

OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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Highlights in Ovarian Cancer From the American Society of Clinical Oncology Annual Meeting



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H&O First, let's talk about secondary cytoreduction. Could you describe the DESKTOP III trial, and what makes it so important?

TH The DESKTOP III trial, which Dr Andreas du Bois presented at the virtual annual meeting of the American Society of Clinical Oncology (ASCO), is the culmination of efforts to define the role of secondary cytoreduction in ovarian cancer. Surgeons have been using secondary reduction since the 1980s to remove recurrent ovarian cancer, but the studies that supported this approach were largely single-institution case series. The patients who underwent surgery in these series were those with the least-diffuse disease, so of course their outcomes were better. Would these patients have done just as well with chemotherapy? We did not know, which is what made a randomized trial essential.

The first step was DESKTOP I, which was designed to develop a score to identify those patients in whom a complete resection was most likely to be achieved during secondary cytoreduction. This study identified good performance status, complete resection during frontline therapy, and no more than 500 cm³ of ascites as predictors of complete resection. DESKTOP II was a prospective trial conducted to evaluate the score and confirm that it could predict, at least two-thirds of the time, which patients would go on to have a complete cytoreduction. DESKTOP III, of course, was a prospective randomized trial to see if implementing the score worked to improve overall survival (OS).

The team first presented progression-free survival (PFS) data at the 2017 ASCO annual meeting. Although these data were favorable, reducing tumor size during surgery automatically and artificially manipulates PFS.

At this year's virtual meeting, the researchers presented OS data on 407 evaluable patients who were randomly assigned to either cytoreductive surgery followed by platinum-based chemotherapy or immediate platinum-based chemotherapy. Patients were platinum-sensitive at their first relapse and had a positive German Oncology Group (AGO) score. Their median age was approximately 61 years, and nearly 80% had grade 2 or 3 serous tumors. Almost all of the patients had previously undergone platinum-based chemotherapy as their frontline treatment. Three-quarters of the patients in each group had a platinum-free interval that exceeded 12 months, although the median platinum-free interval was slightly shorter in the no-surgery arm than in the surgery arm, at 19 vs 21 months.

In both arms, most of the patients went on to have platinum-based chemotherapy after randomization. The mean duration of surgery was 222 minutes, with approximately 4% of the patients receiving an ostomy. The mortality rate was less than 1%. A total of 74% of patients had no gross disease after surgery.

Secondary resection improved OS from 46 to 53.7 months, for a difference of 7.7 months (hazard ratio [HR], 0.75; $P=.02$). Secondary resection also improved median PFS by 4.4 months. Subgroup analyses showed that the patients with a complete resection rather than

residual tumor after surgery had a tremendously better OS, at 62 vs 29 months.

DESKTOP III was very important because it was the first prospective randomized trial to show an OS benefit with debulking surgery in recurrent ovarian cancer. The procedure significantly improved OS in those who had a platinum-free interval greater than 6 months and a positive AGO score. Benefit was seen only in those with a complete resection, so achieving that is critical.

H&O What did the SOC 1 trial find?

TH Dr Rongyu Zang presented interim results from SOC 1, which also addressed the role of secondary cytoreduction in ovarian cancer. The study enrolled patients who were experiencing a first recurrence of ovarian cancer and had a platinum-free interval of at least 6 months, along with an iMODEL score of no more than 4.7; this score takes into account stage, presence or absence of residual disease after primary surgery, length of the platinum-free interval, performance status, CA125 level, positron emission tomography/computed tomography findings, and presence or absence of ascites at recurrence. A total of 357 patients were randomly assigned to surgery or no surgery.

The co-primary endpoints were PFS and OS. After a median follow-up of 36 months, the median PFS was significantly longer in the surgery group than in the no-surgery group, at 17.4 months vs 11.9 months (HR, 0.58; $P < .001$). The difference in OS was not statistically significant at this interim analysis, however, at 58.1 vs 53.9 months (HR, 0.82; 95% CI, 0.57-1.19). We are still waiting for mature data on OS, which should be the primary endpoint for these types of trials because again, one would expect PFS to be improved if a tumor is removed.

H&O Why did the results of these trials differ from those of GOG-0213?

TH We do not yet know whether SOC 1 will show that secondary cytoreduction truly improves patient outcomes because we are still waiting for the OS results. But if the OS results for SOC 1 are consistent with those for DESKTOP III, that would be 2 trials showing an improvement with secondary cytoreduction. Both studies had strict entry criteria (the AGO score for DESKTOP III and the iMODEL score for SOC 1), and both studies achieved a complete cytoreduction rate of approximately 75%. Did something about the criteria used to enroll patients in GOG-0213 make a difference?

GOG-0213, which Dr Robert Coleman and colleagues published in the *New England Journal of Medicine*

in 2019, was a complicated trial because it had 2 objectives. The first objective was to test the benefit of adding bevacizumab to carboplatin and paclitaxel in treating platinum-sensitive recurrent ovarian cancer. The second objective was to examine the role of surgical cytoreduction. The fact that surgical cytoreduction did not improve OS—in fact, the trend actually favored no surgery—draws attention to the possibility that a subgroup may exist that is harmed by the procedure. The patients for whom we are unable to achieve no gross residual disease actually seem to do worse with secondary cytoreduction, so that is an important point to keep in mind.

