2 in combination with carboplatin at AUC of 6 administered IV every three weeks in comparison to every three week paclitaxel IV at 175 mg/m2 and carboplatin AUC 6. A hazard ratio of 0.71 in favor of dose dense paclitaxel with the progression free survival improved from 17.2 months in the control arm to 28 months in the experimental arm. The final survival results remain unreported, but preliminary results demonstrate improvement as well p= 0.03.

Due the combination of all these results, the GOG launched GOG 252, Phase III Clinical Trial of Bevacizumab with IV versus IP Chemotherapy in Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma. The control arm was the same as the Japanese GOG dose dense paclitaxel and carboplatin with the addition of bevacizumab cycles 2-22. Arm 2 was the same drug dose and schedule except the carboplatin was delivered by the IP route. Arm 3 was similar to the experimental arm of GOG 172 with the addition of bevacizumab. The doses were adjusted to allow for them to be delivered as an outpatient using paclitaxel 135 mg/m2 IV over 3 hours day 1, IP cisplatin 75 mg/m2 day 2, and IP paclitaxel 60 mg/m2 day 8 and repeated every three weeks for six cycles. Bevacizumab was administered at the dose of 15 mg/kg every three weeks on day 1 on cycles 2-22. This trial opened to enrollment on July 27, 2009 and closed after accrual of 1560 patients on Nov 30, 2011. The analysis of this trial awaits 360 events in the control arm.■


GOG 252
Phase A: Cycles 1-6*
Phase B: Cycles 7-22*
RANDOMIZE
Paclitaxel
80 mg/m² IV over 1 hour days 1, 8, and 15
Carboplatin
AUC 6 IV on day 1
Bevacizumab
15 mg/kg IV on day 1 beginning on cycle 2
Paclitaxel
80 mg/m² IV over 1 hour days 1, 8, and 15
Carboplatin
AUC 6 IP on day 1
Bevacizumab
15 mg/kg IV on day 1 beginning on cycle 2
Paclitaxel
135 mg/m² IV over 3 hours day 1
Cisplatin
75 mg/m² IP on day 2
Paclitaxel
60 mg/m² IP on day 8
Bevacizumab
15 mg/kg IV on day 1 beginning on cycle 2
Bevacizumab
15 mg/kg IV on day 1 for cycles 7-22
*Continue regimen every 3 weeks for six cycles of chemotherapy and a total of 22 cycles including bevacizumb unless toxicity or progression intervenes.

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9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

SESSION 3 SYSTEMIC THERAPY IN OVARIAN CANCER: 1st LINE

Update on Non-Serous Ovarian Cancer Trials

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Introduction

Among the epithelial cancer of the ovary, it has become a consensus that clear cell carcinoma (CCC) and mucinous carcinoma of the ovary is more resistant to chemotherapy and prognosis is worse than serous carcinoma[1,2]. Therefore, gynecologic trial groups have been conducting histo-type specific trials for these two entities. In this presentation, we discuss the updated status of trials that are ongoing, or under planning worldwide on non-serous ovarian cancer, particularly for clear cell and mucinous adenocarcinoma of the ovary.

Clear Cell Carcinoma

First-line Trials

JGOG3017 (Chemotherapy Trial)

The first histotype-specific clinical trial was the JGOG3017, targeting newly diagnosed clear cell carcinoma of the ovary, stages Ia to IV. In this trial, investigators try to find better cytotoxic chemotherapy regimens than current standard regimen of carboplatin plus paclitaxel (TC). The experimental regimen is irinotecan (CPT-11) plus cisplatin (CPT-P). Irinotecan is a topoisomerase-1 inhibitor and in a retrospective study the CPT-P regimen has shown activity in CCC[3]. The study opened in 2006 and closed for accrual in 2009 with 642 patients. The data will hopefully be matured in 2014.

Molecular Agent Trial

CCC has a molecular similarity to renal cell carcinoma. Also, there may be a possibility that those molecular targeted agents such as mTOR inhibitors or anti-angiogenesis compounds that have been used as therapeutics in renal cell carcinoma may be efficacious in CCC.

GOG268

Since more than 80% of the CCC of the ovary has shown activation of AKT-mTOR pathway, it is of great interest to explore the potential of mTOR inhibitors. GOG268 is an open label phase II trial for newly diagnosed stages III and IV CCC. Temsirolimus will be administered in combination with paclitaxel and carboplatin for 6 cycles, and then given as a single agent for 11 cycles as a maintenance therapy. In this trial, 45 patients will be enrolled from the US and another 45 patients will be enrolled from Japan. This sample size would give 80% power to detect an improvement in median PFS from 3 to 5 months at the 10% 1-sided level of statistical significance. Genetic differences in CCC will be compared between the two countries.

GOG254

GOG is now conducting a single arm phase II trial to evaluate the efficacy of sunitinib in recurrent CCC of the ovary. Sunitinib is an inhibitor of VEGFR and PDGFR tyrosine kinase. This trial opened in April 2010 and accrual of the first stage (24 patients) was completed in October 2012.

Nintedanib

SGCTG, NCRI, and NSGO are planning “A randomised phase II study of nintedanib (BIBF1120) versus chemotherapy in recurrent CCC of the ovary”. Nintedanib is a novel triple angiokinase inhibitor that inhibits VEGFR, PDGFR, and FGFR. In this trial platinum-resistant recurrent CCC will be randomized either to nintedanib 200mg bid until progression or one of the single agents pegylated liposomal doxorubicin (PLD), weekly paclitaxel, or weekly topotecan. Primary endpoint of this study is PFS. Moreover, OS, toxicity, response rate, and QoL will be evaluated.

JGOG3021/EVEROCC Trial

JGOG is planning a phase II trial of another mTOR inhibitor, everolimus, for recurrent CCC of the ovary. This is an open label single arm trial to examine whether everolimus will improve the clinical control rate (CR, PR, SD>8 weeks). An extensive translational research component will be incorporated in this trial.

Mucinous Adenocarcinoma

Mucinous adenocarcinoma is another rare entity of ovarian cancer, which has been known to be resistant to chemotherapy, when it is found in an advanced disease stage or in the recurrent disease setting[4]. It has been hypothesized that mucinous adenocarcinoma is not similar to serous adenocarcinoma, but similar to colon cancer[5]. Therefore, a number of trial concepts using chemotherapy regimen or molecular agents suitable to colorectal cancer have been proposed. However, due to the rarity of the tumor, it is extremely difficult to conduct the trial even with international collaboration.

mEOC Trial

To the best of our knowledge, mEOC/GOG241 is the only ongoing prospective clinical trial for mucinous adenocarcinoma. This is a GCIG Intergroup multicenter trial of open label carboplatin and paclitaxel +/- bevacizumab compared with oxaliplatin and capecitabine +/- bevacizumab as first line chemotherapy in patients with mucinous epithelial ovarian cancer. Eligible patients are newly diagnosed stages II to IV mucinous carcinoma of the ovary or fallopian tube, or recurrent stage I. Target sample size is 332, but the accrual is slow because of the rarity of the disease and/or availability of oxaliplatin and capecitabine for the ovarian cancer in the US.

Because of its rarity, there is no trial either ongoing or close to open for recurrent mucinous adenocarcinoma. Therefore, it is obvious that international collaboration is needed. Differences in regulatory mechanism or drug availability in different countries are hurdles to hopefully may be overcome in the near future.■

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9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

Valencia, Spain, 1st March 2013

SESSION 4 SYSTEMIC THERAPY IN OVARIAN CANCER: RECURRENT

Update on Randomized Trials on Recurrent Disease

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Introduction

The majority of patients with advanced ovarian cancer, especially those without an optimal upfront cytoreduction, will develop a relapse of the disease. Although surgery may be an option in selected patients, the majority of patients will be candidates for receiving systemic therapy in order to control the symptoms and prolong the time without progression.

