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Conference Report

International Gynecologic Cancer Society (IGCS) 2018: Meeting report

1. Introduction

The 17th Biennial Meeting of the International Gynecologic Cancer Society (IGCS 2018) was held September 14–16, 2018 in collaboration with the Japan Society of Gynecologic Oncology in the beautiful city of Kyoto, Japan. IGCS President Michael Quinn and Japan SGO (JSGO) President Aikou Okamoto, in conjunction with Scientific Program Chair Keiichi Fujiwara and Organizing Program Chair Ikuo Konishi, presented an outstanding program. Dr. Agnes Binagwaho from Rwanda served as the presidential speaker. IGCS awards were presented to Henry Kitchener, MD (UK) for lifetime achievement, Peter Heintz, MD, PhD (Netherlands) for excellence in teaching, Ted Trimble, MD, MPH (US) and Agnes Binagwaho, MD, PhD (Rwanda) for Community Advancement in Resource-Limited Settings.

Dr. Michael Quinn continued his theme of women in leadership with the Women's Leadership panel composed of Agnes Binagwaho, MD, PhD, Etsuko Miyagi, MD, PhD from Japan and Ellen Baker, MD, MPH from the US. The panel fielded questions addressing approach to leadership and overcoming barriers for women in the different countries of origin. A total of 3056 delegates attended the meeting, representing approximately 100 countries. The meeting was multidisciplinary and drew on expertise from around the world. In the summary that follows, we report on notable studies and areas of controversy from the meeting.

2. Cervical cancer

Treatment of early-stage cervical cancer was the subject of intense discussion largely as a result of additional data regarding the Laparoscopic Approach to Cervical Cancer (LACC) trial. The LACC trial, as reported previously (SGO 2018), is a randomized, multi-center, phase III trial designed to test for non-inferiority of abdominal radical hysterectomy (TARH) versus minimally invasive radical hysterectomy (MIRH) in patients with stage IA1 with lymphovascular space invasion (LVSI) to IB1 tumors. The primary endpoint was disease-free survival (DFS). In June 2017, patient enrollment was put on hold by the data and safety monitoring committee as the TARH group (312 patients) had better disease-free survival (DFS) (HR, 3.74; 95% CI, 1.63–8.58; $p = 0.002$) and overall survival (OS) (HR, 6.00; 95% CI, 1.77–20.3; $p = 0.004$) at 4.5 years than the MIRH group (319 patients). At the IGCS meeting's opening session, Andreas Obermair reported adverse events associated with the LACC trial (#1195) and Michael Frumovitz reported quality of life (QoL) and symptoms (#0506). The TARH group had greater intraoperative blood loss (200 ml vs 100 ml, $p < 0.001$) and shorter operation time (190 min vs 215 min, $p < 0.001$). There was no difference in the rate of gastrointestinal, genitourinary or lymphocyst/lymphocele complications between the two groups. QoL and symptoms assessed by the functional assessment of cancer therapy-cervix, short form-12, EuroQoL-5 dimensions, and MD Anderson Symptom Index were similar between the two groups at 1 week postoperatively and thereafter. The presenters suggested that patients be counselled about the poorer survival outcomes with no significant benefits in reduction of adverse events or improvement in QoL from MIS. These two abstracts added to the data presented by Dr. Ramirez at SGO and generated robust discussion by the presenters and the audience.

