OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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HIPEC in Ovarian Cancer: Hip or Hype?

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H&O What does hyperthermic intraperitoneal chemotherapy (HIPEC) involve?

LR HIPEC is always used in conjunction with cytoreductive surgery, in which a maximal effort is made to remove all the tumors that are located in the peritoneal cavity. After the surgery is completed, we insert an inflow and outflow catheter system to infuse chemotherapeutic agents into the abdomen. The duration of the perfusion is usually 90 minutes, although some regimens specify 60 or 120 minutes. The infusion is usually heated to 41°C, which is approximately 106°F. After we complete the infusion, we wash out the agents and close the abdominal incision.

H&O Which patients with ovarian cancer are candidates for HIPEC?

LR Candidates for HIPEC are patients with frontline ovarian cancer who have received neoadjuvant chemotherapy, have had a partial or complete response to that treatment, and are scheduled for interval cytoreductive surgery, and for whom maintenance therapy with bevacizumab or a poly(ADP-ribose) polymerase (PARP) inhibitor is not planned. This is the population that van Driel and colleagues examined in the OVHIPEC study, which produced the best data we have in support of HIPEC in ovarian cancer. Any use outside ovarian cancer is investigational.

H&O Do candidates need to have stage III ovarian cancer?

LR Candidates can have stage III ovarian cancer, stage IV by virtue of a malignant pleural effusion that has responded to neoadjuvant chemotherapy, or stage IV based on a splenic or other visceral metastasis that can be removed with surgery. Patients who have metastases to lung, to bone, or to lymph nodes outside the abdomen are not good candidates because HIPEC is a regional therapy.

H&O What are the potential advantages of this approach to chemotherapy?

LR On a biological level, the heat increases the penetration of chemotherapy into the tumor. Basic research has shown that heat increases platinum DNA adduct formation in the cell. Heat also enhances cell membrane transport permeability, allowing more platinum to enter the cancer cell.

On a clinical level, we know that chemotherapy works best when the tumor burden is as low as possible. The bulk of the disease is at its absolute lowest right at the time of cytoreductive surgery, so that is the best time to administer chemotherapy. Intraoperative HIPEC also bridges the delay in chemotherapy cycles associated with interval debulking surgery.

H&O What are the drawbacks of HIPEC?

LR The main drawbacks of HIPEC are the resources required to deliver the treatments and the extra time needed for the procedure, which means that a patient who has already been under anesthesia for a fair amount

of time for the surgery will be under anesthesia for an additional 2 hours.

The question of toxicity is a matter of debate. Many people assume that HIPEC is toxic, but the data from the phase 3 trial of van Driel and colleagues do not support excessive toxicity with HIPEC. In fact, the better we get at HIPEC, the less likely we are to see side effects like renal failure, infection, and extended recovery time. I have watched 2 programs evolve, and in both cases I saw the additional toxicity dissipate over time. My opinion is that after we have gone through the learning curve, almost all of the toxicity is from the surgery, not the HIPEC. We are able to modify our supportive perioperative care to protect the kidneys and mitigate the risk for infection, so that the likelihood of side effects is decreased. Here at Virginia Commonwealth University, our surgical oncology colleagues have refined the HIPEC technique, and we have started to use a minimally invasive approach to cytoreductive surgery and HIPEC to speed recovery time.

H&O How well accepted is the minimally invasive approach to cytoreductive surgery?

LR We do not have enough data to support a complete move from open to minimally invasive cytoreductive surgery for interval debulking. Several small, retrospective studies presented at the most recent meeting of the Society of Gynecologic Oncology (SGO) suggested no compromise in outcomes with minimally invasive surgery for interval debulking. Those results have not been confirmed with a prospective study, however, and no such study is planned at this point. Still, we do know that minimally invasive surgery offers benefits for patients in terms of faster recovery time, and as a specialty we should think about looking at that in a more formal way. We have seen a benefit here at our center.

H&O How often is HIPEC being used?

LR HIPEC is being done only at specialized centers, and even at the specialized centers only in selected cases. So we are not certain how many people are using it. The best estimate is found in a recent publication by Charo and colleagues, in which 152 women with ovarian cancer had HIPEC at 39 hospitals and 20,014 women with ovarian cancer had surgery without HIPEC at 256 hospitals.

H&O Could you describe the trial of van Driel and colleagues and what it found?