During the last two decades, several concepts and trials have been evolved in order to guide therapy of recurrent patients. However, few categorical recommendations can be made in this scenario.

One of the essential concepts that should be highlighted is that the prognosis and probability of response to subsequent therapy is not identical for all recurrent patients, as it is influenced by the previous response to platinum-based first line of therapy and the elapsed time from the last dose of platinum until the relapse. Essentially, the longer the platinum-free interval, the better the response to a new platinum-based therapy. According to the 4th Ovarian Cancer Consensus Conference (4th OCCC)[1], patients with recurrent ovarian cancer should be classified according to the platinum-free interval in four categories: 1) Progression while receiving last line of platinum-based therapy or within 4 weeks of last platinum dose, 2) Progression-free interval since last line of platinum of less than 6 months, 3) Progression-free interval since last line of platinum of 6 to 12 months, 4) Progression-free interval since last line of platinum of more than 12 months. This classification in subgroups is especially necessary for the development of clinical trials for distinct subpopulations of patients.

A second important concept is that epithelial ovarian cancer is not a unique disease. Several distinct histological subtypes can be identified, with different molecular and genetic profiles, and different clinical behaviour patterns for some of them. Until recently, clinical trials in recurrent ovarian cancer have included all the different histological subtypes. However, new trials with targeted therapies have started to recruit patients with specific subtypes, for instance high-grade serous, low-grade serous or clear cell carcinoma.

Update on randomized trials with chemotherapy

During the last 15 years, several clinical trials have tried to define the optimal chemotherapy approach for recurrent ovarian carcinoma in the different scenarios, however, as mentioned above, few categorical recommendations can be made regarding a specific drug or regimen. In this section we expose the update of the most relevant trials and we try to clarify what is considered standard of care regarding chemotherapy and what are the options in the different situations with available drugs or strategies.

Chemotherapy in patients with a platinum-free interval of less than 6 months (platinum-resistant patients)

Several drugs have shown activity in phase II studies for patients with platinum-resistant disease. However, only a few of them, paclitaxel, topotecan, pegylated liposomal doxorubicin and gemcitabine have been shown to have enough activity in phase III trials, and have obtained the approval for their use in clinical practice. Although there is a clear evidence of efficacy, the results are not very impressive with an overall response rate ranging from 7% to 17% and a median overall survival no longer than 12 months in this specific group of patients[2]. For these reasons, to maintain quality of life is crucial in the management of this patient population. Combination chemotherapy has produced a higher proportion of responses, however the overall survival has not been improved and the toxicity was constantly higher, affecting the quality of life of the patients.

We can conclude that the treatment of this population is still an unmet medical need in which new approaches and strategies are required. In the absence of a clinical trial, a judicious sequential use of the available drugs and the selection of them based on the toxicity and clinical situation of the patient should be the standard clinical approach.

Chemotherapy in patients with platinum-free interval of more than 12 months (fully platinum-sensitive patients)

Two phase III trials, ICON-4 with paclitaxel-platinum and AGO-OVAR 2.4 with gemcitabine-carboplatin, and some small randomized phase II trials showed that a carboplatin-based combination was superior to carboplatin as monotherapy in platinum-sensitive patients (defined as a patient relapsing with a platinum-free interval longer than 6 months) in terms of progression-free survival and overall survival, this efficacy parameter was only observed in the ICON-4 trial. Based on these results the 4th OCCC, has stated that a platinum-based combination therapy should be the control arm for randomized trials in patients with platinum sensitive disease with a progression-free interval longer to 12 months.

Update on Randomized Trials on Recurrent Disease

Antonio González

A meta-analysis of individual patients included in 4 randomized trials involving 1300 patients has been presented recently[3]. Two trials compared paclitaxel-carboplatin versus carboplatin (ICON-4, GEICO-0199), one trial compared carboplatin-gemcitabine versus carboplatin (AGO-OVAR 2.4) and one trial compared carboplatin-PLD vs carboplatin (SWOG).

The progression free-survival (PFS) analyses were based on 1,167 events and it showed a highly statistically significant benefit of combination platinum chemotherapy (HR, 0.68; 95% CI, 0.57 to 0.81; p < 0.001). The overall survival (OS) analyses were based on 865 deaths and it also showed a statistically significant benefit of combination platinum chemotherapy on survival (HR, 0.80; 95% CI, 0.64 to 1.00; p = 0.05).

Additionally, there was no clear evidence of a difference in the relative effect of combination platinum chemotherapy on OS or PFS in patient subgroups defined by previous paclitaxel chemotherapy (p-values: OS = 0.49, PFS = 0.28); duration of platinum-free interval (p-values: OS = 0.86, PFS = 0.57); or number of previous lines of chemotherapy (p-values: OS = 0.21, PFS = 0.26).

Besides, the above-mentioned platinum-based combinations with paclitaxel and gemcitabine, a different combination of pegylated liposomal doxorubicin (PLD) and carboplatin was explored in the CALYPSO trial[4]. This large randomized non-inferiority trial included more than 900 patients with a platinum-free interval longer than 6 months and showed that PFS for carboplatin-PLD was statistically superior to paclitaxel-carboplatin (hazard ratio, 0.821; 95% CI, 0.72 to 0.94; P 0.005). Moreover, the combination of carboplatin-PLD had a different safety profile with significant less frequent grade 2 or greater alopecia (83.6% v 7%), hypersensitivity reactions (18.8% v 5.6%), and sensory neuropathy (26.9% v 4.9%), but a higher incidence of hand-foot syndrome (grade 2 to 3, 12.0% v 2.2%), nausea (35.2% v 24.2%), and mucositis (grade 2-3, 13.9% v 7%). An updated analysis of the CALYPSO trial, showed no significant differences in overall survival after a median follow-up of 49 months[5]. Median survival times were 30.7 months in the Carbp-PLD arm and 33.0 months in the Carbo-Paclitaxel arm, HR 0.99 (95% CI, 0.85-1.16).

In summary, patients with recurrent ovarian cancer after a platinum-free interval longer than 12 months should receive a platinum-based combination. As none of the combinations has been proven to be superior in terms of efficacy, the selection between the different combos of carboplatin, with paclitaxel, gemcitabine or PLD, should be based on residual toxicity of the patient, the expected toxicity of the combo and the desires of the patient.

Chemotherapy in patients with platinum-free interval of 6 to 12 months (partially platinum-sensitive patients)

Patients relapsing between 6 to 12 months after the last platinum based chemotherapy use to have a lower response to platinum than those considered fully platinum-sensitive (PFI > 12 months) and also a shorter PFS and OS. For this reason, different strategies beyond carboplatin-based regimens are under investigation in this group of patients.

One of these strategies is the use of non-platinum based regimen, based on the results of the OVA-301 trial[6]. This multinational, multicentre trial assessed the safety and efficacy of trabectedin plus PLD versus PLD alone in platinum-sensitive and platinum-resistant patients with recurrent ovarian cancer. The primary endpoint was PFS. Patients were randomly assigned to receive a 90-minute infusion of PLD 50 mg/m2 every 4 weeks (n = 330) or a 90-minute infusion of PLD 30 mg/m2 followed by a 3-hour infusion of trabectedin 1.1 mg/m2 every 3 weeks (n = 333). The groups were well matched for baseline characteristics, with 63-65% of patients classified as platinum-sensitive (PFI ≥ 6 months). PFS was 7.3 months in patients receiving the combination of PLD and trabectedin versus 5.8 months for patients who received PLD alone (HR 0.79; 95% CI, 0.65-0.96; p = 0.0190). Stratifying results according to platinum-resistant or platinum-sensitive status demonstrated that the benefit is observed only in platinum-sensitive patients.

