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Meeting Report

Summary of the 45th Annual Meeting on Women's Cancers

The 45th Annual Meeting on Women's Cancer was held in Tampa Florida March 22–25. The meeting was responsive to the diverse and expanding membership offering sunrise sessions, education forums, plenary and focused plenary presentations with focused lecturettes, controversial topic debates and much more. Five key concepts served as the platform for the meeting and timely discussions addressing changes in health practice, quality care and reimbursement and work–life balance. The breadth of the practice of gynecologic cancer care was highlighted throughout the meeting.

Key concept 1: Cancer care delivery systems and payment reform

As we continue to make progress in the care of women affected by gynecological cancers, a critical evaluation of our cancer care delivery systems has become necessary.

Dr Brown (abstract 81) reported on the effect of advanced age on postoperative outcomes in endometrial cancer patients who underwent hysterectomy. Elderly women had more co-morbidities and less favorable surgical outcomes. Compared to patients younger than 80 years of age, older patients were five times more likely to die (odds ratio, 5.31) and this was significant.

Dr Amneus (abstract 83) presented an early report on a newly initiated cervical cancer navigation program within their institution as a means to optimize the care of patients undergoing chemoradiation by improving the time for therapy and adequately managing anemia. The median number of days with hemoglobin of less than 11 g/dl among patients on the program was 1 compared to 12 among historical controls. Patients treated under the navigation program did much better than historical controls.

Adequate counseling may lead to improvement in cancer treatment outcome as reported by Dr Lin (abstract 84). He evaluated the impact of refusal of recommended therapy by cervical cancer patients. After controlling for other adverse risk factors, refusal of recommended treatment was associated with a 2-fold increase of dying of disease. This problem may improve with counseling.

According to Dr Eskander (abstract 107), readmission of ovarian cancer patients within 30 days of undergoing cytoreductive surgery is associated with increased cost of care and less favorable treatment outcome. There was a higher one-year mortality (41.1% vs 25.1% respectively; $p < 0.0001$). The median cost of readmission hospital stay was \$9220 ± \$14,296, with a total cost of \$9.3 million over the study period. Some of the causes of readmission are modifiable.

Key concept 2: Global effects to end women's cancer

Comparison of the performance of human papillomavirus (HPV) primary screening strategies with cytology-based strategies: results from the ATHENA trial 3-year follow-up phase was presented by Dr Wright (abstract 3). High risk HPV primary screening with triage to colposcopy based on HPV16/18 genotyping and reflex cytology had an overall sensitivity of 80.0% and detected most disease at the baseline screening round. They concluded that this is a more sensitive cervical screening strategy than cytology and is more efficient than cotesting.

In an effort to improve cervical cancer screening globally, Dr Belinson and colleagues reported (abstract 37) on the applicability of a new next generation sequencing, high risk HPV assay for primary cervical cancer screening based on self-collection. The throughput (40,000+/week), accuracy, improved specificity, and low cost per case (<\$5.00), with 14 high-risk genotypes reported, make the technology particularly suited for large-scale screening programs with centralized laboratories especially targeting the medically underserved.

Key concept 3: Clinical trials in GYN cancers

Anti-angiogenesis

Three abstracts (2, 62 and 144) evaluated the utility of anti-vascular endothelial growth factor (anti-VEGF), bevacizumab in different gynecologic cancers. Essentially, it was shown that carefully selected subgroups of patients based on defined risk factors or markers may derive more benefit from bevacizumab.

Abstract 2 is a randomized phase III trial of gemcitabine + docetaxel + bevacizumab (GD + B) or placebo (GD + P) as first-line treatment for metastatic uterine leiomyosarcoma (uLMS) presented on behalf of the Gynecologic Oncology Group (GOG) by Dr Hensley. The median overall survival (OS) among the 47 patients randomized to GD + B was 23.3 months which was statistically similar to the OS of 19.4 months in the placebo arm. Overall response rate, progression free survival and grade 3 and 4 toxicity were similar between the 2 arms. The study was closed based on the futility analysis.