Another randomized phase III trial in early-stage cervical cancer was presented by Dr. He Huang from China (#0739). The study compared efficacy and safety of three adjuvant regimens after radical surgery: radiation alone (RT), concurrent chemoradiation (CCRT), or sequential chemotherapy and radiation (SCRT) with 2 cycles of paclitaxel combined with platinum before and after RT, respectively. A total of 1055 patients with stage IB1-IIA2 cervical cancer who had one or more postoperative pathologic risk factors were randomly assigned to one of three groups. Risk factors included lymph node (LN) metastasis, positive parametrium or margins, LVSI, and deep stromal invasion. Median follow-up was 45 months. Per protocol (PP) population that completed the assigned treatment was highest in the RT group. Except for LN metastasis, which was significantly higher (30%) in the CCRT and SCRT groups than the RT group (20%), all clinicopathologic characteristics were similar. While the DFS of the SCRT group was significantly better than that of the RT group (2-year DFS, 91.0% vs. 82.0%; HR, 0.47; 95% CI, 0.29–0.75; $p = 0.039$), the DFS of CCRT was not different from that of RT group (2-year DFS, 84.0% vs. 82.0%; HR, 0.75; 95% CI, 0.48–1.19; $p > 0.05$). In a subgroup analysis of patients with high-risk factors, 2-year DFS of SCRT group was better than the CCRT or RT group (91% vs. 68% vs. 68%, $p = 0.003$). However, there was no difference in DFS between the three groups in patients with intermediate-risk factors and no difference in OS. The authors suggest that SCRT could replace CCRT in patients with high-risk cervical cancer. However, uneven distribution of LN metastasis between groups is a confounding factor, in this study.

Dr. Tangjitgamol from Thailand presented a phase III trial analyzing adjuvant chemotherapy for locally advanced stage IIB-IVA cervical cancer (ACT-LACC) trial (#0561). This trial compared treatment outcomes of CCRT plus adjuvant chemotherapy with CCRT alone in stage IIB-IVA cervical cancer. Primary endpoint was 3-year progression-free survival (PFS). A total of 259 patients without para-aortic LN metastasis on imaging were randomized to CCRT ($n = 129$) or CCRT-ACT group ($n = 130$) with adjuvant paclitaxel and carboplatin. During the median follow-up of 27.4 months, total recurrence was similar between the two groups (15.5% vs. 10.8%; $p = 0.123$). Systemic metastasis occurred more frequently in CCRT alone group (10.1% vs. 5.4%; $p = 0.029$). Nevertheless, survival analyses failed to show any significant 3-year PFS difference in intention to treat (ITT) population (66.6% vs. 63.4%; HR, 1.26; 95% CI, 0.82–1.96; $p = 0.293$) or PP population. Three-year OS outcomes were

also similar for ITT (80.1% vs. 69.5%; HR, 1.42; 95% CI, 0.81–2.49; $p = 0.221$) and PP population. Given these results, the results of the ongoing OUTBACK trial are eagerly awaited [1].

3. Epithelial ovarian, peritoneal, and fallopian tube cancer

3.1. Surgery

Updated outcomes from several surgical studies were reported. Dr. Coleman reported surgical outcomes from the GOG 213 study, an international, open-label randomized phase III trial evaluating secondary cytoreduction and bevacizumab in women with platinum sensitive recurrence (#1475). Initial results demonstrated an improvement in OS in the bevacizumab containing arm, and no difference in OS for those undergoing surgery [2,3]. The majority of patients (63%) had 1–2 sites of oligometastatic disease. While there was an improvement in PFS with complete resection of visible disease (CGR) vs non-CGR (HR 0.51 (96% CI 0.36–0.72), there was no difference in OS even in those with a long pre-operative platinum free interval. Therefore, the benefit of secondary cytoreduction in platinum sensitive disease remains undefined.

3.2. PARP inhibitors

Three PARP inhibitors have been approved in the United States – niraparib, olaparib and rucaparib [4–7]. Dr. Oza et al. presented a follow-up analysis from the ARIEL3 trial which led to the approval of rucaparib [4]. The study compared the safety and efficacy of rucaparib in 126 patients who had received prior bevacizumab, overall, 22.3% of the population (#0758). Progression free survival was analyzed by 3 predefined cohorts, BRCA mutant; BRCA mutant or BRCA wild type/high loss of heterozygosity (LOH high) and the intent to treat population. Rucaparib significantly improved PFS in all cohorts independent of the prior use of bevacizumab without increases in toxicity.

Dr. Mansour and colleagues presented data on the long-term safety of niraparib from the ENGOT-OV16/NOVA trial [5]. The median duration of exposure was 13 months (range 0–41 months) in the germline BRCA cohort and 7 months (range 0–41 months) in the non-gBRCA cohort. Of 546 patients, 79 have remained on treatment for >2 years. Haematological toxicity occurred more frequently early and most resolved with dose adjustment within the first 3 months, with the incidence of grade 3 anemia <1% after 1 year. After dose modifications, niraparib demonstrated good long-term tolerability including for those patients who received treatment for >2 years. These results have led to dose individualisation recommendations based on body weight and platelet count.