A subgroup analysis showed that the group of patients with a PFI of 6-12 months obtained an increment in OS when treated with trabectedin and PLD than compared to PLD monotherapy. This difference was more evident when platinum was the next regimen used after the progression of the patient to the trial medication, raising the hypothesis that a prolongation of the platinum-free interval by a non-platinum based regimen could restore the platinum sensitivity and be beneficial for the patient[7]. This hypothesis is the background of the randomized clinical trial INOVATYON (INternational OVArian Cancer Patients Trial With YONdelis), which includes patients with recurrent OC and a PFI of 6-12 months and compares the combination of carboplatin-PLD followed by the regimen selected by the investigator at progression or trabectedine-PLD followed by a platinum-based regimen at progression.

Based on the above-mentioned sub-analysis the combination of trabectedine and PLD has been proposed as an alternative for patients with a PFI of 6-12 months.

Update on randomized trials with targeted therapies

Several targeted therapies are being developed in ovarian cancer. Two of them, anti-angiogenic therapy and homologous recombination deficiency, have been considered the most promising in the 4th OCCC. However, only bevacizumab, a monoclonal anti-body against VEGF is available in the clinical practice.

Bevacizumab has been studied in combination with chemotherapy in recurrent patients with platinum-sensitive (PFI > 6 months) and platinum-resistant (PFI < 6 months) disease.

The OCEANS randomized clinical trial explored the association of bevacizumab to backbone chemotherapy of carboplatin-gemcitabine and continued until progression in 484 patients with a recurrent ovarian cancer over 6 months after first line of platinum based chemotherapy[8]. Patients included had to have measurable disease; the primary endpoint was progression-free survival determined by RECIST progression. The association of bevacizumab increased the median progression-free survival from 8.4 months to 12.4 months (HR 0.48; CI 95% 0.34-0.60). Additionally, the response rate was also higher (78.5% vs 57.4%; P< 0.0001). The third pre-planned analysis of overall survival has not shown significant differences (33.4 with bevacizumab v 33.7 with placebo), and it has been explained more probably for the high rate of patients in the control arm receiving bevacizumab in subsequent lines. On the basis of these results bevacizumab was approved for the platinum-sensitive recurrent ovarian cancer by the EMA (European Medicines Agency).

AURELIA is a randomized clinical trial for platinum resistant patients with up to two previous chemotherapy lines, that has explored the association of bevacizumab to standard therapy selected by the physician between the following options: topotecan weekly or daily for 5 days, weekly paclitaxel or pegylated liposomal doxorubicin[9]. The association of bevacizumab has produced a significant increment in PFS from 3.4 to 6.7 months (HR 0.48; CI 95% 0.38-0.60). Overall survival analysis is expected for ASCO 2013.

In summary, two trials have confirmed the clinical value of adding bevacizumab to chemotherapy in patients with recurrent platinum-sensitive and platinum-resistant ovarian cancer. These results are the proof-of-concept of the value of anti-angiogenic therapy in this scenario. Additional anti-angiogenic drugs remain under study in the context of recurrent ovarian cancer.■

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SESSION 4 SYSTEMIC THERAPY IN OVARIAN CANCER: RECURRENT

Bevacizumab Should Preferably Be Used in Recurrent Disease: In Favor

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We have currently plenty of evidence about the activity of bevacizumab in the treatment of ovarian cancer patients when bevacizumab is added to standard chemotherapy and pursued in maintenance. Four randomized consecutive trials have reached their primary end-point, i.e. a progression-free survival (PFS) prolongation in the bevacizumab arm, either in first-line (GOG218[1] and ICON7[2]) or in recurrent disease (OCEANS[3] in platinum-sensitive and AURELIA[4]in platinum-resistant relapse).

The most debatable question today is thus not IF we should treat our ovarian cancer patients with bevacizumab, but WHEN. As bevacizumab is active both in first-line and in recurrent disease, it seems adequate to discuss now what the optimal setting for bevacizumab treatment is. In order to respond in the best way, we need to find answers to the following questions.

What are the treatment objectives in first line and in relapse?

The optimal setting of a new treatment will highly depend on what can be achieved by this new treatment and how it fulfills the main treatment goals expected by the community at the different timepoints during the course of the disease.

In first line, treatment tolerance is an important consideration, but the main treatment objective is to cure patients[5]. In relapse, however, cure is rarely achievable and the main treatment objectives are disease and symptom control[6].

Does bevacizumab increase the cure rate of patients with advanced ovarian cancer?

Globally, none of the 2 large trials of bevacizumab in first line (GOG218 and ICON7) has shown a significant overall survival (OS) benefit. There is still a debate on the possibility of bevacizumab to increase OS in a subgroup of patients in ICON7 trial, those with tumor residue over 1 cm after initial surgery (high risk group)[7]. More mature data will be needed to confirm the encouraging results of this interim OS analysis.

In platinum-sensitive relapse, again, OS is not significantly prolonged by the addition of bevacizumab to chemotherapy (OCEAN trial). OS is still too early in patients with resistant disease in the AURELIA trial.

Thus, there is currently no firm evidence that bevacizumab is able to increase the cure rate of ovarian cancer patients, the main objective of first-line treatments in OC patients.

Is the magnitude of disease control (progression-free survival) longer if bevacizumab is offered in patients in first line rather than in relapse?

If we stick to the primary analysis of PFS in the different trials, the absolute median PFS advantage of bevacizumab combined to chemotherapy and in maintenance compared to chemotherapy alone in first line was 3.8 months (GOG218, from 10.3 to 14.1 months with and without bevacizumab), and 1.5 months (ICON7, from 20.3 to 21.8 months). The median PFS benefit with bevacizumab added to chemotherapy seems to be greater in recurrent ovarian cancer, being 4 months in platinum-sensitive relapse (OCEANS, from 8.4 to 12.4 months) and 3.3 months in platinum-resistant disease (AURELIA, from 3.4 to 6.7 months).

The hazard ratios (HR) which have the advantage of comparing the Kaplan-Meier curves globally instead of median points suggest an even greater benefit of adding bevacizumab to chemotherapy in relapse rather than in first line. The HR are 0.71 and 0.81 for GOG218 and ICON7 in first line and 0.48 for both OCEANS and AURELIA trial in relapse.

Thus, the addition of bevacizumab to chemotherapy prolongs disease control in OC both in first line and in relapse. However, bevacizumab PFS advantage, expressed in absolute (months) as well as in proportion (HR) is more striking in relapse than in first line.

Treatment benefit has also to be evaluated in relationship with treatment duration. Does the ratio disease control (PFS) prolongation /duration of treatment prolongation with bevacizumab maintenance therapy favors the use of bevacizumab in first line?

To evaluate the disease control benefit of a new treatment, this benefit has to be compared with the costs needed to the patient for achieving it. Costs can be financial when the patient has to pay the drug and administration, but also costs for the patient can be evaluated in terms of duration of treatment, time without treatment and disease symptom and finally toxicity.

Bevacizumab Should Preferably Be Used in Recurrent Disease: In Favor

Eric Pujade-Lauraine

Maintenance therapy with bevacizumab increases the total duration of treatment which includes duration of chemotherapy and additional duration of treatment due to bevacizumab maintenance. Thus bevacizumab maintenance treatment is a supplementary burden for patients who would be otherwise free of disease symptom and of treatment if they were treated by chemotherapy alone without maintenance treatment.

To try to measure the treatment burden versus the benefit, we can calculate the ratio of bevacizumab maintenance treatment length/additional progression-free survival length achieved with bevacizumab therapy added to chemotherapy compared to chemotherapy alone. For instance, median time of maintenance bevacizumab treatment is equal to the median PFS of 14.1 months (shorter than the planned 15 months of treatment) to which you substract the chemotherapy treatment length arbitrary fixed at 5 months (median of 6 cycles) for a median maintenance treatment estimated of 9.1 months. PFS advantage for bevacizumab is 3.8 months. Thus the ratio length of maintenance BEV/PFS BEV benefit will be 2.39. This ratio means that patients in GOG218 will need to be treated 2.9 months in maintenance by bevacizumab to get a PFS benefit of 1 month. This ratio is 4.7 for ICON7, 1.85 and 0.52 for OCEANS and AURELIA respectively in relapse.

