Gynecologic Oncology 153 (2019) 467–470

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Conference Report

Highlights from the Society of Gynecologic Oncology's 50th Annual Meeting on Women's Cancer

1. Introduction

The Society of Gynecologic Oncology hosted the 50th Annual Meeting on Women's Cancer in Honolulu, Hawaii from March 16–19, 2019. There was record attendance to this year's meeting, which opened with traditional Hawaiian music and a procession of past SGO presidents. The conference was a celebration of the sub-specialty of Gynecologic Oncology and had an inclusive atmosphere. The continually growing membership including advance practice providers, trainees, and international members was readily apparent. The theme of the meeting and presidential address was advocacy for health equity.

2. Theme 1: PARP inhibitors

The opening plenary session presented the results of several post-hoc analyses of large clinical trials involving PARP inhibitors. Dr. Ursula Matulonis presented a TWIST analysis of ENGOT-OV16/NOVA trial which demonstrated that patients treated with niraparib experienced more progression-free time without symptoms or toxicities due to nausea, vomiting or fatigue compared to placebo (abstract 1). In the second abstract, an exploratory post hoc analysis of all treated patients in QUADRA by baseline body weight and platelet count was presented. Results demonstrated that early dose reduction does not appear to compromise efficacy in patients with baseline body weight <77 kg or platelet count <150,000/μL. This was followed by data from the blinded pooled interim safety data from the PRIMA/ENGOT-OV26/GOG 3012 study which confirmed that adverse events decreased among patients receiving a 200 or 300 mg individualized starting dose of study drug versus those receiving a 300 mg fixed starting dose with no apparent decrease in efficacy. Individualized dosing significantly decreased grade 4 thrombocytopenia as well as ≥grade 3 hematologic and non-hematologic toxicities (abstract 3).

In another post hoc exploratory analysis, the effect of age on the efficacy and safety of rucaparib among platinum sensitive ovarian cancer patients in ARIEL 3 was explored. Generally, the safety profile was consistent across the age subgroups (<65, 65–74, or ≥75 years) but rates of dose modification and discontinuation were higher in patients >65 years than in patients <65 years (abstract 4).

The data from SOLO-1 which compared olaparib maintenance to placebo in platinum-sensitive patients (at 50.6% maturity), demonstrated a significant progression-free survival (PFS) benefit for the olaparib arm with a hazard ratio of 0.30 (95% CI 0.23–0.41) and highlights the importance of considering upfront somatic testing. While SOLO-1 included only a few patients with somatic BRCA mutations, a review of prior trials demonstrated benefit of PARP inhibitors in this cohort (abstract 6). The seminal abstract session reviewed the outcomes from the SOLO-1 trial and demonstrated an improvement in PFS among BRCA mutation carriers with the difference in median PFS for olaparib versus placebo of approximately 3 years. There was also statistically significant improvement in PFS2 suggesting that olaparib did not diminish a patient's ability to benefit from subsequent therapy (abstract 24). With the increasing number of front-line trials including PARPi, re-challenge with PARPi was addressed by abstract 7, which showed 13.6% partial response and 59.1% stable disease in a small cohort, suggesting further research is warranted.

3. Theme 2: Immunotherapy

While PARP inhibitors are now a part of the standard of care in ovarian cancer treatment, the application of immunotherapy is still largely being explored in ovarian and other gynecologic cancers. Recurrent ovarian cancer (mainly platinum-resistant disease) is the leading cause of death from gynecologic cancers. In the late-breaking abstract session, Dr. Pujade-Lauriane presented results from Javelin Ovarian 200 trial, which was a randomized trial in platinum resistant or refractory ovarian cancer patients. Patients received avelumab alone, doxil alone, or avelumab plus doxil. The primary objective of improved PFS or overall survival (OS) was not met (late-breaking abstract # 1). Keynote-100, a phase 2 trial in patients with recurrent ovarian cancer treated with single agent pembrolizumab, showed an objective response rate (ORR) of only 8%. A PD-L1 immunohistochemistry (IHC) analysis showed that a combined positive score (CPS), as determined by the number of PD-L1 staining cells divided by the total number of viable tumor cells times 100, was predictive of response (CPS ≥1 and ≥10). Patients who experienced complete responses, all had CPS of ≥10 (abstract 26).