PARP inhibitor toxicity in the Chinese population was addressed by Dr. Liu and colleagues (#0917) as side effects vary significantly in different patient populations. For example, the rates of toxicity from pazopanib were significantly higher in patients with ovarian cancer of Asian ethnicity [8,9]. SOLO2 investigated maintenance olaparib in 295 women with platinum sensitive recurrent ovarian cancer and an underlying BRCA mutation [6]. Overall, 32 patients from 13 sites in China were enrolled in SOLO2 (10.8%). In contrast to the pazopanib study [8,9], side effect profiles were comparable in the Chinese patient cohort and the overall patient population.

3.3. Immunotherapy

To date, immunotherapy has resulted in modest activity in patients with ovarian cancer [10–12]. Dr. Burger and colleagues investigated the combination of ipilimumab and nivolumab (NRG GY003) in 100 women with persistent or recurrent epithelial ovarian cancer with a platinum free interval of <12 months (#1481). Patients received 4 doses of induction therapy with either nivolumab alone or the combination of nivolimab and ipilimumab followed by maintenance nivolumab to a maximum of 42 doses. Most patients had serous histology (82%) and 63% were platinum resistant; 12% had clear cell histology. The primary endpoint, response rates at 6 months, was higher in the combination arm (31.4% vs 12.2%; OR 3.28, $p = 0.034$). Median PFS was significantly better in the combination arm: HR 0.528 (95% CI 0.339–0.821). Median OS was 21.8 months in the nivolumab arm alone and 28.1 months in the combination arm: HR 0.789 (95% CI 0.439–1.418). Higher rates of toxicity were seen in the combination arm. Efficacy appeared independent of age, performance status and number of prior cytotoxic regimens and was higher in patients with clear cell tumors.

Wenham performed a single arm phase II study to investigate synergy of the combination of paclitaxel and pembrolizumab in women with platinum resistant ovarian cancer (#1482). The study met its primary endpoint with a 6 month PFS of 52.5%. The response rate and disease control rate were 51.4% and 86.5%, respectively, in the 37 evaluable patients. This response rate is similar to the 53% response rate seen with the combination of bevacizumab and paclitaxel in AURELIA [13]. The median PFS was 6.7 months for women receiving paclitaxel and pembrolizumab, with a median OS of 13.4 months. Importantly, 10 patients were still on treatment at the time of reporting. Both these studies demonstrated a signal of activity but ongoing questions remain regarding the optimal timing of immunotherapy and the best combination to use.

3.4. Response to therapy

Dr. Cohen et al. presented data from 14 centers to validate use of a chemotherapy response score in patients with stage III/IV high grade serous ovarian cancer undergoing 3–4 cycles of neoadjuvant chemotherapy (#0471). A 3 tier scoring system on omental sections, published by Bohm et al. [14] allows for stratification of patients into complete/near complete response (CRS3), partial response (CRS2) and no/minimal response (CRS1) to chemotherapy. With a median PFS of 14.9 months (range 3.5–224.5 months), adjusting for age, stage, debulking and BRCA mutation status, CRS3 was associated with a 22.0 month PFS compared to 14.4 months for CRS 1 or 2, HR 1.97 (95% CI 1.65–2.35, $p < 0.001$). OS was also significantly associated with CRS3 score as compared to CRS 1 or 2 with median OS 54. 6 months vs 37.7 months, HR 1.71 (95% CI 1.35–2.16, $p < 0.001$). The authors have proposed CRS as a possible primary endpoint in clinical trials of neoadjuvant chemotherapy.