Thus, the ratio between the gain in disease control length compared to the length of additional treatment with Bevacizumab maintenance required to obtain this benefit favors again bevacizumab treatment at relapse.

Is bevacizumab toxicity increasing with tumor burden, which would favor the use of bevacizumab in first line after a debulking surgery?

Cross comparisons of toxicity between trials are difficult to perform as toxicity capture and report may vary from one trial to the other. However, table 1 shows the different toxicity of interest observed in the 4 bevacizumab trials. The incidence of the principal toxicities observed during bevacizumab treatment does not seem to vary significantly according to the patient has been treated in first-line or in relapse. The only variation noticed is the unexpected high incidence of grade ≥3 proteinuria and bleeding in the OCEANS trial, which was not observed in all the other trials.

In conclusion, bevacizumab prolongs disease control and delays the relapse. It has also been shown to significantly increase response rate to chemotherapy in relapse and is thus expected to improve the symptom relief in those patients suffering from their disease. These bevacizumab results fulfill the treatment objectives in patients with ovarian cancer relapse.

There is not yet, however, an absolute evidence that bevacizumab is able to increase the overall survival, ultimate goal of first-line treatment. An interim analysis gives a hope that this goal might be achieved in those patients with FIGO stage IV and FIGO stage III residual disease after initial debulking surgery.

Thus the current optimal strategy of bevacizumab administration would be to offer this drug combined with chemotherapy and in maintenance for poor prognostic stage III patients who did not achieve an initial complete resection in the hands of a trained surgeon or those with stage IV disease. For the others patients, the option of waiting the eventual relapse to propose bevacizumab cannot be excluded. In this setting, patients in relapse keep the absolute length of bevacizumab PFS benefit compared to first line, but with a shorter treatment and roughly similar safety.

However, AURELIA trial has shown that about 60% of the patients treated at first/second resistant relapse with chemotherapy alone are unable for various reasons (ileus, thrombosis, performance status) to receive subsequent bevacizumab treatment. Thus, if the patient has not been treated in first-line with bevacizumab, bevacizumab should be offered if possible at the first relapse.

This statement should be appreciated in light of the future results of overall survival data from ICON7 and AURELIA trials. In addition, trials are on-going evaluating longer period of treatment in first-line (BOOST trial evaluating 15 versus 30 months of bevacizumab treatment) or in relapse after first-line treatment (MITO16).■

Table 1: Toxicity of interest during bevacizumab treatment in first-line (GOG218 & ICON7 trials) and in relapse (OCEANS & AURELIA trials)

Adverse event n (%)	GOG218	ICON7	OCEANS	AURELIA
GI events	2.6 [a]	3 [b]	2.4[c]	4.4[d]
Hypertension	22.9 (gr≥2)	18 (gr≥3)	17.4 (gr≥3)	20 (gr≥2)
Proteinuria (grade ≥3)	1.6	<1	8.5	1.7
Thromboembolic event[e]	7.4	8	6.8	5.0
Bleeding (grade ≥3)	2.4	1	6.5	1.1
PRES	0.2	0	1	0.6

PRES = posterior reversible encephalopathy syndrome; gr: grade; [a]perforation, fistula, necrosis and leak grade ≥2; [b]perforation, fistula, abscess and wound-healing complications grade ≥3; [c] perforation, fistula and abscess all grades, wound-healing complications grade ≥3; [d]perforation and fistula/ abscess grade ≥2; [e]arterial any grade, venous grade ≥3.

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SESSION 4 SYSTEMIC THERAPY IN OVARIAN CANCER: RECURRENT

Bevacizumab Should Preferably Be Used in Recurrent Disease: Contra

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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 front-line 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. 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 this 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)[7]. 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] and patient reported outcomes have not shown improvements in quality of life with the addition of bevacizumab[16]. Importantly, both AUERLIA and ICON7 were not placebo-controlled trials creating a potential bias in evaluating both PRO and PFS.

So, since bevacizumab is active as a single agent, should it be used alone or in combination? Single agent use is clearly less toxic making single agent maintenance therapy with bevacizumab as part of front-line treatment attractive[1]. However, the choice of using it in the upfront treatment of EOC or at the time of recurrence should be based on the relative efficacy and safety. Apparently, front-line bevacizumab is safer and associated with greater improvements in PFS compared to use in the recurrent setting. One should not be tempted to use bevacizumab at the time of recurrence alone simply because the PFS hazard ratio (HR) for AURELIA and OCEANS (0.48) are greater than the PFS HR in GOG 218 (0.72) or ICON7 (.81). The absolute improvements in PFS (6 months when CA125 progressions are censored) associated with GOG 218 and the benefit in OS among stage IV patients in GOG 218 as well as among the high-risk subset in ICON7 are very provocative. Finally, bevacizumab can be used over and over again so front-line use does not preclude a benefit in the recurrent setting[16]. In fact, retreatment with bevacizumab in colorectal cancer has been shown to prolong survival by 19%, for a median of 1.4 months compared to a strategy of chemotherapy alone after progression on first-line bevacizumab (P=0.0062)[18].■

Study	Arms	Sample Size	Median PFS (months)	Hazard Ratio	P Value	Survival Advantage
GOG 218[6]	Arm 1 Carboplatin + Paclitaxel + Placebo	625	10.3 12.0 ∞			
	Arm 2 Carboplatin + Paclitaxel + Bevacizumab + Placebo	623	11.2	.91	0.16	No
	Arm 3 Carboplatin + Paclitaxel + Bevacizumab with maintenance (total 15 months)	625	14.1 18.0 π	.72 0.65 π	<0.0001 <0.0001 π	Stage IV
ICON7[7]	Arm 1 Carboplatin + Paclitaxel	764	17.3 α			
	Arm 2 Carboplatin + Paclitaxel + Bevacizumab with maintenance (total 12 months)	764	19.0 α	0.81	0.004	"Patients at high risk for progression"
AURELIA[8]	Arm 1 Chemotherapy*	182	3.4 α			
	Arm 2 Chemotherapy* + Bevacizumab	179	6.7 α	.48	0.001	No
OCEANS[9]	Arm 1 Carboplatin + Gemcitabine + Placebo	242	8.4 α			
	Arm 2 Carboplatin + Gemcitabine + Bevacizumab until progression	242	12. 4 α	0.48	<0.0001	No

PFS = Progression-free survival
π = Increased CA125 levels censored
α = Response Evaluation Criteria In Solid Tumors (RECIST)
** = Weekly paclitaxel, topotecaen, or pegylated liposomal doxorubicin*

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9th International Symposium

Advanced Ovarian Cancer: Optimal Therapy. Update

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SESSION 5 NEW DEVELOPMENTS

Targeted Therapies and Clinical Trials

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Multimodality management including surgery and systemic and intraperitoneal drug therapies is the mainstay for improving outcomes for patients with ovarian cancer. These interventions provide demonstrated benefits to patients. In addition, these interventions create opportunities for incorporating translational research evaluating the histological and molecular features of patients' cancers and the specific impact of current and novel treatments. Knowledge of the molecular alterations that drive ovarian cancer will hopefully lead to therapeutic strategies of greater benefit to individual patients.

The evaluation of experimental therapeutics in ovarian carcinoma increasingly is directed at molecular characterization of the tumor and host. With this knowledge, specific targeting of oncogenic and host immunological pathways is possible. Clinical trials are evaluating novel agents targeting tumor and host stromal and immunologic elements as single agents and in combinations. The clinical trials testing these interventions stratify patients based on histological and molecular features to evaluate the impact of treatment on both clinical and molecular outcomes.

