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Conference Report

Society of Gynecologic Oncology 2016 Annual Meeting: Highlights and context

1. Introduction

The Society of Gynecologic Oncology hosted the 47th Annual Meeting on Women's Cancer in San Diego March 19 to 22, 2016. This year's meeting eclipsed 2100 attendees and member engagement was stronger than ever. Dr. Robert Coleman's presidential address opened with a flashback to the post-World War II era when, as Devita recounts, "the main issue of the day was whether cancer drugs caused more harm than good, and talk of curing cancer with drugs was not considered compatible with sanity." [1]. Flash forward to now and Dr. Andrew Futreal's invited lectureship where he spoke of the creation of a "big data interchange" that will enable clinicians working in collaboration with computational scientists to dynamically reinterrogate hundreds of thousands of cancer cases over time. The major scientific discoveries presented at this year's meeting and discussed below center around several prevailing themes: (1) genetics and genomics; (2) novel pathways and clinical trials; (3) surgical innovation; (4) health care reform and value based care; and (5) screening and prevention.

2. Theme 1: genetics & genomics

The discovery and interrogation of the putative effects of germline mutations in *BRCA1* and *BRCA2* was eloquently discussed at the SGO ABOG lectureship held on Sunday, March 20.

We have learned over the past few years that there are additional, less prevalent mutations which are also considered high penetrance for risk of ovarian cancer. This knowledge stems from the increasing availability and reduced cost of massively parallel sequencing, which allowed for testing for a panel of genetic mutations. Interrogation of tumors for somatic mutations has increased due in large part to the same set of circumstances that allowed for germline panel testing. Somatic mutations in genes involved in homologous recombination (HRD) not only have been identified in tumor samples from women with ovarian cancer, but also correlated with prognosis and response to chemotherapy [2–4]. This knowledge has led to the development of reproducible "HRD assays" which may be run on patient tumor samples and used to select patients for particular therapies, most commonly, PARP inhibitors [5,6]. **Abstract 2** presented by Dr. Gordon Mills was a very large retrospective validation of a HRD score as predictive of progression free (PFS) and overall survival (OS) among over 800 women treated with platinum-based chemotherapy. The score was comprised of the sum of 3 independent measures of HRD; loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large scale state transitions (LST). In previous work, the sum of these measures ≥42 was identified as HR deficient, defining the cutpoint used in this present work. As reported, the combined HRD score was highly predictive for PFS ($p = 2.2 \times 10^{-6}$) and OS ($p = 1.0 \times 10^{-8}$), whereas the individual components were not significantly predictive.

Abstract 1 presented by Dr. Barbara Norquist on behalf of the NRG is one of the largest assessments of germline and somatic mutation association with response to front line therapy and outcome performed in a copiously annotated dataset to date. Here the authors sequenced 64% of the participants in GOG protocol 218 (n = 1195/1873) using the BROCA-HR targeted capture, multiplex sequencing assay. Defects in HRD were defined as damaging mutations in *ATM*, *ATR*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, *RBBP8*, *SLX4*, and *XRCC2*. They found that 12.4% of patients had a mutation in *BRCA1*, 6.5% in *BRCA2*, and 6.8% in other HRD genes for a total of 25.7% of patients with a germline and/or somatic mutation in genes related to HRD. The adjusted hazard ration (HR) for PFS by mutation category was 0.52($p < 0.0001$) for *BRCA2*, 0.80 ($p = 0.02$) for *BRCA1* and 0.73 ($p < 0.01$) for other HRD mutations using the reference group of no HRD mutation = 1. The adjusted HR for OS was 0.36 ($p < 0.0001$) for *BRCA2*, 0.74($p = 0.01$) for *BRCA1* and 0.67 ($p < 0.007$) for other HRD genes.

Norquist et al. evaluated this question and found that HRD mutation status did not significantly modify the effect of bevacizumab on progression free survival.

Finally, on the topic of genetics, Dr. Andrew Berchuck (**Abstract 25**) presented data from the Ovarian Cancer Association Consortium evaluating racial differences in the prevalence of ovarian cancer risks related single nucleotide polymorphism (SNPs). 18 SNPs associated with ovarian cancer risk were studied. There was a difference in the distribution of these SNPs by race (attributable genetic risk 15.1% vs. 29.1% in Africans vs. Europeans respectively); indicating that common genetic variants that increase risk for ovarian cancer are more common among those with European ancestry accounting for much of the racial disparity in incidence.

