Editorial Commentary

Discussing maintenance therapy for ovarian, peritoneal, and fallopian tube cancers

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Understanding ovarian, peritoneal, or fallopian tube (O/PC/FT) cancer maintenance therapy is becoming increasingly important due to the better understood chronic nature of the disease. Despite having a complete clinical response to front line treatment with cytoreductive surgery and combination platinum-taxane based chemotherapy (1), in most cases, advanced stage ovarian cancer recurs and requires multiple lines of treatment (2,3). Maintenance therapy is recommended for women that have had a complete clinical response after frontline treatment. Mounting data indicate that maintenance therapy delays clinical recurrence and prolongs the chemotherapy-free interval. It is well known that the platinum free interval closely correlates with significantly improved survival and second line treatment response (4,5). Bevacizumab and poly-ADP ribose polymerase (PARP) inhibitor maintenance therapies are FDA approved for O/PC/FT cancers, and their use has significantly increased in this population after several trials showed improved progression-free survival (PFS) (6,7). Maintenance therapies are unique in that they need to be well tolerated by patients, easy to receive and administer, and have relatively manageable side effect profiles with limited adverse events to ensure long-term patient compliance and quality of life.

In June 2022, the American Society of Clinical Oncology published the Gynecologic Oncology Group (GOG) study 212 which further investigated taxane based options for ovarian cancer maintenance therapy. The first study to explore this concept was GOG-178. GOG-178 evaluated the use of single agent paclitaxel as maintenance therapy (8). This trial was closed at a planned interim analysis after 12 cycles because results determined that this regimen extended PFS to 28 months from 21 months (P=0.0023). However, 6 years later, when long-term data were available, the overall survival (OS) showed no benefit (9). Importantly, this study reported significant neurotoxicity, 23% grade 2 and 10% grade 3–4 (8). Overall, the results from GOG-178 were inconclusive. Investigators sought to determine whether taxane based therapy has a role in modern day ovarian cancer maintenance therapy options and understand the long-term benefits and associated toxicities with this approach. In this study, taxane based therapy was chosen due to its long history of anti-angiogenic activity on O/PC/FT cancers and relative safe drug profilein terms of organ toxicity. In addition, unlike other chemotherapies, taxanes do not cause secondary malignancies.

GOG-212 was a three-arm, randomized phase 3 trial that compared two taxane maintenance regimens with surveillance in patients with advanced stage O/PC/FT cancers of epithelial cell types who had a complete clinical response to primary treatment. Primary endpoint was OS; PFS was a secondary efficacy end point. Taxane regimens utilized were single agent paclitaxel and paclitaxel poliglumex. Paclitaxel poliglumex is a novel taxane with an aqueous solution that was selected for GOG-212 for several reasons including its short infusion duration, low rate of

hypersensitivity reactions, and potential to avoid multidrug resistance by pinocytosis mechanism. It was also reported to have less neurotoxicity and alopecia. Because it was well tolerated by patients and had short infusion times, this drug was practical to receive as a long-term maintenance therapy option.

The study included patients with advanced stage O/PC/FT cancers of epithelial cell types. Patients received a combination of surgery and chemotherapy (adjuvant chemotherapy or interval debulking surgery was included). Platinum and taxane based chemotherapy were administered intravenously or intraperitoneally for 5–8 cycles and completed within 12 weeks.

The maintenance taxane therapy arms were associated with significantly greater adverse events compared to the surveillance arm. These included gastrointestinal, hematologic, musculoskeletal, and neurologic adverse events. Ten percent of paclitaxel poliglumex patients and 5.4% of paclitaxel group had grade 3–4 sensory neuropathy, compared to 0.8% of women in the surveillance arm (P<0.001). Forty-four patients (11.6%) on paclitaxel poliglumex and 31 (8.3%) on paclitaxel stopped treatment due to these neurotoxicities. Severe neutropenia occurred more in the maintenance taxane treatment groups, 21.6% in the paclitaxel poliglumex arm and 16.6% in the paclitaxel arm, compared to 0.5% in the surveillance arm (P<0.01). Grade 3–4 hypokalemia was also seen in 2.4% of paclitaxel poliglumex patients and 0.5% of paclitaxel patients, compared to 0.0% of surveillance patients (P<0.001).

PFS was superior for patients who received paclitaxel maintenance therapy, 18.9 months with paclitaxel and 16.3 months for paclitaxel poliglumex; PFS was 13.4 months in the surveillance group. When comparing the surveillance arm to maintenance therapy groups, the paclitaxel maintenance group had a PFS hazard ratio (HR) of 0.80, while the paclitaxel poliglumex maintenance group was 0.85. However, median OS compared among the three groups had no significance (58.3, 56.8, and 60 months for surveillance, paclitaxel, and paclitaxel poliglumex respectively). Efforts were made to better define a subgroup of advanced stage O/PC/FT cancer patients who would benefit from taxane based maintenance therapy. However, sub-analysis by CA-125 levels, R=0 cytoreduction, and serous *vs.* non-serous histology did not find improved outcomes.

When comparing GOG-212 to alternative O/PC/FT cancer maintenance therapy options, maintenance with Bevacizumab resulted in 14.1-month PFS, HR 0.72 when given for 22 cycles in advanced stage disease (10), and 21.8-month PFS, HR 0.81 when given for 12 cycles in early stage high risk subtype or advanced stage epithelial ovarian cancer patients (11). Similarly, PARP inhibitors have shown to increase PFS in patients with recurrent ovarian cancer with or without a somatic or germline BRCA mutation. PFS was 39.8 months, HR 0.3 with maintenance Olaparib (6), and PFS 21.9 months, HR 0.43 with Niraparib maintenance used in tumors with homologous-recombination deficiency and 13.8 months in the overall ovarian cancer population, HR 0.7 (12). While 17.9 months PFS, HR 0.77 was reported in advanced stage O/PC/FT cancer patients receiving pazopanib, a vascular endothelial growth factor receptor inhibitor (13,14).

Conclusions

Maintenance therapy with PARP inhibitors or antiangiogenic drugs is becoming more widely utilized in the treatment of ovarian cancer. Most maintenance trials have shown improved PFS but not OS. It is important to remember the role of maintenance therapy in ovarian cancer patients and that they too can have side effects. All in all, this study indicates that taxanes do not appear to be a beneficial option for maintenance therapy in O/PC/FT cancer patients due to significant adverse effects with the longer duration of use and similar PFS rates to other maintenance therapy options.

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Footnote

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