Epithelial ovarian tumors have been broadly classified into two distinct groups with unique histological, clinical and molecular profiles. Type I tumors have low grade serous, clear cell, endometrioid, and mucinous histologies. These tumors are often indolent, less likely to metastasize and less sensitive to standard chemotherapy. BRAF and KRAS somatic mutations are relatively common in these tumors. HER2 gene amplification and protein overexpression was observed in 14% of ovarian clear cell carcinomas, suggesting that this may constitute a potential therapeutic target for a subgroup of these tumors[1]. Type II tumors are high grade serous, high grade endometrioid, poorly differentiated ovarian cancers and carcinosarcomas. These tumors are often widely metastatic at the time of presentation. Genomic instability is common in high grade serous ovarian tumors. TP53 is altered in over 90% of the cases. Somatic mutations are uncommon and gene amplifications are far more common. Germline mutations in BRCA1/2 occur in 10–20% of high grade ovarian cancers[2]. Somatic alterations in BRCA1/2 and other genes associated with DNA repair are seen in approximately 50% of high grade ovarian cancers[3] and tumors with a 'BRCAness' molecular profile are relatively sensitive to treatment with DNA damaging agents cisplatin and PARP inhibitors[4]. Epigenetic deregulation is more prominent, and ovarian cancers are replete with such aberrations that repress tumor suppressors and activate proto-oncogenes.

Chemotherapy will continue to play an important role for the foreseeable future; however, molecular targeted agents, on an individualized basis, will become increasingly important. Molecular profiling is available to help prioritize treatments in certain cancer setting and will be increasingly utilized to stratify patients for treatment trials. Currently, the most common 'actionable' alterations with potential for small molecule targeted therapy in ovarian tumors are in the PIK3CA/PTEN and KRAS/BRAF signaling pathways and inhibitors to components in the DNA damage repair pathway such as PARP inhibitors. Targeted delivery of cytotoxic therapy to tumors over expressing surface receptors such as HER2 as has been demonstrated with T-DM1 in HER2 amplified breast carcinoma[5] is also of interest. Epigenetic therapies are emerging as promising agents for resensitizing platinum-resistant ovarian cancers. These drugs may also have the potential to alter epigenetic programming in cancer progenitor cells and provide a strategy for improving therapy of ovarian cancer[6].

In the search for additional effective treatments for the management of recurrent disease, researchers have focused on the potential usefulness of immunotherapeutic modulation to stimulate antitumor host responses. There are now demonstrated benefits for a number of immunotherapeutic approaches in certain disease settings that may be applicable to ovarian cancer patients. These include tumor cell based vaccines in prostate cancer and anti-CTLA4 and PD1 antibodies in melanoma[7,8,9]. With evidence that ovarian cancers are immunogenic tumors[10], immunotherapy should be further pursued and optimized. The advances in knowledge of tumor immunity and laboratory and clinical procedures in cellular immunotherapy, along with the development of effective immune modulatory approaches, create new opportunities in ovarian cancer therapeutics.

There are thus considerable opportunities to incorporate and evaluate novel approaches into the current standard multimodality treatment of ovarian cancer, combining classical cytoreductive surgery, (neo) adjuvant chemotherapy, immunotherapy and/or targeted therapy. The challenge for the ovarian cancer research community is to continue to design and execute these trials to provide robust answers to both clinical and biomarker research questions. This presentation will selectively highlight novel targeted therapy trials under evaluation in clinical trials.■

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SESSION 5 NEW DEVELOPMENTS

Patient Reported Outcome in Clinical Trials

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A "patient reported outcome" (PRO) is defined by the USA's Federal Drug Agency as the "measurement of any aspect of a patient's health status that comes directly from the patient without the interpretation of the patient responses by a physician or anyone else"[1]. The term "PRO" is fast eclipsing "quality of life" in the health lexicon as an all-encompassing term for a wide range of possible impacts of disease and treatment on a patient's welling being. Just like the term "health-related quality of life" (HRQOL), it encompasses symptoms of disease, side-effects of treatment, anxiety, depression, and various aspects of functioning (e.g. physical, role, social, sexual). In the UK, the slight variant "patient-reported outcome measure" (PROM) has emerged, and is used for the same purpose. These terms, PRO and PROM, solve the intractable problem of coming up with a standard definition of quality of life that fits all purposes, but still acknowledge and respect the centrality of patients' perceptions to good health care, policy and research. Examining and measuring the patient's subjective experience in prospective comparative effectiveness research (CER) is now considered essential to informing clinical decision making and health policy[2]. Regulatory authorities such as the FDA and EMEA routinely consider evidence from PRO's in the evaluation of treatment benefit and have provided guidance to Industry on how to use PRO's to support labelling claims[1,3]. There is a great deal of science involved in producing good quality PROMs and there are a number of key issues to be considered in the development of PROMs[4]. There are also many challenges in the good conduct of PRO research, including how PROMs are selected, evaluated, analysed and interpreted[5,6].

PROMs provide the means to validly and reliably quantify subjective information provided by patients in response to specific questions using carefully developed and rigorously validated instruments. There are many instruments to choose from. There is no "right" PRO measure in any absolute sense; one needs to carefully select the best measure for any particular clinical trial from available candidate measures[7,8]. Here, the "best" questionnaire is the one that best matches the specific aims and objectives of the study. This in turn depends on the expected effects of interventions under study on the target patient population.

PROs have long been included in clinical trials, but their value and importance is now more widely appreciated and accepted. As a consequence, the methods used to collect, analyse and report PRO data are receiving greater scrutiny. Rather than simply adding an instrument to measure HRQOL as afterthought in clinical trials, there needs to be a close dialogue with QOL experts and experienced statisticians during the design and planning phase of the clinical trial in order to select the most appropriate instruments for the study as well as involving them in the development of a statistical analysis plan in order to generate meaningful patient centred outcomes data. The results of PRO data analyses are commonly only briefly mentioned in the primary publication of clinical trials of ovarian cancer or included in an on-line appendix or published in a different journal with a lower impact factor, at a later date, or perhaps not published at all. Given the importance of PRO's, the results should ideally be included in detail in the primary publication or in a companion paper in the same journal.

Brundage et al recently raised important concerns on the standard of reporting HRQOL in clinical trials which all clinical researchers should take note of[9]. The authors carried out a systematic review of 794 randomised trials undertaken between 2002-2008 that reported HRQOL across a range of medical conditions and found that only 56% provided a rationale for the selected outcome measure, 50% provided a HRQOL hypothesis, 28% provided information about missing data and 36% did not discuss HRQOL findings in the context of other trial outcomes[9]. It is unlikely that the reporting of HRQOL in clinical trials of ovarian cancer is significantly different or any better and the ovarian cancer research community need to take up the challenge to improve the design and reporting of PRO's in clinical trials. It is worth noting that this group have developed a CONSORT (Consolidated Standards of Reporting Clinical Trials) - PRO extension statement that should improve the reporting of PRO data from clinical trials[10]. This should be published soon and will be of particular value and interest to all clinical trialists as well journal editors.

Instruments to measure HRQOL

HRQOL is a complex multidimensional construct with a range of conceptual definitions[11]. There is wide agreement that HRQOL assessment should include the core domains of physical, social and emotional functioning or wellbeing, as well as a number of disease-related or treatment-related symptoms such as pain, fatigue and nausea. Some PROMs cover only symptoms which are often the main reason for administering treatment. Comprehensive coverage of the symptom experience includes three aspects: prevalence, severity and distress[5]. A symptom assessment tool should also be easy to understand and complete, must be reliable and valid for the symptoms it is supposed to measure and ideally present minimal burden to patients and clinical research staff.

The recent effectiveness guidance document on PRO's developed by the Center for Medical Technology Policy recommended 5 PRO measures: the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire, QLQ-C30; the Functional Assessment of Cancer Therapy - General (FACT-G) FACT-G; M. D. Anderson Cancer Centre's Symptom Index (MDASI); PRO-CTCAE; and the Patient Reported Outcome Measurement Information System (PROMIS)[12]. These are all quite general and the authors made the point that the measure selection should be based on the needs of the study, the psychometric properties of the PRO measure and the characteristics of the population. The EORTC and the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system are both modular systems, such that the general issues covered by QLQ-C30 and FACT-G, respectively, can be augmented by site- and/or treatment-specific modules. Both EORTC and FACIT have developed ovarian cancer-specific modules, and because these are often used in clinical trials, they are briefly reviewed below, along with the core module of each suite.