While single agent checkpoint inhibitor therapy may not have significant activity, combination with other agents may lead to increased efficacy. Dr. Emese Zsiros presented a single arm phase 2 trial of patients with platinum-resistant disease or patients who refused re-treatment with a platinum agent, who were treated with pembrolizumab in combination with bevacizumab and cyclophosphamide. The combination therapy demonstrated an ORR of 40% (compared to prior data of 8% with pembrolizumab monotherapy and 24% with bevacizumab/cyclophosphamide) with an approximate 30% long-term clinical benefit rate in patients receiving over 12 cycles of treatment (late-breaking abstract # 4). Indoleamine 2,3-dioxygenase (IDO) pathway is implicated in cancer immune escape. Dr. Rod Rocconi and colleagues demonstrated that patients with African ancestry had the highest upregulation of 5 genes in the IDO pathway which allows for tumor escape from immune control and adaptive resistance, correlating to a poorer survival. These

* Corresponding author.
E-mail address: denglish@stanford.edu (D.P. English).

https://doi.org/10.1016/j.ygyno.2019.04.652
0090-8258/

findings suggest that black patients demonstrated an enhanced IDO pathway expression and may benefit from targeted immunotherapy which offers a potential to close the racial disparity gap (abstract 21).

There are currently two FDA approved anti-PD1 inhibitors (nivolumab and pembrolizumab), three anti-PD-L1 (avelumab, atezolizumab, and durvalumab), and one anti-CTLA 4 (ipilimumab), all of which are immune checkpoint inhibitors (ICI). In gynecologic cancers, pembrolizumab was FDA approved in 2017 for patients with mismatch repair deficient (MMRd) tumors who have failed standard therapy and just this past year, pembrolizumab was approved for PD-L1 positive cervical cancers. Dr. Christine Walsh presented data from a phase 2 trial in platinum-resistant ovarian cancer which combined pembrolizumab with chemotherapy. The regimen was well tolerated but it did not demonstrate an improvement in PFS (abstract 32). The NCI 10010 study of atezolizumab in combination with bevacizumab in patients with recurrent, persistent, or metastatic cervical cancer did not meet the needed number of confirmed objective responses to expand successfully to the second stage. There were two grade 3 neurologic events reported which may be due to the combination therapy (abstract 34). Preliminary data from the Garnet, phase 1/2 clinical trial in patients with recurrent or advanced endometrial cancer utilizing dostarlimab, an anti-PD1 inhibitor, showed ORR of 30% (ORR of 49% in patients with microsatellite instability-high and 20% in microsatellite stable patients) that was durable in both cohorts. Dostarlimab presents a unique dosing schema from the other ICIs currently available, with the first four doses administered every 3 weeks then subsequent doses every 6 weeks (abstract 33).

The only immunotherapy trial presented that did not utilize checkpoint inhibition was the phase 2 study of dendritic cell vaccine (DCVac) combined with second line chemotherapy in recurrent ovarian cancer (SOV02). The study randomized patients to standard carboplatin/gemcitabine (GC) versus GC plus in parallel DCVac. In the 32 patients treated in each cohort, concomitant DCVac increased PFS by 1.2 months and OS by 13.4 months with a favorable toxicity profile (abstract 35). Dr. Kunle Odunsi categorized immunotherapy treatment in his distillation into (1) eliciting antigen-specific T cells, (2) enhancing infiltration of T cells into tumor and (3) rescuing T cells from exhaustion. However, further research is needed to examine mechanisms of resistance to ICIs in gynecologic malignancies, identify likely responders versus non-responders, and identify biomarkers that may guide selection of the most appropriate immunotherapy.

4. Theme 3: Cervical cancer management

The discussion around the surgical management of early stage cervical cancer, as expected, was filled with passion and vigor. Dr. Pedro Ramirez, lead investigator of the minimally invasive versus abdominal radical hysterectomy for cervical cancer (LACC) trial, gave an update.

