OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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Should Secondary Cytoreduction Be Used in Recurrent Ovarian Cancer?

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H&O What is the rationale behind secondary cytoreduction in recurrent ovarian cancer?

SNW The goal of upfront optimal cytoreduction is to improve outcomes—both progression-free survival (PFS) and overall survival (OS). Given the success of primary cytoreduction in ovarian cancer, the question became, can secondary cytoreduction provide the same benefit? After retrospective studies started to define a population that might benefit from a second cytoreduction, researchers undertook several prospective trials.

H&O What are the potential disadvantages of secondary cytoreduction?

SNW We certainly do not want to put patients through surgery if it will not help them live longer, and surgical cytoreduction can lead to morbidity and mortality. Patients who undergo extensive surgery to eradicate extensive disease are at increased risk for complications, which can adversely affect outcomes. Another disadvantage of surgery is that it limits the use of novel agents such as bevacizumab, which interferes with wound healing when used within a month of surgery. If a patient will benefit more from the addition of a novel agent to chemotherapy than from secondary cytoreduction, we want to choose the novel agent.

H&O What is the most compelling evidence against the use of secondary cytoreduction in ovarian cancer?

SNW The first randomized study reported in this space was GOG-0213 from the Gynecologic Oncology Group, which Coleman and colleagues published in the *New England Journal of Medicine* in 2019. In this phase 3 study, 485 women with recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer who were considered candidates for surgery were randomly assigned to either secondary cytoreduction or platinum-based chemotherapy plus bevacizumab. The researchers found that PFS improved with surgery, which is what we expect to see—it takes time for disease to recur after you remove it. However, when they looked at OS, they did not find a benefit with surgery. In fact, OS was significantly better with chemotherapy than with surgery, which was the opposite of what we had expected to find. That finding sent shock waves through our field and put everyone into a "pump-the-brakes" kind of situation.

An important caveat regarding this study is the way in which it was decided that the patients were eligible for surgery; the decision was based simply on the surgeon's opinion that the disease could be resected. If the surgeon thought that the patient's disease could be effectively debulked, that was it—no specific criteria were used to determine surgical eligibility.

H&O What is the most compelling evidence in favor of secondary cytoreduction?

SNW The most compelling evidence in favor of secondary cytoreduction is from the DESKTOP III trial. In this phase 3 trial, 407 patients with recurrent ovarian cancer

who were candidates for surgery were randomly assigned either to secondary cytoreduction followed by platinum-based chemotherapy or to platinum-based chemotherapy alone. Unlike the GOG-0213 study, DESKTOP III used a specific predictive score, the German Gynecological Oncology Group (AGO) score, to determine who was a candidate for surgery. Patients who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, a complete resection at first surgery, and ascites of no more than 500 mL were categorized as having a positive AGO score and were considered candidates for surgery.

In DESKTOP III, surgery improved not only PFS but also OS. A planned subgroup analysis demonstrated that the population of patients who had a complete surgical resection was the population of patients who derived an OS benefit. Predicting who was most likely to have a complete resection, and then achieving that complete resection, led to the best possible outcome. Conversely, the presence of any residual disease at the time of secondary cytoreduction was associated with worse outcomes. The key was using a validated model, not just leaving it up to a surgeon to say, "Here are 2 sites of disease and I can get all that out."

H&O Have any other factors in the studies been identified that might explain the discrepancies between the results?

SNW We know that the regimen used for systemic therapy can make a difference; this is something we see over and over in studies of chemotherapy. Bevacizumab is a great equalizer, meaning that the use of bevacizumab may negate any benefit from surgery, and the percentage of patients who received bevacizumab was much higher in GOG-0213 than in DESKTOP III.

H&O What do meta-analyses reveal about the data?

SNW A meta-analysis by Baek and colleagues, recently published online in the *Journal of Clinical Oncology*, looked at 36 studies published between 1983 and 2021. These studies included a total of 2805 patients who underwent secondary cytoreduction for platinum-sensitive recurrent ovarian cancer. The researchers found a significant increase in OS when maximal tumor resection was achieved. Using a linear regression model to analyze 57 studies, the researchers found that OS improved by 9% for every 10% increase in the rate of complete cytoreduction and by 7% for every 10% increase in the rate of optimal cytoreduction. These findings support the results of DESKTOP III.

H&O What ongoing studies are looking at secondary cytoreduction?

SNW Like DESKTOP III, the phase 3 SOC 1 study is randomly assigning patients with platinum-sensitive recurrent ovarian cancer to secondary cytoreduction plus chemotherapy or chemotherapy alone (NCT01611766). Patient eligibility for surgery is determined with a validated selector. Unlike DESKTOP III, which used the 3-variable AGO score, SOC 1 is using the international model (iMODEL) score, which comprises 6 variables: disease stage, residual disease after primary surgery, platinum-free interval, ECOG performance status, CA-125 level at recurrence, and ascites at recurrence. The researchers have reported only PFS at this time, which, as expected, is better in the secondary cytoreduction group. We do not yet have OS data from this study, so I would say the data from SOC 1 are neutral at this point. We eagerly anticipate OS data from this study to see whether they support the use of secondary reduction.

> After we get the results of SOC 1, we should have clearer guidelines to follow.

H&O What does the Society of Gynecologic Oncology Clinical Practice Committee recommend regarding secondary cytoreduction?

SNW The committee acknowledges that the evidence is mixed, and it advises surgeons to select patients carefully if they are considering the use of secondary cytoreduction. If the SOC 1 trial ends up supporting secondary cytoreduction, I expect the committee to state that secondary cytoreduction is an appropriate option for selected patients.

H&O What factors should be used to determine which patients are most likely to benefit from secondary cytoreduction?

SNW The AGO score and iMODEL score both have the advantage of providing clarity, but we do not know whether one is better than the other. The final results from the SOC 1 trial may help us determine how extensive the scoring model needs to be. Can we keep it to 3 factors, or do we need to use a more-extensive model?

H&O Does the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) make secondary cytoreduction more effective?

SNW Retrospective data suggested that it might, but a phase 2 prospective trial from Zivanovic and colleagues at Memorial Sloan Kettering Cancer Center did not show a benefit. In this study, 98 patients undergoing secondary cytoreduction were randomly assigned to HIPEC or no HIPEC, followed by carboplatin-based chemotherapy; HIPEC did not improve PFS or OS. Several other studies are also looking at HIPEC, but so far the data are not encouraging.

H&O Does secondary cytoreduction still benefit patients if maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors is being used?

SNW We do not have any idea at this point because the studies were conducted before the widespread use of PARP inhibitors. We do see benefit with the use of PARP inhibitors after upfront surgery, but we do not have any data regarding secondary cytoreduction.

H&O What is the most common approach to secondary cytoreduction now?

SNW The pendulum in clinical practice swung a little bit away from secondary cytoreduction after the negative data were reported from GOG-0213, but now I think it has shifted back to consideration of surgery with the results of DESKTOP III. What I am seeing at my institution is a more careful selection of patients for secondary cytoreduction with either the AGO or iMODEL score. After we get the results of SOC 1, we should have clearer guidelines to follow.

Disclosure

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Suggested Readings

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