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Proceedings from the 9th International Conference on Ovarian Cancer

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Introduction

The 9th International Conference on Ovarian Cancer was held on December 2 and 3, 2012 in Houston, Texas. This biannual conference is jointly sponsored by The University of Texas MD Anderson Cancer Center (MDACC) and the Memorial Sloan Kettering Cancer Center (MSKCC). The goals of this meeting were to discuss the most current information regarding the screening, diagnosis and treatment of ovarian cancer, as well as to provide updates on current basic and translational research related to ovarian cancer. There were approximately 240 participants, with representation from 16 countries including the United States, Canada, United Kingdom, Belgium, Sweden, Greece, Korea, Venezuela, Colombia, El Salvador, Tunisia, Nigeria, India, Syria, Indonesia, and Thailand. The following is a brief overview of the meeting.

Ovarian cancer screening and hereditary ovarian cancer

Dr. Karen Lu discussed the recently published results of the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO). This study randomized 78,216 postmenopausal women to annual screening with simultaneous transvaginal ultrasound (TVUS) and CA 125 versus usual care, and found no difference in stage at diagnosis or mortality. However, promising preliminary results have been noted in an ongoing multi-center single-arm study led by MD Anderson that uses the Risk of Ovarian Cancer Algorithm (ROCA), which measures change in CA-125 over time, and allows each woman to establish her own baseline. The ROCA is also being used in the ongoing UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), but the final results are pending.

Dr. Noah Kauff reviewed that approximately 10% of ovarian cancers are caused by an inherited predisposition, primarily *BRCA1* and *BRCA2* mutations. Strategies for risk reduction including screening, chemoprevention with oral contraceptive pills, and risk-reducing surgery were discussed. To date, the evidence is equivocal that screening provides a survival benefit in this high-risk population, and all women with a *BRCA* mutation should be offered risk-reducing surgery following completion of childbearing. Molly Daniels, MS, CGC reviewed current guidelines for genetic counseling and testing for women with ovarian

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cancer. Identification of a *BRCA* mutation can have significant treatment and prognostic implications for the ovarian cancer patient. Furthermore, it allows for accurate predictive genetic testing of at-risk relatives. Existing data to support incorporating *BRCA* testing into standard care for all high-grade ovarian cancer patients were discussed by both presenters during this session.

Rare ovarian tumors

Dr. David Huntsman provided an overview of rare ovarian tumors. The current strategy of treating all epithelial ovarian cancers similarly requires careful reassessment. Discoveries in rare tumors may also help stratify care for more common cancers. For example, based on genomic and molecular profiles, there appear to be substantial differences within serous carcinomas that could require different treatment algorithms in the future.

Approximately 10% of all serous ovarian cancers are low-grade. Dr. David Gershenson reviewed that the MD Anderson two-tier grading system of serous ovarian cancer (low- and high-grade) is highly reproducible with excellent inter- and intra-observer agreement compared to the three-tier system. Molecularly, low-grade serous ovarian cancers have a higher frequency of *KRAS* and *BRAF* mutations, ER/PR positivity, and a lower frequency of *p53* mutations than their high-grade counterparts. In GOG 239 (AZD6244, a MEK inhibitor, in women with recurrent low-grade serous cancer), >80% of enrolled patients had either stable disease or partial response, with one patient achieving a complete response. The study of this rare subtype of serous ovarian cancer has led to unique treatment strategies.

Primary mucinous ovarian cancers differ histologically, molecularly, and clinically from other epithelial subtypes. Dr. Michael Frumovitz reviewed that primary mucinous ovarian tumors have a significantly higher prevalence of *KRAS* mutations and a lower frequency of *BRCA* and *p53* abnormalities compared with serous ovarian tumors. Patients with mucinous cancers tend to have worse prognosis compared to other epithelial ovarian cancers due to chemotherapy resistance. These tumors may be more sensitive to combination oxaliplatin and 5-fluorouracil or combination oxaliplatin and src kinase inhibitors. The GOG and the GCIG have recently launched a phase III study to compare the efficacy of carboplatin and paclitaxel±bevacizumab to oxaliplatin and capecitabine±bevacizumab (GOG 241).