The primary objective of the trial was to compare the disease-free survival (DFS) at 4.5 years among patients who were randomized to minimally invasive (MIS) hysterectomy versus open radical hysterectomy for early stage cervical cancer (stage 1A1 with lymphovascular invasion – stage 1B1) [1]. 84% of the MIS arm had laparoscopy. The hazard ratio for DFS was 3.96 (95% CI 1.91–8.21) in favor of open surgery. In the intention-to-treat population, the disease-free survival proportion at 4.5 years was 96.3% in the open surgery arm and 84.3% in the MIS arm. Dr. Ramirez also summarized the findings from Dr. Alexander Melamed's study that showed a 4-year mortality of 9.1% among patients who had MIS versus 5.3% among those who had open surgery ($p = 0.002$). Dr. Melamed's study also reported that the adoption of MIS coincided with a decline in 4-year relative survival rate of 0.8% per year after 2006 [2]. Dr. Ramirez went on to judiciously address several points of discussion regarding this randomized controlled surgical trial. The audience was also reminded about the limitations of prior studies on this topic with mainly retrospective, single institution data existing in the literature before the results of this trial. The question thus remains whether it is ethical to perform another such trial and more so, whether there is a need for another randomized control trial on this subject?

Dr. Anna Fagotti reviewed the data available from multiple institutions on the use of MIS versus open radical hysterectomy in early stage cervical cancer patients. Included in this overview was the Korean retrospective case-control study comparing survival outcomes of MIS versus open surgery for radical hysterectomy in patients with stage 1B1-IIA2 cervical cancer presented by Dr. Kim. MIS radical hysterectomy was associated with higher recurrence rates than open radical hysterectomy in early stage cervical cancer. However, this study group suggested that MIS may have a role for FIGO stage 1B1 disease with cervical mass size ≤2 cm on preoperative MRI based on a subgroup analysis revealing no compromise in survival for this subset of patients (abstract 17).

In regards to management of locally advanced cervical cancer, a National Cancer Database (NCDB) study validated the current standard care of external beam radiation (with chemotherapy for radiation sensitization) combined with brachytherapy. Despite this being the standard of care, brachytherapy has declined in the United States since the 1980s with continued racial disparities in the delivery of care. Dr. Korenaga of the University of California, San Francisco (UCSF) reported their NCDB study of >10,000 patients diagnosed with locally advanced cervical cancer in the USA in the period 2004–2015 treated with chemo-radiation. 75% patients received a brachytherapy boost, half of which received treatment within the recommended 8 weeks timeframe (abstract 10). The results strongly support performing the brachytherapy boost/intracavitary radiation regardless of the total duration of treatment. Access to care challenges exist for intracavitary radiation therapy throughout the United States, however practitioners must advocate that their patients receive the standard of care management of locally advanced cervical cancer despite delays in completion.

Drs. Alimena and King presented their data on the racial disparities for the receipt of brachytherapy. Black women who received brachytherapy within the recommended timeframe had similar survival rates to white women, indicating that the survival difference by race was mediated by brachytherapy use in the interaction model (abstract 11). Dr. Catheryn Yashar reported on the decrease in use of brachytherapy (from 96.7% to 86.1%) with increases in IMRT (intensity-modulated radiation therapy)/SBRT (stereotactic body radiation therapy) from 3.3% to 13.9%. This change in practice has resulted in a more pronounced mortality rate for those that did not receive brachytherapy than for those who did not receive chemotherapy.

The Japanese Gynecologic Oncology Group (JGOG) performed a multicenter retrospective analysis on paclitaxel and weekly cisplatin with radiation versus weekly cisplatin with radiation, demonstrating, an improved 2-year DFS of 72.5% vs 41.8% respectively (abstract 81).

5. Theme 4: Genetic testing and molecular targeted therapy

A population based study in Thailand aimed to evaluate the prevalence of MMR-deficiency in endometrial tumors and germline MMR mutation in endometrial cancer patients.

MMR deficient patients were referred for genetic counseling and offered germline testing using gene panel next-generation sequencing (abstract 84). MMR deficiency was detected in 36.1% of endometrial cancer patients. At least 1/3 of patients that did not meet the revised Bethesda criteria were MMR deficient. A germline MMR mutation was found in 2.5% of the patients.

Germline genetic testing is recommended for all patients diagnosed with ovarian cancer however germline testing for high-grade serous ovarian cancer has a relatively low referral rate. An interesting simulation model was presented to compare universal germline testing of all high grade serous ovarian cancer to tumor testing as triage for pursuing germline testing (abstract 5). This strategy of triage with tumor testing was found to be cost-effective and 2 way sensitivity analyses showed good sensitivity of this approach however this approach can miss up

to 5% of germline BRCA patients as pointed out by Dr. Kathleen Moore. Germline testing therefore remains the standard of care for genetic testing as it is more effective at identifying BRCA mutation carriers.