The FACT-O, like all the FACIT measures, starts with the 27 items of the FACT-G version 4[13]. These cover the four well-being domains: physical, functional, social/family and emotional well-being. The FACT-O also contains 12 additional concerns specific to ovarian cancer. The recall period is "the past 7 days", and all items are rated on a 5-point Likert scale: 0 = "not at all", 1 = "a little bit", 2 = "somewhat", 3 = "quite a bit", 4 = "very much". The scoring algorithm allows for 8 summary scales: the four core subscales, a subtotal of the 27 core items, a subtotal of the 12 ovarian-specific additional concerns, a grand total of the 39 items, and a trial outcome index (sum of the 17 physical and functional wellbeing items plus the 12 ovarian-specific items)[14]. The FACIT ovarian cancer symptom index (FOSI) is a subset of 8 items from the FACT-O[15,16]. The general FACIT scoring algorithm is to simply sum component items within a scale, after reversing negatively phrased items, such that a higher score represents better wellbeing or function and less symptom burden.

It is interesting to note that the item pool for the FACT-O was developed through semi-structured interviews with five gynaecological oncology nurses and 17 ovarian cancer patients with a range of disease severity with subsequent review by an expert panel at the GOG meeting in 1995[5]. The FACT-O was subsequently found to be a reliable and valid assessment of quality of life of women with ovarian cancer in a study of 232 patients at MD Anderson Cancer Centre[17]. However, it should be noted that the study items are quite general and may not fully reflect all the disease specific symptoms that patients experience. The validation study included patients with both early and advanced ovarian cancer and almost half were having routine surveillance while most of those on chemotherapy were having first line chemotherapy. The instrument was not specifically developed or validated in women with platinum resistant recurrent ovarian cancer who are the most symptomatic subset of patients. In an effort to better capture symptoms in women with advanced ovarian cancer, the FACT-O has been modified to the Ovarian Symptom Index (FOSI) which is a subset of 8 of the FACT-O items[15], and the NFOSI-18 is a subset of 18 of the FACT-O items[18].

The EORTC QLQ-C30 version 3 is a widely used measure of HRQOL in oncology and is extensively validated[19]. It contains 30 items which assess five domains of functioning (physical, role, emotional, social, cognitive), global HRQOL, and nine symptoms which commonly occur in cancer, regardless of primary site (pain, fatigue, nausea, vomiting, constipation, diarrhea, dyspnea, problems with sleep, appetite). It is complemented by the EORTC's ovarian cancer module, QLQ-OV28, which contains 28 items which assess body image, sexuality, and attitude to disease/treatment, abdominal/gastrointestinal symptoms, peripheral neuropathy, hormonal/menopausal symptoms, and other chemotherapy side-effects[20]. Summary scales for both questionnaires are based on the average of the component items, rescaled to a 0-100 range. For global HRQOL and functioning scales, a higher score reflects better functioning and HRQOL, while for symptom scales, a higher score reflects greater symptom burden. Subsequent analysis supported its validity as a supplement to QLQC30 in terms of both clinical and psychometric measures[20].

It is noteworthy that neither the QLQ-C30 nor the FACT-O were specifically developed and validated in patients with platinum resistant recurrent ovarian cancer, where the aim of treatment is symptom benefit and palliation. These instruments have been widely used in ovarian cancer clinical trials, including studies of patients with recurrent ovarian cancer where the symptom burden may be high, but they have not detected any differences or improvements in HRQOL in patients with recurrent ovarian cancer with the exception of the Calypso study[21] which only included platinum sensitive patients. Potential explanations for a failure to demonstrate differences in HRQOL include a true absence of any differences or improvements in HRQOL with treatment, or alternatively that the instruments developed to measure global HRQOL are unable to capture symptom improvement. These instruments measure a wide range of issues, such as pre-existing side effects of prior therapy, menopausal symptoms, body image and sexual functioning as well as some symptoms. Given standard scoring algorithms of these instruments, the impact of symptoms specific to recurrent

ovarian cancer may be diluted by being combined with various other QOL-related issues (FACT) or dissipated by being split into numerous scales (EORTC).

The 3rd Ovarian Cancer Consensus meeting concluded that objective response rates and progression free survival alone were inadequate endpoints of treatment in patients with platinum resistant ovarian cancer and recommended the development of a specific instrument to measure symptom benefit that could be used in clinical trial[22]. In 2010, the 4th Ovarian Cancer Consensus meeting emphasized the need for the development and validation measures of clinical benefit endpoints in clinical trials, including HRQOL and, more generally, patient-reported outcomes[23]. The Symptom Benefit working group was established under the auspices of the Gynecologic Cancer Intergroup (GCIG) to address the recommendations of the 3rd Ovarian Cancer Consensus meeting and has developed an instrument called MOST (Measure of Ovarian Cancer Symptoms and Treatment Concerns). It comprises 35 items. The first 15 items relate to disease symptoms, identified in a study of 126 patients with platinum resistant recurrent ovarian cancer. A further 17 items deal with adverse effects of treatment. Each of these 32 symptoms is rated over a recall period of "the last 3-4 weeks" (reflecting the typical time between cycles of chemotherapy) on an 11-point numeric rating scale, from 0 = "no trouble at all" to 10 = "worst I can imagine", with intermediate verbal anchors at 2 = "mild", 5 = "moderate" and 8 = "severe". Pending psychometric analyses, we envisage two symptom index style summary scales: one based on the average of the 15 disease symptoms, the other on the 17 adverse effects of treatment. The MOST also contains 3 items that assess wellbeing: physical, emotional and overall, on a scale from 0 = worst possible to 10 = best possible, also "in the past 3-4 weeks". These 3 items will be reported individually. This instrument is currently undergoing validation in stage 2 of the GCIG Symptom Benefit Study. The aim is that this instrument will offer both clinical utility and statistical efficiency in capturing changes in symptoms over time as well as the adverse effects of treatment. The two symptom index scales are intended to provide statistically efficient PROMs for clinical trials.

Recommendations for Incorporating PRO's into Clinical Trials and Clinical Comparative Research

The Center for Medical Technology Policy (CMTP) has developed a detailed effectiveness guidance document (EGD) on incorporating PRO's into clinical comparativeness research in adult oncology (http://www.cmtpnet.org)[12]. This was published online in May 2012 and has been well summarised by Basch et al in the December 1 2012 issue of the Journal of Clinical Oncology[24]. Significant effort and extensive consultation went into developing this guidance document with input from many individuals and organisations. The purpose of the document is to provide clear recommendations and guidance to clinical investigators on the appropriate inclusion of PRO measures and how they should be incorporated into prospective CER and is essential reading for all involved in clinical trial research. The ultimate aim is to provide good evidence and reliable data that reflects the patient experience. The FDA has also developed a separate PRO guidance document entitled "Patient Reported Outcomes Measures: Use in Medical Product Development to Support Labelling Claims" which provides information regarding what is required if PRO's are going to be used to support a US labelling claim[1].

Fifteen specific recommendations were made in the CMPT-EGD which are divided into 3 categories including: 1. Selection of Measures, 2. Implementation Methods and 3. Data Analysis and Reporting. The reader is directed to the excellent review paper by Basch et al as well as the full guidance document for full details[12,24].