If you look across all 3 trials, the patients were similar in terms of age, initial disease stage, and histology. The platinum-free interval was a little bit shorter and the rate of crossover to surgery was a little bit higher in the SOC 1 trial, whereas the rate of complete gross resection was a little bit lower in the GOG-0213 trial (67% in GOG-0213 vs 74% in DESKTOP III and 77% in SOC 1). The mortality rate was very low—less than 1%—in all the trials, and the platinum-based combination was pretty much the same in all 3 trials.

The biggest difference was in how the patients were treated after surgery; stark differences were found in the percentages of patients who received bevacizumab: 84% in GOG-0213, 23% in DESKTOP III, and 1% in SOC 1. This difference in treatment may explain a lot of the difference in the findings because the median OS results in the surgery groups were nearly identical in GOG-0213 and DESKTOP III, at 53.6 vs 53.7 months, and OS was very similar in SOC 1, at 58.1 months. The control arm, however, did much better in GOG-0213 than in the other studies. So the fact that the patients in the control arm received much more bevacizumab may have made up for the omission of surgery. Indeed, we see a median OS of 66 months in GOG-0213 vs 46 months in DESKTOP III and 54 months in SOC 1. That was the most impressive finding. I think the 2 most important factors that explain the differences among the trials are (1) subsequent treatment and (2) the fact that the determination of who was a surgical candidate was left to the investigator's discretion in GOG-0213, whereas the other 2 trials used a rigid score (AGO or iMODEL). The question now is, what do clinicians do with this information?

We know from GOG-0213 that you can achieve nearly the same effect with bevacizumab as with secondary cytoreduction. So we may wish to reserve surgery for patients who are young, have only solitary metastases, have a long platinum-free interval, and require an especially aggressive approach. Other clinicians may wish to continue doing surgery in more patients. We eagerly await the OS data from SOC 1 to see if this trial becomes the tie breaker one way or the other.

H&O Moving on to PARP inhibitors, could you describe the final results from SOLO2 that were presented?

TH A total of 3 randomized trials have looked at the role of poly(ADP-ribose) polymerase (PARP) maintenance therapy in patients who have platinum-sensitive recurrent ovarian cancer and have responded to platinum-based second-line therapy. The first of these was the NOVA trial with niraparib (Zejula, GSK/Tesaro), followed by SOLO2 with olaparib (Lynparza, AstraZeneca) and ARIEL3 with rucaparib (Rubraca, Clovis Oncology). These 3 trials all support the benefit of PARP maintenance therapy in patients with serous or *BRCA*-mutated tumors, but we were lacking long-term OS data until Dr Andreas Poveda presented the results of SOLO2 at the virtual meeting.

The trial enrolled patients with platinum-sensitive relapsed ovarian cancer and a *BRCA* mutation who had received at least 2 lines of treatment and were responding to their most recent platinum-based chemotherapy. A total of 295 patients were randomly assigned in a 2:1 ratio to maintenance olaparib or placebo. The researchers found that median OS was significantly longer in the olaparib group than in the placebo group, at 51.7 vs 38.8 months, for a statistically significant difference of 12.9 months (HR, 0.71; 95% CI, 0.54-1.00; $P=.0537$). This finding is very important because it is difficult to detect differences between treatments in patients with platinum-sensitive recurrent ovarian cancer. The true benefit may be even greater, given that more than 38% of the patients in the placebo group crossed over to a PARP inhibitor.

Although the safety signals overall were fairly similar in the 2 arms, the rate of myelodysplastic syndrome was 8% in the olaparib arm, which is much higher than what we have seen in other trials. This is something we will need to monitor closely as we move forward.

H&O What about the updated results from AVANOVA2?

TH AVANOVA2, which was presented by Dr Mansoor Mirza at the virtual meeting, looked at the use of niraparib plus bevacizumab vs niraparib alone for treating platinum-sensitive recurrent ovarian cancer. The use of a non-chemotherapy regimen is an interesting strategy. This was a phase 2 trial that was randomized but open-label. Patients were eligible if they had measurable or evaluable platinum-sensitive, relapsed high-grade serous or endometrioid ovarian cancer.

Patients received niraparib ($n=48$) at 300 mg/d either alone or in combination with bevacizumab ($n=49$) at 15 mg/kg every 3 weeks; they continued treatment until disease progression. The primary endpoint was PFS. The

researchers did stratify patients by homologous recombination deficiency (HRD) status and by a chemotherapy-free interval of 6 to 12 months vs an interval longer than 12 months. First-line maintenance bevacizumab was permitted.