Dr. Jorge reported on experience with simultaneous clinical testing for both germline and somatic mutations in 43 ovarian cancer patients. This combined testing approach is important early on in the treatment of ovarian cancer given the role for PARP inhibitors in the upfront maintenance setting for platinum-sensitive patients. The overall BRCA mutation rate (germline and somatic) was 30%. This study team found that the results of testing impacted clinical decision-making such as enrollment in clinical trials and receipt of parp inhibitors in 23.3% of cases (abstract 6).

The late-breaking abstract session also featured the prospective multicenter TUBA study, about worry and regret in BRCA1/2 mutation carriers (late-breaking abstract # 2) and the WISP trial, a prospective, multicenter trial of salpingectomy with delayed oophorectomy versus risk-reducing salpingo-oophorectomy in women at increased risk for hereditary cancer (late-breaking abstract # 3). Both trials demonstrated decreased worry/distress after risk-reducing surgery and that delayed risk-reducing oophorectomy is feasible. Patients who had risk-reducing bilateral salpingo-oophorectomy and menopausal symptoms had the highest level of regret. At this time, salpingectomy and delayed oophorectomy is not recommended outside of a clinical trial despite the feasibility of this approach for patients at increased risk for hereditary cancer.

An innovative therapeutic approach for patients with recurrent endometrial, ovarian, fallopian tube or primary peritoneal cancer was investigated in a phase 1 trial of weekly paclitaxel in combination with the oral multi-targeted tyrosine kinase inhibitor, Lenvatinib. This combination was found to be safe and tolerable with demonstrable activity in recurrent platinum resistant ovarian cancer as well as endometrial cancer. The ORR was 71% for platinum-resistant ovarian cancer with a median PFS of 14 months. Recurrent endometrial cancer patients in this study had an ORR of 50% and median PFS of 12.8 months (late-breaking abstract # 5).

Dr. Anishka D'Souza, the winner of the SGO Presidential Award, presented abstract 18, Neratinib in patients with HER2-mutant metastatic cervical cancer. Neratinib monotherapy led to durable responses and disease control in metastatic HER2-mutated cervical cancer patients in this clinical trial. The ORR was 27.3% in these patients with a median PFS of 7.0 months. Neratinib was fairly well tolerated and diarrhea was not a treatment-limiting toxicity with the use of anti-diarrheal prophylaxis.

6. Theme 5: Palliative care, wellness and survivorship

SGO has embraced the value of palliative care as a critical component of comprehensive cancer care. At this year's conference, leaders in the field addressed developing a curriculum for clinicians at all levels.

Wellness and mitigating burn-out or moral injury featured again in this year's program [3,4]. The prevalence of burn-out among gynecologic oncology fellowship trainees and risk factors associated with reduced career fulfillment was highlighted in abstract 14. This data was collected from an electronic survey to ACGME-accredited Gynecologic Oncology fellowship programs in Spring 2018. Rates of burn-out among gynecologic oncology trainees were much greater than anticipated with one quarter of respondents reporting a lack of formalized training and resources for physician wellness. This sobering report was followed appropriately by the presentation of the SGO wellness curriculum pilot: A groundbreaking initiative for fellowship training (abstract 15). This wellness curriculum for gynecologic oncology fellowships was created by members of the wellness taskforce and included 15 beta sites. The modules included resiliency, managing priorities, empathy and positivity and communication training. The pilot was a success with the instructor training course leading to increased comfort of the fellows discussing wellness topics.

Survivorship topics abounded in the Honolulu conference with the spotlight being turned on the prevalence of abuse history and sexual distress among women with cancer seeking care for sexual dysfunction (abstract 37). Also highlighted were opportunities to improve sexual health and quality of life in endometrial cancer survivors presented by Dr. Glaser (abstract 38). Over 60% of sexually active women with early stage endometrial cancer and stress urinary incontinence in this study were found to have sexual dysfunction. This was associated with a poorer quality of life for these patients and is an important consideration in the setting of prolonged survivorship.