3. Theme 2: clinical trials

3.1. Theme 2.1: ovarian cancer

Dr. Joan Walker on behalf of the NRG presented the very preliminary results of GOG 252 (**LBA 6**). This was a randomized phase III trial for patients who had undergone primary cytoreductive surgery (pCRS) and had residual disease <1 cm. Participants were randomized to 1 of 3 arms: Arm 1: paclitaxel 80 mg/m^2 (IV) day 1, 8, 15 and carboplatin AUC 6(IV) day 1; Arm 2: paclitaxel 80 mg/m^2 day 1, 8, 15 and

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carboplatin AUC 6 (IP); Arm 3: paclitaxel 135 mg/m^2 (IV) day 1, cisplatin 75 mg/m^2 (IP) day 2 and paclitaxel 60 mg/m^2 (IP) day 8. All arms had bevacizumab 15 mg/kg both during and following chemotherapy ×22 cycles. Patients in Arm 2 and 3 crossed over to IV chemotherapy 16 and 28% of the time. There was no difference in PFS with a median of 26.8, 28.7 and 27.8 months in Arms 1–3 respectively (p = ns).

Not only was there no superior arm, but the median PFS seemed much lower than expected for this population. Looking at only those patients deemed to be left with no gross residual at the time of pCRS, the results of GOG 172 appear to be the outlier at median of 60.4 months as compared to 33.8 months in Arm 3 of GOG 252. So what happened here? In her distillation of this presentation, Dr. Gini Fleming brought up several questions regarding these results. Could the dose of cisplatin in GOG 252 have played a role in the attenuated survival data? Prior IP studies all used a cisplatin dose of 100 mg/m^2 [7–9]. Reports from cisplatin dose finding studies comparing 75 mg/m^2 to 100 mg/m^2 (GOG 132) would suggest these doses are equivalent [10]. Could the change from 24 to 3 h paclitaxel between 172 and 252 have muted the results in the IP arm? Studies of 24 vs. 96 h paclitaxel in ovarian cancer have not demonstrated differences in OS and a direct comparison of 3 vs. 24 h paclitaxel in breast cancer patients similarly found no differences [11–13]. Further analysis of the GOG 252 data and consideration of selection biases for this trial and the original GOG 172 may help discern these results.

With the publication of EORTC 55971 [14] and the CHORUS trial [15], use of neoadjuvant chemotherapy (NACT) has increased. This increase has prompted evaluation of prognostic markers for those patients who undergo iCRS. These markers include radiographic complete response or pathologic complete response (pCR) at the time of iCRS, the later mirroring clinical trial outcomes in breast cancer where pCR is strongly prognostic for both disease free and OS [16] and is used as a method to rapidly assess the efficacy of new therapeutics. **LBA 1** presented by Dr. Stan Kehoe on behalf of the CHORUS investigators reported their analysis of complete radiographic response among the women randomized to NACT and underwent iCRS. Of these 217 women, 4% had no evidence of disease, 87% had stable disease (which included partial responses) and 9% had progression on CT following cycle 3. At time of surgery, 4% had no visible disease, 12% had ≤1 cm and 84% > 1 cm. Correlation of these values with outcome has not yet been performed.

Dr. Peter Rose for the NRG presented an analysis of GOG 152 which was a study of patients with suboptimal residual disease who were then randomized to a secondary CRS or not. **LBA 2** presents the findings at the secondary cytoreduction. Of 216 women randomized to the secondary surgery, 70.8% had grossly evident disease remaining after 3 cycles of chemotherapy, 3.7% had microscopic disease only and 18.5% had a pCR. Women with a pCR had statistically improved PFS with median of 16.1, 13.5 and 11.5 months respectively for pCR, microscopic and gross disease (p = 0.002). OS medians were 51.5 vs. 42.6 vs. 30.8 months respectively (p = 0.008). These results suggest a possible role of pCR as an early study endpoint in ovarian cancer.