ICON7 and GOG218 were two key trials investigating the benefit of bevacizumab in combination with carboplatin and paclitaxel for first line therapy in ovarian cancer patients [15,16]. Kommoss and colleagues correlated molecular biomarker subtypes with outcome to identify which ICON7 patient cohorts derive most benefit from bevacizumab (#1390) [16]. As defined by the cancer genome atlas (TCGA), only patients with tumors of the proliferative subtype had a statistically significant improvement in PFS with the addition of bevacizumab with a median PFS benefit of 10.2 months (HR 0.48; $p = 0.002$) and median OS benefit of 17.2 months (HR 0.54; $p = 0.021$). No statistically significant benefit was seen in the non-proliferative subtypes. In addition to validation in other cohorts, further consideration of correlation of this subtype with clinical characteristics is warranted.

3.5. Rare cancers

Mucinous ovarian cancer (5–10% of ovarian epithelial cancers), is a challenging disease to study prospectively. Dimitrios and colleagues used the United States National Cancer Database to explore the role of treatment in this patient population (#0328). Between 2004 and 2015, 4811 patients with stage I mucinous ovarian cancer were identified. Chemotherapy was administered to 30.9% of patients. No difference was seen in OS for patients who did and did not receive chemotherapy (86.8% vs 89.7%) even after controlling for substage, age, grade, lymphadenectomy and presence of comorbidities. This

study supports the role for observation in early stage mucinous ovarian cancer and highlights the value of utilizing databases in rare cancers.

4. Endometrial cancer

There were six oral abstracts presented and discussed at the endometrial cancer session. Three were biomarker studies from Canada. Dr. Rachel Kim utilized a retrospective population based cohort from Vancouver to analyze MMR status in endometrial cancer as a predictor of response to adjuvant therapy (#0298) Primary outcomes were PFS and OS. Of 535 eligible cases, 30% were MMR deficient. MMR status was associated with younger age at diagnosis (62 vs. 64.8, $p = 0.005$), endometrioid histology (86 vs.61%), stage I disease, and higher proportion of LVSI (65% vs 53%). Radiotherapy was administered to a higher proportion of MMR deficient patients while adjuvant chemotherapy was given to a higher proportion of MMR proficient patients. When adjusted for co-variates, MMR status was not independently associated with better survival outcomes. At the time of discussion, the authors clarified that all MMR data were immunohistochemistry data only, but they do have access to germline versus somatic data and plan to analyze this data in the future.

Additional biomarker studies were presented by Dr. Jessica McAlpine on behalf of her research group. The first study collected all available data on POLE endometrial cancers for the purposes of performing a meta-analysis (#1322). The investigators contacted authors who had published on POLE mutations in conjunction with clinicopathological data and outcomes. Ten centers provided data for 268 POLE mutated endometrial cancers. Almost 90% of patients were stage I, and 44% of cases had grade 3 disease. Endometrioid histology was the prevalent sub-type. 37% of cases had deep myo-invasion, 35% had LVSI, and 31% were high risk by ESMO 2016 designation. 54% of patients received some type of adjuvant therapy (vaginal brachytherapy, EBRT, or combination of chemotherapy and radiotherapy). In the meta-analysis, when adjusted for histology, grade and stage, there was no evidence to support survival benefit with adjuvant treatment in this cohort. During discussion, participants agreed that a prospective trial to address the role of adjuvant therapy would be important, but likely not feasible. The willingness of other authors/groups to share their data in a rare disease subset was admirable and another effective tool in providing useful data for patients.

A second abstract presented by Dr. McAlpine sought to characterize molecular subtypes of endometrial cancer in young women and correlate these subtypes with outcome (#1256). The ultimate goal of the study was to provide counseling to those women who wished to preserve fertility. Per the authors, young women (<50 years) fall into 3 categories or "clinical risk groups": "excess estrogen", suspected or known Lynch syndrome, and no apparent risk factors [17]. To these categories they added an algorithm called Promise (**Pro**active **M**olecular risk classifier for **E**ndometrial Carcinoma). The ProMisE algorithm is inspired by the TCGA molecular classification of endometrial cancer, can be applied to diagnostic biopsies, with high interobserver agreement (Plotkin, poster 424), and can be performed on paraffin material. Immunohistochemistry for MSH6, PMS2, and p53 was performed in addition to sequencing for POLE exons 9–14. The objective of the study was to assess the feasibility and prognostic value of the ProMisE molecular classification in an age-stratified cohort of women with endometrial cancer.