Despite the impact of obesity and physical activity on inflammation and cancer mortality in women (abstract 39), a randomized controlled trial of behavioral weight loss interventions in endometrial cancer survivors showed that weight-loss interventions are feasible but insufficient to address the scale of obesity in the participating survivors (abstract 40).

7. Theme 6: Challenges in cancer care delivery

Several abstracts focused on the challenges in cancer care delivery and were punctuated by two dynamic speakers, Dr. Agnes Binagwaho and Dr. Groesbeck Parham. Among gynecologic cancers, cervical cancer, is the fourth most common, and has the most significant racial and socioeconomic disparities. Dr. Jessica Gillen evaluated the effect of social service programs among women receiving chemo-radiation therapy in a retrospective study. Dr. Gillen and her team noted that low income patients who received assistance from cancer centers did not experience a significantly different median PFS or OS (abstract 9). Further studies tailoring assistance programs based on patients' self-identified barriers to completion of care will further guide interventions. Dr. Margaret Liang identified younger age and lower income as risk factors for financial toxicity while having insurance was not protective. Financial toxicity was found to affect approximate 50% of gynecologic cancers patients receiving systemic therapy (abstract 8).

Dr. Binagwaho, the SGO presidential invited guest speaker, framed her address around the importance of social capital which is built on trust. Dr. Binagwaho was very motivated to establish a HPV vaccination program in Rwanda. She spoke of the violence and hate that the country had seen and how addressing prior wrongs and apologizing was a way forward to restore the country's spirit after mass genocide. Communities then began to heal and forgave each other over time. Dr. Binagwaho was able to skillfully engage the government, the religious leaders, the community leaders and other stake holders to recognize the critical importance of a school-based HPV vaccination program by way of a widespread educational campaign.

Dr. Parham, for his ABOG lectureship, similarly tackled programmatic and leadership challenges, and how overcoming these relies on having imagination with a definite aim to guide progress. He ultimately encouraged the audience to not be afraid and spoke to the audience as all prospective leaders. Dr. Parham reminded us of the need to cherish our vision and dreams and also to remain excited about the future.

In conclusion, the research presented was of the usual high-quality that has come to be expected from this well-organized scientific conference. The program committee, led by Drs. Wendy Brewster and Diane Yamada, put together a well-structured program with ample time for attendees to experience the mystical and beautiful meeting location. The conference had an air of excitement, passion and comradery. The highlights of the meeting are many as noted in this review and speak to the progress we have made in understanding the biology of disease, appropriate interventions for diseases and the value of quality of life indicators for the patients we serve. We encourage readers to visit the SGO mobile app and the online abstract supplement to access the publications discussed in this paper as well as others from this outstanding meeting.

References

[1] P.T. Ramirez, M. Frumovitz, R. Pareja, A. Lopez, M. Vieira, R. Ribeiro, A. Buda, X. Yan, Y. Shuzhong, N. Chetty, D. Isla, M. Tamura, T. Zhu, K.P. Robledo, V. Gebski, R. Asher, V. Behan, J.L. Nicklin, R.L. Coleman, A. Obermair, Minimally invasive versus abdominal radical hysterectomy for cervical cancer, N. Engl. J. Med. 379 (2018) 1895–1904.
[2] A. Melamed, D.J. Margul, L. Chen, N.L. Keating, M.G. Del Carmen, J. Yang, B.L. Seagle, A. Alexander, E.L. Barber, L.W. Rice, J.D. Wright, M. Kocherginsky, S. Shahabi, J.A. Rauh-Hain, Survival after minimally invasive radical hysterectomy for early-stage cervical cancer, N. Engl. J. Med. 379 (2018) 1905–1914.
[3] M.L. Kelley, A.J. Bravo, R.L. Davies, H.C. Hamrick, C. Vinci, J.C. Redman, Moral injury and suicidality among combat-wounded veterans: the moderating effects of social connectedness and self-compassion, Psychol. Trauma (2019)https://doi.org/10.1037/tra0000447 [Epub ahead of print].
[4] K.G. Meador, J.A. Nieuwsma, Moral injury: contextualized care, J. Med. Humanit. 39 (2018) 93–99.

Diana P. English
Stanford University, CA, United States of America
Corresponding author.
E-mail address: denglish@stanford.edu.

Marilyn Huang
Department of Obstetrics and Gynecology, Sylvester Cancer Center/ University of Miami, United States of America