In abstract 62, Dr Ferriss presented a secondary analysis of the data from GOG 218, a phase III, double-blinded, placebo-controlled, randomized trial of standard cytotoxic chemotherapy with or without bevacizumab. Data from 1151 patients was utilized. They were divided into two groups according to ascites (79%) or no ascites (21%). Although, ascites was an independent poor prognostic factor, ascitic patients who received bevacizumab had significantly improved PFS (HR 0.72, 95% CI 0.63–0.83, $P < 0.001$) and improved OS (HR 0.82, 95% CI 0.7–0.96, $P = 0.01$). However, nonascitic patients had no significant improvement in PFS (HR 0.77, 95% CI 0.57–1.04, $P = 0.091$) or OS (HR 0.88, 95% CI 0.61–1.28, $P = 0.5$). They concluded that ovarian cancer patients with ascites may benefit more from bevacizumab.

Dr Tewari presented a secondary analysis of GOG 240 data. Patients were stratified into low, intermediate and high risk groups according to

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the following risk factors; black race, performance status (PS) 1, measureable disease in the pelvis, prior cisplatin, and progression-free interval (PFI) <365 days. Although, bevacizumab was beneficial in all the 3 risk categories, the benefit was maximum in the high risk group. The estimated hazard ratios for death were 0.96 (low), 0.67 (intermediate), and 0.54 (high). He concluded that these clinical prognostic factors in combination with molecular factors may help identify patients likely to be refractory to anti-VEGF therapy.

PARP inhibitors

Inhibitors of poly (ADP-ribose) polymerases (PARP) are among the latest generation of targeted therapies against ovarian cancer that have been evaluated in the last few years. The main focus for their utility has been among patients with BRCA mutation although accumulating evidence suggests that they may benefit select groups of patients without BRCA mutation.

A phase I study of veliparib (ABT-888), an oral PARP inhibitor in combination with carboplatin (C) and gemcitabine (G) in subjects with advanced ovarian cancer was presented by Dr Gray (abstract 131). Data related to the ovarian cancer subgroup (n = 39) is highlighted in Table 1. They conclude ABT-888 combined with C and G followed by V maintenance therapy was well-tolerated, with a safety profile similar to C and G alone.

Ovarian cancer subgroup (n = total pts)	PR/CR	Response rate (evaluate pts, %)	Median decrease tumor diameter (%)	Progression free survival (median [95% CI], mos.)
Dose < MTD (n = 30)	10/2	52%	−65.5%	7.6 [5,2, 10.3]
Dose < MTD (n = 9)	3/0	38%	−60.7%	Not yet reached
gBRCA mutation (n = 24)	10/1	58%	−64.6%	8.2 [5.2, 14.3]
gBRCA wildtype/unknown (n = 15)	3/1	33%	−60.7%	5.9 [2,4 10.0]

In abstract 132, Dr Matulonis presented an ancillary analysis of intermediate clinical endpoints (time to first subsequent therapy or death [TFST]; time to second subsequent therapy or death [TSST]) from a Phase II trial of olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). Olaparib maintenance monotherapy delayed TFST compared with placebo, and the benefits of olaparib therapy persisted beyond the first RECIST progression. Significant benefits in favor of olaparib were observed in the overall patient population and in both the BRCA mutation and non-BRCA mutation subgroups.

