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SGO Journal Club Commentary

Society of Gynecologic Oncology Journal Club: Controversial conversations in gynecologic cancer – Navigating maintenance therapy for homologous recombinant proficient ovarian cancer

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A B S T R A C T

The Society of Gynecologic Oncology (SGO) Journal Club is an open forum to review pertinent studies relevant to controversial topics in the management of gynecologic cancers. On August 3rd, 2022, SGO hosted a Journal Club focused on the role of maintenance therapy for homologous recombinant proficient (HRP) patients with ovarian cancer. Navigating optimal therapies has become more complex with the emergence of new clinical trial data and the evolving understanding of how to classify ovarian cancers as HRP. Our speakers, Drs. Susan Modesitt, Barbara Norquist and Rodney Rocconi presented Gynecologic Oncology Group (GOG) 218 (Burger et al., 2011), the VITAL Trial (Rocconi et al., 2021), and the PRIMA study (Gonzalez-Martin et al., 2019). We asked our experts to discuss their opinions and interpretations on the application of these data to current clinical practice. Poll questions were presented to the audience for a pre- and post-webinar comparison (Table 1). Results of the poll questions are shown in Table 1.

1. Current state of maintenance therapy

The concept of maintenance therapy in the treatment of ovarian cancer is not novel. Previous efforts included the GOG 178 (Markman et al., 2003) and GOG 212 trial (Copeland et al., 2022) investigating the benefit of maintenance taxanes, the MIMOSA study investigating the role of abagovomab, a murine monoclonal antibody recognizing CA 125 (Sabbatini et al., 2013) and the AGO-OVAR-16 trial investigating maintenance pazopanib (Vergote et al., 2019). Such efforts have been limited by lack of efficacy and/or treatment-limiting toxicity (see Table 1).

The SOLO-1 trial was the first trial to show the substantial progression-free survival (PFS) benefit of maintenance poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor (PARPi) therapy in patients with BRCA1 or BRCA2 mutations, an important cause of homologous recombination deficiency (HRD) (Frey and Pothuri, 2017). Subsequent trials investigating FDA-approved PARPi include PAOLA (Ray-Coquard et al., 2019) and PRIMA (Gonzalez-Martin et al., 2019) which included patients with and without BRCA mutations and also showed significant PFS benefit. These trials conducted pre-planned analyses of patients with BRCA1 and BRCA2 mutations, patients without these mutations but with evidence of HRD, and those with HRP tumors. The PRIMA trial demonstrated a PFS benefit for the combined cohort; however, this benefit was significantly higher in those patients with a BRCA mutation or another source of HRD. Some have suggested that the “PARP for all strategy” may be inappropriate given the more limited benefit of maintenance PARPi therapy in patients with HRP tumors, as well as the clinical and financial toxicities of this therapy (Shah et al., 2021). Given that more than 50 % of patients with epithelial ovarian cancer will have HRP tumors, there is a continued need to investigate additional strategies to optimize the care of such patients.

2. GOG 218

Dr. Norquist first presented a review of GOG 218, a prospective randomized three-armed trial comparing carboplatin and paclitaxel with bevacizumab, or followed by bevacizumab maintenance in patients with primary ovarian cancer post debulking surgery (Burger et al., 2011). Patients who received bevacizumab with chemotherapy and as maintenance had a 3.8-month improvement in PFS (HR 0.72, 95 % CI

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month improvement in OS (HR 0.75, 95% CI 0.59–0.97) to upfront treatment for high grade epithelial ovarian cancer who have a germline mutation in BRCA, your standard recommendation for maintenance therapy (assuming no trial available) is the following:

|                | Pre-responses | Post-responses |
|----------------|---------------|----------------|
| * Taxane/platinum | 29            | 20             |
| * Taxane/platinum/bevacizumab | (72.5%) | (95.2%) |
| * Non-taxane/platinum | 22            | 15             |
| * Non-taxane/platinum/bevacizumab | (25%) | (4.8%) |
| * Other          | 0%            | 0%             |
| * Bevacizumab alone | 1            | 0%             |
| * PARP inhibitor alone | 14          | 0%             |
| * PARP plus bevacizumab | 12          | 0%             |

2. For women with a complete response/remission to upfront treatment for high grade epithelial ovarian cancer with an HRD tumor, your standard recommendation for maintenance therapy (assuming no trial available) is the following:

|                | Pre-responses | Post-responses |
|----------------|---------------|----------------|
| * Nothing      | 1             | 0%             |
| * Bevacizumab alone | (2.3%) | 0% |
| * PARP inhibitor alone | (88.4%) | 0% |
| * PARP plus bevacizumab | (7%) | 0% |

3. For women with a complete response/remission to upfront treatment for high grade epithelial ovarian cancer who have an HRP tumor, your standard recommendation for maintenance therapy (assuming no trial available) is the following:

|                | Pre-responses | Post-responses |
|----------------|---------------|----------------|
| * Nothing      | 2             | 0%             |
| * PARP inhibitor alone | (6.5%) | 0% |
| * Bevacizumab alone | (83.9%) | 0% |
| * PARP plus bevacizumab | (3.2%) | 0% |
| * Other        | 0%            | 0%             |

4. For women with a complete response/remission to upfront treatment for high grade epithelial ovarian cancer who have an HRP tumor, your standard recommendation for maintenance therapy (assuming no trial available) is the following:

|                | Pre-responses | Post-responses |
|----------------|---------------|----------------|
| * Nothing      | 16            | 18             |
| * PARP inhibitor alone | (44.4%) | (75%) |
| * Bevacizumab alone | (33.3%) | (12.5%) |
| * PARP plus bevacizumab | (16.7%) | (8.3%) |
| * Other        | (2.8%)        | (4.2%)         |

Table 1
Pre and post webinar poll questions.