3.1.1. Recurrent ovarian cancer

Two trials from the NRG were presented evaluating therapies in patients with up to 3 prior therapies and PFI < 12 months (if only 1 prior therapy). **Abstract 10,** presented by Dr. David Cohn reported the results of NRG/GOG 186h. This trial was a randomized phase 2 comparing weekly paclitaxel at 80 mg/m^2 (IV) day 1, 8, 15 with or without Reolysin 3×10^{10} $TCID_{50}$ per day IV on days 1–5 q 28 days. There was no difference PFS or OS. The response rate for the Reolysin vs. paclitaxel alone arm was 17 vs. 20% (OR 0.84; 0.30–2.33). NRG/GOG protocol 186k was presented by Dr. Ursula Matulonis as **LBA 4**. This trial had the same eligibility as 186h but compared weekly paclitaxel 80 mg/m^2 IV day 1, 8, 15 to cabozantinib 60 mg po qd continuous dosing q 28 days. PFS did not differ and neither did OS. Response rates actually favored the weekly paclitaxel arm (8.3 vs. 28.3%) (OR 0.23; 0.06–0.72). While the lack of difference was disappointing, both studies reconfirmed the high activity of weekly paclitaxel (20 and 28%) in this setting.

3.2. Theme 2.2: endometrial cancer/sarcoma

Despite the presence of putative "actionable mutations of interest," targeted therapies in endometrial cancer have been disappointing. Attention has shifted to dual blockade (preventing cross talk) as was presented at this annual meeting. Dr. Shannon Westin on behalf of the NRG presented the results of GOG 229O (**Abstract 6**) which combined the MEK inhibitor Trametinib with GSK2141795, an AKT inhibitor. This study, contained a safety lead in which found that dose level 1 was not feasible and dose level −1, while feasible, had minimal activity with only 1 partial response reported. This level of activity did not warrant additional study. However, targeting the AKT pathway may still be an active intervention with a different partner. This was addressed in **Abstract 7** presented evaluating blockade of both AKT and P70S6K which is a downstream target of mTORC using MSC2363318A.

Dr. Westin also presented a prospective, single arm study using the levonorgestrel intrauterine system to treat complex atypical hyperplasia (CAH) and grade 1 endometrial carcinoma (EC). (**Abstract 41**) The primary outcome was response at 12 months. Of the 43 evaluable patients, the 12 month response was 90% (12/43) among those with CAH and 54% (12/43) among those with EC. Presence of exogenous progesterone effect on the 3 month surveillance biopsy was predictive of 12 month response (p < 0.001) as was lower Ki67 (p = 0.04). Baseline higher gene expression of estrogen induced genes such as sFRP4 (p = 0.04), sFRP1(p = 0.04), IGF1 (p = 0.02)and RALDH2 (p = 0.03) were all also predictive for 12 month response.

Dr. Amanda Nickles Fader presented early results of an endometrial cohort treated with an anti-PD-1 monoclonal antibody (**LBA 3**). In this clinical trial, patients with mismatch repair deficiency are treated with the anti PD-1 pembrolizumab 10 m/kg IV q 2 weeks and the primary endpoint is immune related response rate and immune related PFS at 20 weeks. Eligibility was based on the Promega MSI Analysis system. Among the 9 patients enrolled, the overall immune related response rate was 66.7% including 2 complete responses. Immune related PFS at 20 weeks was 77.9% and 6/9 patients remain on study beyond 50 weeks. Although limited to only 9 patients, this level of activity outside of front line is rarely reported and warrants definitive clinical trials to validate these findings and expand availability of these agents to appropriately selected patients.

3.2.1. Sarcomas

Treatment outcomes for patients with advanced/recurrent uterine leiomyosarcoma (uLMS) are poor. Front line therapy include either gemcitabine/taxotere [17] or adriamycin/ifosfamide. Pazopanib has approval as second line or beyond with an overall response rate of 6% and median PFS of 5 months [18]. Dr. Martee Hensley presented a subgroup analysis of a larger randomized phase III trial of trabectedin 1.5 mg/m^2 24 h infusion vs. dacarbazine 1 mg/m^2 in L-type sarcomas following treatment with an anthracycline. **(Abstract 3)** Of 577 patients, 232 (40%) were uLMS. The median PFS was 4 vs. 1.5 months for trabectedin vs. dacarbazine respectively (p = 0.0012). Overall response rate is 11.2 vs. 9% (p = 0.816). OS did not differ at 13.4 vs. 12.9 months (p = 0.6107). This, now FDA approved agent, provides another line of therapy for our patients.

4. Theme #3: surgical innovation

4.1. Enhanced recovery after surgery for gynecologic malignancies

At this year's surgical innovations session, Professor Olle Ljungqvist took us through his 15 year journey with implementing an evidence-based, multimodal perioperative care protocol (or "enhanced recovery