The third main PARP related abstract is a phase II evaluation of the potent, highly selective oral PARP inhibitor, veliparib in the treatment of persistent or recurrent epithelial ovarian cancer in patients who carry a germline *BRCA1* or *BRCA2* mutation, a GOG study presented by Dr Coleman (abstract 136). The purpose was to estimate the clinical activity and toxicity of single-agent veliparib administered at 400 mg po BID over a cycle of 28 days. The confirmed response rate (RR) was 26%. RR in platinum-resistant and platinum-sensitive patients was 20% and 35%, respectively. This confirmed activity warrants further investigation

Novel biomarkers

Biomarker discovery and validation continues to bring new insights of actionable targets for gynecologic cancers and predictors of treatment response. A landmark discovery by Mueller et al. (late breaking abstract 4) reports unequivocal mutations in SMARCA4 a SWI/SNF chromatin-remodeling complex in all 12 patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) using target capture and massively parallel DNA sequencing technology. All mutations were validated via RNA and functional analyses. This is a novel discovery that can be utilized for diagnosis as well as a future drug target for this rare disease. (http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.2922.html)

Technologies for deep sequencing and output from The Cancer Genome Atlas (TCGA) Research Network have allowed identification of other novel biomarkers in gynecologic malignancies. Billingsley et al. reported POLE mutations were found to characterize a subtype of endometrial cancers that had markedly increased numbers of mutations (abstract 6). Mutations were found in 5% of microsatellite stable endometrioid endometrial cancers and 5% of MSI + tumors with the highest rate in MSI + unmethylated tumors. Recurrences were rare. POLE mutations may be helpful in discriminating MSI + unmethylated tumors in Lynch testing for endometrial cancer.

Germline mutations in DNA repair genes are a focus for predicting different patterns of disease. Dr. Shu reports that BRCA1 mutation carriers were found to have an increased risk of high risk uterine cancer (late breaking abstract 5). BRCA + women may have an increased risk of developing high risk uterine cancer (1% at 10 years) after RRSO — although numbers in this study are small. An ancillary analysis of GOG 218 and GOG 262 (abstract 10) reported 20% germline mutation rate of which 30% were NOT BRCA1/2 mutations but other loss of function mutations in the DNA repair pathway.

Drug repurposing

The field of drug repurposing is expanding as there are observations of potential cancer preventive effects or better cancer outcomes of common drugs used for standard FDA indications. The main drug of interest and the rationale for GOG 286B is metformin leading to improved treatment outcomes in patients with endometrial and ovarian cancer. There were 14 abstracts in the meeting evaluating clinical effects or biologic mechanisms of metformin use in gynecologic cancer patients. Dr. Schuler performed a prospective preoperative trial in 20 evaluable patients demonstrated that 850 mg of metformin twice daily resulted in significantly reduced endometrial cancer proliferation in obese patients which was most significant in tumors with high Ki-67 indices (abstract 8). The effect was mediated through downstream targets of the mTOR pathway. Metformin users were found to have better survival than nonusers without additive effect of statins or aspirin (abstract 104) with a plausible biologic effect in an obese murine model (abstract 105). The role as a chemoprevention agent for endometrial cancer however is not supported in a population-based cohort (abstract 79).

Operative predictors

One of the key themes in this meeting (Scientific Plenary IV) is the role of optimal debulking to no gross residual disease (R0) and any predictors that can be used to triage frontline debulking versus neoadjuvant chemotherapy in patients with ovarian cancer while minimizing perioperative morbidity. But what is the best approach: clinical disease indicators, molecular profiles of aggressive biology or patient indicators? Using debulking to R0 as an outcome, Dr Suidan and colleagues (abstract 59) prospectively evaluated preoperative CT and CA-125 measures obtained in 2 high volume centers resulting in a 9 criteria model that produced a predictive value score with a prognostic accuracy of 0.758. Dr. Horowitz reported on a second preoperative clinical model (abstract 60) to predict optimal (R0) debulking status using a previously described Disease Score applied to GOG 182 data in a test and validation set which failed to find an adequate clinical based model to predict surgical outcome. Dr. Sood described molecular predictors of R0 cytoreduction in abstract 61 from molecular data extracted from the TCGA and Tothill datasets. High expression of FABP4 and ADH1B was significantly associated with residual disease and FABP4 is recommended for further investigation as a predictive marker. Patient clinical parameters were evaluated utilizing a frailty index (abstract 63) and a preoperative quality of life index (abstract 64). Lastly, Dr. Uppal