The median PFS was 12.5 months with the combination vs 5.5 months with niraparib alone, which was a pretty impressive difference, and the numbers are consistent with what we would expect for chemotherapy in the combination arm in this cohort. The median PFS in GOG-0213 with the combination of bevacizumab, carboplatin, and paclitaxel was 13.8 months, so niraparib did almost as well as carboplatin plus paclitaxel. The control arm looked exactly like the control arms in other trials, such as SOLO2, ARIEL3, and NOVA, which was interesting. The numbers in AVANOVA2 are relatively small and the confidence intervals are fairly wide, but the results are statistically significant and look even better in patients with HRD-positive tumors, as one would expect. This phase 2 trial was not powered to look at OS, but the combination also improved other secondary endpoints, including time to first subsequent therapy and time to second subsequent therapy.

The researchers did see a higher rate of some grade 3/4 toxicities with the combination vs niraparib alone, specifically hypertension (23% vs 0%) and neutropenia (8% vs 2%). But overall, I thought the data regarding adverse events were reassuring, so this approach is another option for clinicians.

H&O What did you take away from KEYNOTE-100?

TH Dr Ursula Matulonis presented the final results of KEYNOTE-100, which was designed to look at the activity of pembrolizumab (Keytruda, Merck) monotherapy in recurrent, advanced ovarian cancer. As we look at all these combinations, it is helpful to know the effect of each agent individually.

The trial was somewhat unusual because it had 2 cohorts. The first cohort ($n=285$) included patients who had no more than 3 prior lines of chemotherapy and a platinum-free interval of anywhere between 3 and 12 months. In the second cohort ($n=91$), patients could have as many as 4 to 6 prior lines of chemotherapy, and a platinum-free interval of 3 months or more. Patients received pembrolizumab at 200 mg every 3 weeks for 2 years or until progression, death, or unacceptable toxicity. They underwent tumor imaging every 9 weeks for 1 year and then every 12 weeks thereafter. The primary endpoint was overall response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

The researchers found that the overall response rate was 8% in the first cohort and 10% in the second

cohort. Patients with the highest level of expression of programmed death ligand 1 (PD-L1) had an 18% response rate, which gives us some optimism about the ability to use PD-L1 as a biomarker. Median OS was not statistically significantly different between the first and second groups, at 18.7 and 17.6 months. A trend toward improved OS was noted among those with the highest levels of PD-L1 expression. This is certainly information to bear in mind as we continue to design trials.

The past year has been discouraging overall for the use of immunotherapy in ovarian cancer. The results of JAVELIN Ovarian 200 that were presented at the 2019 ASCO annual meeting were negative regarding the addition of avelumab (Bavencio, EMD Serono/Pfizer) to treatment for platinum-resistant ovarian cancer. JAVELIN Ovarian 100 was halted in April of this year after avelumab failed to improve PFS, and data on atezolizumab (Tecentriq, Genentech) from IMagyn50 that were released in July were also negative.

Although clearly some patients benefit from immunotherapy, the overall response rate is not impressive. I expect that eventually we will be using biomarkers—perhaps some that are not currently in use—to select the patients who are most likely to benefit from immunotherapy in ovarian cancer.

H&O What other studies from the virtual meeting were of special interest?

TH I was interested to hear Dr George Liu's presentation on the experimental WEE1 inhibitor adavosertib in recurrent uterine papillary serous cancers. Most of these patients have *TP53* mutations, just like those with ovarian cancer, and WEE1 inhibition has been theorized to work well in patients with dysfunctional *TP53*. This phase 2 trial enrolled 35 patients who had received at least one prior platinum-based chemotherapy agent. If patients were microsatellite instability–high, they were required to have received a checkpoint inhibitor, with no upper limit on the number of prior lines.

The overall response rate was pretty impressive, at 29.4%, although the confidence interval was wide (95% CI, 15.1%–47.5%). The 6-month PFS rate was 59%, which is also high, and the median PFS was 6.1 months, which is pretty reasonable in this patient group. The median duration of response was favorable, at 9 months. Grade 3 adverse events included neutropenia (32%), anemia (21%), and fatigue (24%).

Although this trial was not in ovarian cancer, I thought it was interesting because I have been waiting to see clinical trial results with WEE1. Uterine papillary serous cancer is related to ovarian cancer, at least in microscopic morphology.

H&O Do you have anything else you would like to add regarding the news about ovarian cancer from the virtual meeting?

TH The biggest take-home message is the role of clinical trials in ovarian cancer. It is amazing that we have had 13 new regulatory approvals in the last 6 years in this area. If clinicians were not enrolling patients in clinical trials, data of this type, which have led to new treatment opportunities for patients with ovarian cancer, would not be available. I applaud the Gynecologic Oncology Group (GOG) and NRG Oncology in the United States, the European Network for Gynaecological Oncological Trial (ENGOT) groups in Europe, and additional groups in Asia. Cooperation between GOG and ENGOT has been especially helpful in moving the field forward without duplicating resources; thus, we need to continue this collaboration and expand it further globally.

Disclosures

Dr Herzog has served on the scientific advisory boards of AstraZeneca, Caris, Clovis, Genentech, GSK, Johnson & Johnson, and Merck.

Suggested Readings

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