Current issues in surgical management

Dr. Ignace Vergote presented data from the EORTC-NCIC randomized trial of primary debulking surgery versus neoadjuvant chemotherapy followed by interval debulking for patients with extensive stage IIIC and IV ovarian cancer. In this study, the post-operative complications and mortality rates were lower after interval debulking surgery; however, for both arms the PFS was 12 months and the OS was 30 months. For all patients, the most important independent prognostic factor for overall survival was complete gross resection at the completion of cytoreductive surgery. Dr. Vergote concluded that aggressive surgery should be tailored according to the general condition of the patient and extent of disease. Dr. Dennis Chi presented contemporary experience from MSKCC. Using the same study selection criteria, Dr. Chi demonstrated that only 10% of patients received neoadjuvant treatment due to extra-abdominal disease, performance status or advanced age (>85 years) with multiple co-morbidities. Optimal cytoreduction (< 1 cm) was achieved in 71% of patients. The PFS and OS were 17 and 50 months, respectively. Given that the cumulative body of data over the last several decades demonstrates a consistent OS of only 30 months for patients that undergo either neoadjuvant treatment or suboptimal resection, Dr. Chi concluded that primary tumor debulking should remain the standard of care for the majority of advanced stage ovarian cancer patients.

Regarding secondary cytoreductive surgery, Dr. Pedro Ramirez discussed that chemotherapy is an appropriate option for patients with recurrent disease, recognizing the limited cure rate for patients with recurrent disease and the large number of active agents available for systemic therapy. Dr. Nadeem Abu-Rustum, highlighted the survival benefit among patients that achieve optimal secondary tumor debulking and the selection criteria which have been developed to identify operative candidates, including disease free interval and distribution of recurrent disease. Currently, GOG 213 and the DESKTOP-III trials are enrolling operative candidates to assess the impact of secondary cytoreductive surgery on overall survival.

Dr. Ginger Gardner discussed the growing role of robotic surgery in the evaluation of a suspicious adnexal mass or newly diagnosed ovarian cancer. Data were presented regarding feasibility of surgical resection, and staging for apparent small volume disease. The utility of robotic laparoscopic resection for isolated recurrent disease was also presented. Dr. Yukio Sonoda discussed approaches for disease resection in the thoracic cavity including resection of enlarged supradiaphragmatic nodes through a small incision, and the feasibility of video assisted thorascopic surgery (VATS) for the evaluation and resection of pleural disease prior to an abdominal exploration.

Updates on chemotherapy

Dr. Katherine Bell-McGuinn reviewed the randomized trial data demonstrating a survival benefit with intraperitoneal chemotherapy for patients with optimally debulked advanced stage disease. Data regarding dose dense therapy was also presented. The rationale for the recent GOG252 trial was discussed, the results of which are currently pending. Data from GOG 218 and ICON 7 trials were reviewed, which showed improved PFS in the frontline setting with no differences in overall survival. For recurrent ovarian cancer, the CALYPSO trial showed a PFS benefit but no OS difference for carboplatin and liposomal doxorubicin when compared to carboplatin and paclitaxel. The OCEANS trial has revealed a PFS benefit with immature OS data for the addition of bevacizumab to carboplatin and gemcitabine.

Dr. Paul Sabbatini provided an update regarding consolidation strategies in ovarian cancer. He highlighted the improvements seen in PFS when paclitaxel or bevacizumab was given in first remission along with the data for bevacizumab and olaparib maintenance strategies in second or second/third remission, respectively. He also discussed immunologic approaches including abagovomab and oregovomab, which despite positive phase II studies failed to show improvements in remission lengths in phase III trials. Patients in second and third remission may represent ideal populations for future consolidation strategies.