257 cases were classified by molecular features/ProMisE and 189 were classified by clinical risk group. The authors found significant diversity: the high estrogen group had 80% p53 wt, while the Lynch-like group was 78% MMRd. Interestingly the "neither" group had twice the usual rate of POLE distribution at 23%. Women with Lynch-like endometrial cancer had the highest proportion of advanced stage, non-endometrioid and high grade tumors. Finally, there was a high proportion of synchronous endometrial and ovarian tumors in the entire cohort (9%), over half of which fell into the "neither" clinical cohort.

The ProMisE algorithm was prognostic for PFS, DSS and OS, and was more reliable than "clinical risk group" in this respect. In the multivariate survival analysis only BMI and ProMisE subtype maintained association with OS and DSS. Because ProMise can be used on endometrial biopsy specimens, it may be extremely useful in counseling patients who wish to preserve the corpus.

Patterns of care, quality of care and outcomes related to radiation treatment were addressed in the remaining abstracts in this session. After GOG 249, use of pelvic radiation has decreased significantly in high intermediate risk endometrial cancer (#0397). Also notable is the high percentage of high intermediate risk patients who are being triaged to observation only. There were high uniformity and low rates of minor and major deviations in the international sites participating in the PORTEC-3 trial (#0599). The incidence of pelvic fractures and changes in bone mineral density following pelvic radiotherapy for gynecologic malignancy are significant. (#1258) Of 97 patients, 43% were diagnosed with vitamin D deficiency at baseline. Sixteen patients (7.8%) had pelvic fractures with actuarial rates of 3.6%, 12.7%, and 15.7% at 1, 2 and 3 years. All fractures were sacrum (81%) or lumbar spine (19%). The authors concluded that bone mineral density screening and pharmacologic intervention should be standard of care in these high risk women.

5. Vulvar cancer

Dr. Te Grootenhuis from the Netherlands presented on the prognostic impact of premalignant disease and pathological margin distance on local recurrence in 287 patients with vulvar cancer (#0772). Pathologic tumor free margin distance was not associated with recurrence (HR, 1.03; 95% CI, 0.99–1.06, $p = 0.153$). Multivariate analyses showed that dVIN in margin with (HR, 2.76; 95% CI, 1.62–4.71; $p < 0.001$) or without LS (HR, 2.14; 95% CI, 1.11–4.12; $p = 0.023$) was associated with more recurrences than no premalignant lesion at margin. Patients with these pathologic risk factors after surgery should be followed carefully for a long period of time.

A national prospective study from Denmark analyzed recurrence and survival rates in node-negative patients after sentinel node (SN) biopsy for early-stage vulvar cancer (#0938). During a median follow-up of 30 months (range 1–83 months), the recurrence rate was 12.3% (24 patients), more than half of which were a local vulvar recurrence (15/24, 62.5%). Only 4 patients (2.1%) had an isolated groin recurrence after surgery. Based on 5-year OS and disease-specific survival of 75% and 92%, respectively, the authors concluded that SN biopsy in early-stage vulvar cancer was an oncologically safe procedure.

6. Conclusions

The 18th biennial IGCS meeting was a successful one, with record breaking attendance. In addition to the above noted presentations, there were multiple tumor board sessions, education sessions in sentinel node dissection and other topics, and presentations regarding fertility preservation and survivorship. Starting in 2019 in Rio De Janeiro, the IGCS meetings will become annual meetings.

Conflict of interest

Dr. Diane Yamada has the following conflicts: Clinical trial funding to OBGYN department at University of Chicago.

Dr. Dong Hoon Suh has no conflicts to report.

Dr. Michelle Wilson has received travel support from Roche and MSD.

Dr. Duska has the following conflicts: Advisory board for Merck, Genentech and MedImmune. DSMB for Inovio. Clinical trial funding to OBGYN department at University of Virginia.

Author contribution

All authors wrote sections, provided content and reviewed final draft. Drs. Yamada and Duska consolidated and edited the manuscript.

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