Dr. Norquist noted that in a sub-analysis of the cohort by Tewari et al. (2019) patients on chemotherapy followed by maintenance bevacizumab with stage IV disease at diagnosis had a 10-month improvement in OS (HR 0.75, 95% CI 0.59–0.95) compared to those patients on carboplatin and paclitaxel alone. Similar findings were also noted in ICON-7 (Oza et al., 2015). In a sub-analysis of ICON-7, the subgroup labeled as high risk (those with inoperable stage III disease, stage IV disease, or suboptimal debulking), a 10-month OS benefit was noted (HR 0.79, 95% CI 0.63–0.97). These trials indicate that the patients with the worst upfront prognostic features, such as stage IV disease or residual disease following surgery or non-operable disease, seem to get the most benefit from bevacizumab.

3. VITAL trial

Dr. Rocconi then followed with a review of the VITAL trial. This trial investigated the role of Vigil, an autologously derived vaccine for maintenance therapy (Rocconi et al., 2021; Rocconi et al., 2020). Dr. Rocconi described Vigil as a means of overcoming the non-specificity of checkpoint inhibition. The technology of Vigil involves tumor collection such that the individual patient’s tumor-specific neoantigens can be presented. The vaccine is genetically modified to encode for granulocyte macrophage colony stem cell factors which enhance the presentation in the tumor microenvironment. Lastly, there is knockdown of furin, an enzyme responsible for and required to activate TGFβ, which directly inhibits the granulocyte macrophage stem cell factors. In the initial phase 2b trial of Vigil (Rocconi et al., 2020), although it was well tolerated, it did not demonstrate an improvement in recurrence free survival (RFS) (11.5 versus 8.4 months in Vigil and placebo respectively; p = 0.075). A subsequent analysis of the phase 2b cohort was performed in which the Myriad MyChoice® Dx assay was used to define those patients (n = 45) with HRP tumors (score < 42). Those patient with HRP tumors had a significant improvement in RFS (10.6 versus 5.7 months in Vigil and placebo respectively, p = 0.011) and three-year OS (70% versus 40% in Vigil and placebo respectively, p = 0.019) (Walter et al., 2021).

Several questions from Journal Club participants were directed towards the vaccine creation and the manufacturing process. The vaccine generation requires pre-treatment collection of “at least a golf-ball size tumor to submit for the manufacturing process for the vaccine.” The impact of neoadjuvant chemotherapy also adds complexity in that viable, live tumor cells are best suited for vaccine creation – patients in the trial underwent laparoscopic tumor harvest prior to chemotherapy.

4. PRIMA

Dr. Modesitt then presented the PRIMA trial investigating the role of niraparib maintenance therapy in primary ovarian cancer. In this trial, approximately half (50.9%) of the cohort had tumors with HRD as defined by the Myriad MyChoice® Dx assay. Within the HRD group, 223/373 (60%) had germline or somatic BRCA1 or BRCA2 mutations. In the overall population, PFS was 13.8 months with niraparib compared with 8.5 months for placebo (HR 0.62, 95% CI 0.50 – 0.76) (Gonzalez-Martin et al., 2019). In a pre-specified analysis, patients with HRD ovarian cancer had an improved PFS of 22.1 months in the niraparib arm compared with 10.5 months in the placebo arm (HR 0.43, 95% CI 0.31 – 0.59). For patients with HRP ovarian cancer, the PFS was 8.1 months for the niraparib arm compared with 5.4 months for the placebo arm (HR 0.68, 95% CI 0.49 – 0.94). Dr. Modesitt noted that the magnitude of the improvement with niraparib was significantly smaller in the group with HRP ovarian cancer and should be discussed with patients when addressing the risks/benefits of maintenance therapy. The toxicity of the agent was reviewed, including the 65.3% rate of any grade 3 adverse event on the niraparib arm compared to 6.6% for the placebo.

Questions from the audience also pertain to which PARPi to utilize for maintenance therapy. Factors considered by the panelists included the toxicity experienced by patients during primary therapy as well as the possible co-pay faced by the patient. Although rarely seen in primary treatment, the ability of niraparib to cross the blood brain barrier was mentioned as a feature for consideration (Kasherman et al., 2021 Jan).

5. Discussion & conclusions

Following the presentations, each expert addressed how they would manage patients with HRP ovarian cancer. A common theme was individualizing for the patient’s disease features, performance status and goals. For patients with HRD tumors and poor prognostic features (e.g., stage IV at diagnosis, profound ascites or persistent disease at the completion of primary therapy), bevacizumab for maintenance therapy was recommended for consideration. Interestingly, in a sub-analysis of PAOLA-1, the HR for PFS for olaparib plus bevacizumab versus bevacizumab alone was 0.93 (95% CI 0.68–1.3) in those patients with HRP...
PARPi maintenance was discussed and offered; most panelists did not result in HRD tumors. For those patients with HRP ovarian tumors, maintenance therapy in patients with HRP ovarian cancers, the panel dedication to the care of ovarian cancer patients.

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