The purpose of the EGD is to better align the design of clinical research with the information needs of patients, clinicians and funding agencies and the guidelines are intended to set a minimum standard to ensure that studies directly measure the patients reported experience. They make the point that patient subjective experience constitutes information that is essential to any study investigating a specific treatment or intervention and that PRO's add value to clinical research and clinical care. PRO data is more reflective of underlying health status than clinician reporting and provides meaningful clinical outcomes including survival and treatment adverse effects. QOL experts and statisticians should be included early and be involved in the study design. They should select the most appropriate instruments based on the primary and secondary aims of the study and develop a power calculation for the key patient reported endpoints as well as a plan for analysing and reporting missing patient reported data, which is a common problem. There should be a concerted effort to engage patients and clinical trials research staff and all participating clinicians and impress them of the importance of collecting PRO data to limit the amount of missing data.

Traditionally, analyses of PRO data have focused on comparisons of means between study arms, but there may be better ways to analyse the results. For example, reporting on the proportion of patients experiencing a specific change from

baseline at a predetermine time point may be a more meaningful way to look at the results. The EGD also suggests that an analysis of the cumulative distribution of responses (i.e. the proportion of patients who experience very magnitude of change in a specific measure at a time point of interest compared with baseline) be included in the statistical analysis plan. This would be particularly useful in studies of symptomatic patients with recurrent ovarian cancer where the aim of treatment is palliation. This would enable the spectrum of response across the study population to be reported and both improvements and decrements in scores from baseline will be very helpful in evaluating the impact of treatment.

Lessons to be learned regarding using PROMs in clinical trials in other cancers

A recent study comparing the quality of life and in patients with metastatic pancreatic randomised to either FOLFIRINOX or gemcitabine is particularly pertinent as there are many parallels with patients with platinum resistant recurrent ovarian cancer with respect to symptom burden and survival and the methodology used could be used in clinical trials in recurrent ovarian cancer studies[26]. The combination chemotherapy was associated with significantly more toxicity than gemcitabine but there was no difference between the treatment arms for EORTC QLQ-C30 domains, with the exception of diarrhoea which was worse in the combination arm. It is not unusual to find no or minimal differences between the treatment arms when overall quality of life is compared in clinical trials. However, the investigators also looked at the Time until Definitive Deterioration (TUDD) defined as a decline of 10 or 20 points on each QLQ-C30 scale. Importantly, they measured QOL every 2 weeks until progression and frequent measurement is important when trying to assess the impact of treatment on symptoms. They showed that TUDD was significantly greater for the combination arm for Global Health Status (GHS), physical role, cognitive and social functioning as well as 6 symptom domains (fatigue, pain, nausea and vomiting, dyspnea, anorexia and constipation). This was particularly well demonstrated in a Kaplan Meier plot for TUDD > 20 points on the GHS scale (HR 4.7, CI 2.3-9.5)[25]. This is a very informative way to graphically compare treatments and a good approach to analyse PRO data, particularly when the aim is to assess symptom benefit and the impact of treatment on various aspects of QOL. Similar approaches have been used in evaluating chemotherapy in lung cancer studies[26] and provide good examples for how to design and analyse the results of studies of palliative chemotherapy in populations of patients who are very symptomatic and have a relatively short survival.

Conclusions

There is general agreement and acceptance of the importance of HRQOL in clinical decision making as well as for comparative effectiveness research and informing health policy. Although HRQOL and PROMs are commonly included in ovarian cancer clinical trials and may be the most important outcome in some studies, there are still problems and inconsistencies with how the data are analysed and reported which could be avoided and improved with relatively little additional effort at the time of protocol development. This has important clinical and ethical implications which have been well expressed by Calvert et al who wrote “the ethics of enrolling a substantial number of patients in clinical trials in which HRQOL is recognised as an important outcome, yet is reported in a way that is ineffective in advising patient care or health policy is questionable”. There are now guidance documents available that detail what is required to improve the assessment of PRO’s is adult oncology as well a new CONSORT-PRO extension group that will soon publish the recommendations and guidance on HRQOL reporting for studies in which HRQOL is an important primary or secondary outcome.■

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SESSION 5 NEW DEVELOPMENTS

New Outlook for the Future

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Summary

In the next 5 – 10 years the treatment of ovarian cancer is set to undergo rapid changes based on a better appreciation of approaches targeting the tumour microenvironment as well as specific subtypes of the disease, with distinct molecular aberrations. Targeting the VEGF pathway through bevacizumab is already shown to be clearly effective, with positive randomized trials at all disease stages; targeting defective homologous recombination repair pathways with PARP inhibitors is also proving successful in a substantial proportion of patients with high grade serous ovarian cancer. The potential certainly exists for targeting other pathways and receptors which may be activated in ovarian cancer, including the RAS/RAF/MEK and PI3K/AKT/mToR pathways, the ErbB and IGF family of receptors, mitotic check points and also the folate receptor. Here, there may be a role for single agent therapy in selected cases but the way forward should include combination treatments aimed at dealing with the key problem of cytotoxic drug resistance, and rational approaches to patient selection will become an essential component of future strategies.

A look to the future

Angiogenesis inhibitors

Vascular Endothelial Growth Factor (VEGF) is a key mediator of angiogenesis, a process that is important in ovarian cancer growth and metastasis. Randomized phase III clinical trials of bevacizumab, a monoclonal antibody against VEGF-A, have shown significant clinical activity in epithelial ovarian cancer in 3 distinct scenarios: first line therapy, platinum-sensitive relapsed disease and platinum-resistant recurrent disease[1-4].

The main limitations of bevacizumab, apart from cost, are toxicities (eg. bowel perforation, hypertension) and resistance to treatment. The key challenges to address next therefore include 1) how to select which patients will derive most benefit and at which point during the treatment pathway? 2) how to overcome resistance to bevacizumab? At present, there are no validated biomarkers predicting clinical efficacy following bevacizumab in ovarian cancer although studies investigating gene expression arrays and isoform-specific plasma VEGF-A measurements are ongoing. Resistance mechanisms include the upregulation of alternative pro-angiogenic signaling pathways (Fibroblast growth factor (FGF), platelet-derived growth factor (PDGFR), c-Met) and have raised the question of whether targeting additional pathways will be a successful strategy. Several tyrosine kinase inhibitors that target VEGF receptors also inhibit other pro-angiogenic molecules eg. FGF- nintedanib, brivanib, dovitinib; PDGFR- cediranib, pazopanib; c-Met- cabozantinib and are under investigation in various randomized trials (first or second line) in ovarian cancer.

Trebananib (AMG 386) is a peptide-Fc fusion protein which prevents interactions between angiopoetin-1 and 2 expressed on vascular endothelial cells and the Tie2 receptors, thereby inhibiting vascular maturation and reducing the impact of VEGF stimulation. In clinical trials so far, trebananib is administered weekly in combination with chemotherapy and as maintenance therapy. Efficacy seems to be dose-dependent and the toxicity profile appears to differ from bevacizumab: peripheral oedema, presumably due to disruption of the angiopoetin axis, is common, whereas hypertension and proteinuria are not seen[5]. Current randomized trials in first-line and recurrent disease will address the future role of AMG 386 as an alternative to bevacizumab, or in the context bevacizumab resistance. Overall the use of “vertical or horizontal” combinations of antiangiogenic agents will be an area of increasing research in future years[6].

There are a number of novel antiangiogenic targets with potential clinical relevance, including Zeste homolog 2 (EZH2) and the Notch/Delta-like ligand 4 (Dll4). EZH2 has been linked to increased angiogenesis through methylation and silencing of the antiangiogenic factor, vasohibin 1. Preclinical studies have shown that silencing of EZH2 using siRNA inhibits angiogenesis and ovarian cancer growth[7]. Dll4 has been associated with poor outcome following anti-VEGF therapy and RNAi-mediated silencing of Dll4 has been shown to reduce angiogenesis and tumour growth in ovarian cancer models[8]. This approach appears promising and a phase I clinical trial of REGN 421, a monoclonal antibody against Dll4 is underway.