Dr. Robert Bast emphasized the importance of developing bio-markers to individualize the care of ovarian cancer patients. Biomarker panels do not yet exist but are needed to identify individuals who do not benefit from frontline platinum/taxane chemotherapy. He discussed molecular pathways contributing to resistance along with genetic signatures corresponding to poorer prognoses. Cell based assays currently available for predicting response to chemotherapy for ovarian cancer patients have not been adequately validated for clinical use.

Novel therapeutics

Dr. Stan Kaye addressed the role of PARP inhibitors in ovarian cancer treatment. *BRCA1* and *BRCA2* are important genes governing homologous recombination, and as such, tumors with mutant copies of these genes become vulnerable to PARP inhibition. PARP inhibitors were initially investigated in patients with a germline *BRCA1* or *BRCA2* mutation, and efficacy was demonstrated even in the phase I trial for olaparib. In a recent phase II trial, 2 dose levels of olaparib were compared with pegylated liposomal doxorubicin (PLD) and

demonstrated the expected clinical activity of olaparib, but an unexpected improved performance of PLD. In a second trial, olaparib nearly doubled the time to progression following response from chemotherapy compared with placebo in patients with recurrent platinum-sensitive disease. There is increasing interest and ongoing investigation in combination strategies with chemotherapy agents, anti-angiogenesis inhibitors and other pathway-targeted agents (such as PI3K/Akt/mTOR inhibitors).

Drs. Robert L. Coleman and Anil K. Sood profiled the use of anti-angiogenesis inhibitors in the clinical and pre-clinical settings. Preliminary results from trials for primary disease (GOG-218 and ICON7) and recurrent disease (OCEANS trial) were reviewed. In each of these major phase III efforts, PFS was extended by an experimental arm, but the impact of therapy on OS is not fully known. Nevertheless, the trials were compared and contrasted in regard to their designs, patient eligibility, bevacizumab dosing and duration of the therapy, response (where appropriate), primary and secondary endpoints, and reported toxicities. It was clearly highlighted in both presentations that the lack of a reliable biomarker for efficacy, toxicity or both, was a significant deficit and a prioritized future objective. Ongoing trials are evaluating several inhibitors including multi-targeted tyrosine kinase inhibitors (e.g. cediranib, BIBF-1120, pazopanib, cabozantinib, etc.), decoy receptor proteins (e.g. aflibercept) and angiopoietin inhibitors (e.g. AMG-386), in the phase II and III settings. To support the clinical investigation of alternative targets, data were presented for mechanisms of escape from anti-VEGF therapies and new approaches to overcome such escape using RNA interference. Several factors, such as non-receptor kinases (e.g., FAK, src), growth factors and transcriptional repressors (e.g., EZH2) were identified as important targets. In addition, alternative strategies for successful tumor control were presented; including other cell types which directly or indirectly regulate tumor blood vessels (e.g. pericytes, platelets, cancer-associated fibroblasts, tumor cells, macrophages, etc.).

Applied genomics

Dr. Doug Levine presented recent data regarding ovarian cancer genomics. Results from The Cancer Genome Atlas (TCGA) Research Network were discussed. Unlike other solid tumors characterized by TCGA, high-grade serous ovarian cancer demonstrates frequent and widespread copy number alterations to the general exclusion of common oncogenic mutations. The main findings from the TCGA demonstrate near universal TP53 somatic mutations, widespread copy number alterations, four gene expression subtypes, and frequent putative defects in homologous recombination. This data provides important insight into the underlying mechanisms of ovarian cancer cell growth, and putative targets for treatment.

Summary

Many challenges remain in the management of ovarian cancer. The 9th International Conference on Ovarian Cancer provided a platform to further generate ideas and opportunities for scientists and clinicians to work collaboratively to improve the prevention, early detection and treatment of this disease.

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