PARP inhibitors

PARP inhibitors exploit the concept of “synthetic lethality”- targeting one of the genes in a synthetic lethal pair, where the other is defective (eg. BRCA mutation), selectively kills tumour cells while sparing normal cells thereby creating a substantial therapeutic window[9]. Patients harbouring mutations in *BRCA1/2* were predicted to be highly susceptible to treatment with PARP Inhibitors and this proof of concept was supported in initial phase I and phase II studies of olaparib in patients with germline *BRCA1* or *BRCA2* mutations with recurrent ovarian cancer with response rates (RECIST and/

or GCIG) of over 50% according to prior platinum sensitivity[10,11]. A wider utility of this approach was envisaged in view of the fact that up to 50% of high-grade serous, sporadic ovarian cancers have defective homologous recombination repair pathways (including BRCA methylation and somatic BRCA mutations) which may confer sensitivity to PARP inhibition. Efficacy was indeed confirmed in a Phase II study of olaparib in this patient population although responders were mainly seen in those with platinum sensitive disease with a response rate of 50%[12]. This was further explored in a double-blind, placebo- controlled randomized phase II study in which patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer were randomized to either olaparib or placebo maintenance therapy[13]. PFS was significantly prolonged with olaparib compared to the placebo arm (median, 8.4 months vs. 4.8 months; HR 0.35, P<0.001), although an initial analysis indicated that this was unlikely to translate into an overall survival benefit. The possibility exists that although PARP inhibitors may delay disease progression, treatment could subsequently impact on response to further chemotherapy. However, an analysis of post olaparib chemotherapy in patients with germ-line BRCA mutations indicates that sensitivity at least in this population appears to be maintained[14].

The impact of PARP inhibitors may in fact differ according to the BRCA mutation status of treated patients and preliminary analysis suggests that the benefit of olaparib maintenance therapy, at least in terms of PFS, was larger in known BRCA germline mutation carriers (PFS HR 0.10)[13]. The key issues for the development of PARP inhibitors are patient selection and single vs combination strategies. There is little doubt that PARP inhibitors should be further developed towards registration in BRCA- mutation associated ovarian cancer, and a maintenance treatment approach is particularly promising. For patients with BRCA associated platinum-resistant disease, a registration strategy for PARP inhibitors incorporating randomized controlled trials is less straight forward as it is becoming clear that higher response rates may be seen with certain chemotherapy agents such as liposomal doxorubicin in BRCA mutation carriers[15]. Combination approaches with chemotherapy, based on the hypothesis of a chemo-sensitization effect, are being tested. However, a limitation is the increased myelosuppression seen with these regimens so far and the optimal duration of PARP inhibition with chemotherapy is not yet defined. In a randomized phase II study of olaparib with carboplatin and paclitaxel, the response rate was not increased compared to chemotherapy alone[16].

In addition to olaparib other PARP inhibitors under active investigation in ovarian cancer include rucaparib, veliparib, niraparib and BMN-673, with randomized trials at an advanced planning stage. Looking ahead, and based on emerging preclinical data indicating marked synergism, other strategies of particular interest include combinations of PARP inhibitors with PI3K inhibitors or antiangiogenic agents.

Ras/Raf/MEK/ERK pathway

In low grade serous ovarian carcinoma (LGSOC), which comprises 15%-20% of epilthelial ovarian carcinoma, activation of the MAPK signaling pathway may be very important as *BRAF* and *KRAS* mutations were initially reported in up to 68% of cases (33% *BRAF*, 35% *KRAS*- mutually exclusive)[17]. Although the incidence of BRAF mutations appears lower in recent reports[18], the Ras/MEK/ERK pathway is still an attractive therapeutic target in this notoriously difficult disease. A phase II trial of the MEK 1/2 inhibitor, Selumetinib (AZD6244) in 52 patients with recurrent LGSOC has shown promising results[19]; phase II trials of other MEK inhibitors are planned and combination strategies of MEK and AKT inhibitors (currently in phase I trials) are also under consideration.

PI3K/AKT/mTOR pathway

Although activation of the PI3Kinase pathway through mutations of PIK3CA or AKT or inactivating mutations of PTEN is rare in the high grade serous subtype (<5%) it may be seen in up to 30% of clear cell and endometrioid ovarian carcinomas and responses to single agent inhibitors have been seen in these subtypes. Amplification of genes in this pathway is more commonly seen but the therapeutic implications are uncertain as regards a single agent approach. Probably of wider clinical applicability are preclinical studies which have suggested a potential for modulation of this pathway to overcome resistance to chemotherapy in ovarian cancer[20] and clinical trials of chemotherapy in combination with either AKT or TORC1/2 inhibitors are planned.

ErbB family

Although increased expression of EGFR is common in ovarian cancer mutations are rare (<4%) and clinical trial results with single agent EGFR inhibitors (erlotinib, gefitinib) are disappointing[21]. HER2 over-expression or amplification has been described in up to 18% of advanced primary mucinous carcinomas and HER2- directed treatment approaches for this subgroup of patients should be considered[22]. However, targeting ErB3 (HER 3) may be more promising for a larger group of patients. ErbB3 (HER3) forms a heterodimer with ErbB2 (HER2) and stimulates cell survival pathways

through activation of MAPK and AKT pathways. HER3 has been associated with poor prognosis[23] and resistance to chemotherapy including taxanes[24]. An autocrine NRG1-driven/activated ErbB3 loop promoting ovarian cancer cell proliferation has been described and disruption of this circuit with a monoclonal ErbB3-directed antibody (MM-121), significantly inhibited tumour growth in mouse xenograft models[25]. MM-121 is currently under investigation in phase II trials combined with paclitaxel in ovarian cancer.

The folate receptor

The alpha folate receptor is overexpressed in >90% of ovarian cancers and several anti-folate receptor strategies are under investigation. These include an anti-FR monoclonal antibody farletuzumab, which is now in randomized trials combined with chemotherapy for recurrent disease[26]. Another approach involves EC145 (Nintafolide), a conjugate of a vinblastine analogue to folate. An analysis of a randomised, phase II study of EC145 + liposomal doxorubicin reported a greater than 2-fold increase in median PFS with the addition of EC145 in platinum-resistant ovarian cancer; clinical benefit was most clearly seen in the subgroup of patients with high folate receptor activity as assessed on whole body SPECT scanning using Tc-labelled folate[27] and a randomized Phase III trial is now underway.

Other approaches to resistance reversal in ovarian cancer

These include targeted agents focusing on the insulin growth factor (IGF) receptor and the oncogene Src based on preclinical data in appropriate models[28,29]. Saracatinib (Src inhibitor) and OSI-906 (a small molecule dual kinase inhibitor of both insulin-like growth factor-1 receptor and insulin receptor) have separately entered phase II clinical trials in combination with weekly paclitaxel in platinum-resistant ovarian cancer. Another potential target is Wee-1 kinase which regulates the G2/M checkpoint. Inhibition of Wee-1 kinase may lead to chemo-sensitization of p53-deficient tumour cells(53) which are characteristic of high grade serous ovarian cancer and a randomized clinical trial of carboplatin-based chemotherapy with/without MK-1775, a selective inhibitor of Wee-1 kinase is now underway in patients with relapsed disease. Drug resistance has generally been considered to be characteristic of so-called ‘stem cells’, although these have proved difficult to isolate and characterize. However, a study on ascites in patients with relapsed disease identified EZH2 as playing a key role in the maintenance of a drug-resistant stem cell-like subpopulation of tumour cells[30] and this is an active area of new drug development.

Final Comment

Recently, key mutations have been identified in genes such as *ARID1A* (in clear cell and endometrioid subtype)[31] although these are not directly ‘druggable’. However, advances in high throughput technologies are providing the opportunity for genomic-based drug discovery studies which may well lead to the identification of new agents both for the treatment of these sub-types and more broadly. In order to link this to an optimal strategy for patient selection, the importance of acquiring tumour tissue for molecular analysis both at presentation and at relapse cannot be over-emphasized.■

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