LR The trial enrolled 245 patients with stage III ovarian cancer that had responded to neoadjuvant chemotherapy, either completely or partially, and who were scheduled for interval debulking surgery. At the time of surgery, the patients were randomly assigned to either receive or not receive HIPEC. The study clearly showed a significant benefit in both recurrence-free survival (14.2 vs. 10.7 months) and overall survival (45.7 vs 33.9 months) with the use of HIPEC. Toxicity was similar in the 2 groups, with slightly more ileus and pain in the HIPEC group. Among the 59 patients who had a bowel resection, a colostomy or ileostomy was more common among those in the HIPEC group than those in the no-HIPEC group (72% vs 43%; *P*=.04), but that probably reflects concern on the part of surgeons that HIPEC might affect the integrity of a colonic anastomosis. Other trials have not shown any difference in the outcome of patients with colonic anastomoses that were not diverted with a colostomy.

HIPEC requires a lot of resources and training, and only one study has shown it to benefit patients with ovarian cancer.

H&O Why did the publication of this trial fail to lead to more widespread acceptance of the procedure?

LR A large body of data over the past 20 years has supported the use of normothermic intraperitoneal chemotherapy, and that also failed to receive widespread uptake. I believe the main barrier to widespread acceptance is that HIPEC requires a lot of resources and training, and only one study has shown a benefit in patients with ovarian cancer. We also do not know whether HIPEC is still beneficial in this era of maintenance treatment. A 2019 trial by Walker and colleagues found that intraperitoneal chemotherapy no longer made a difference when maintenance treatment with bevacizumab was used. Because the study of van Driel and colleagues was done in patients who did not receive maintenance therapy, it is still possible that maintenance therapy will negate the benefit of HIPEC, just as it likely negated the benefit of regular intraperitoneal chemotherapy.

H&O Can you discuss the newer results with HIPEC from the MSK Team Ovary Phase II study?

LR This study, which Zivanovic presented at the virtual 2021 meeting of the American Society of Clinical Oncology, did not find a benefit from HIPEC. It was smaller than the study of van Driel and colleagues, at 98 patients, so a major caveat is that the trial may have been too small to detect a benefit. It also looked at the use of HIPEC with secondary cytoreductive surgery for recurrent ovarian cancer, whereas the study of van Driel and colleagues looked at patients who were receiving frontline surgery. So, does this study point to a lack of benefit with HIPEC at the time of secondary surgery only? Or is there a lack of benefit from HIPEC overall? We now have 3 randomized trials—by Coleman and colleagues, du Bois and colleagues, and Shi and colleagues—showing marginal, limited, or no benefit of secondary surgery for ovarian cancer. The benefit of HIPEC is always tied to the benefit of the surgery that it accompanies, so if the surgery is of limited or no benefit in the second line, HIPEC is unlikely to be of significant benefit in the second line.

H&O Could you describe the design of the OVHIPEC-2 trial?

LR OVHIPEC-2 is a randomized phase 3 study with a design very similar to that of the original OVHIPEC study. Patients are randomly assigned to HIPEC or no HIPEC in the setting of neoadjuvant chemotherapy and interval debulking surgery (NCT03772028). OVHIPEC-2 is a larger trial, however, and allows the use of maintenance treatment with bevacizumab or a PARP inhibitor. We expect to see variation in the use of maintenance treatment across the arms. Although the trial is randomized, which means that the number of people on maintenance treatment in each arm should be roughly the same, I would still like to see a trial that stratifies patients according to whether they receive maintenance treatment or one that mandates and standardizes maintenance. A trial with this design would be the only way to truly isolate the effect of HIPEC.

H&O Are any trials like that planned?

LR We are trying to do that trial here in the United States. The Gynecologic Oncology Group (GOG) Foundation and GOG Partners are prioritizing this study and have been securing the needed funding.

H&O Where do you see the use of HIPEC headed in ovarian cancer?

LR We really need to show a clear benefit of HIPEC in a randomized trial in the setting of maintenance therapy. HIPEC requires a lot of resources and a lot of time in the operating room, and significant toxicity is involved during the learning curve, so if it does not work, we should not be doing it. We do not yet know enough to declare whether it works or not.

Disclosure

Dr Randall has received honoraria from BluPrint Oncology, Physicians' Education Resource (PER), Curio Science, and Products in Knowledge; has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, the GOG Foundation, Merck, Mersana Therapeutics, Agenus, Rubius Therapeutics, Myriad Genetics, EMD Serono, Genentech/Roche, Seagen, and Novartis; has served on the speakers' bureau of AstraZeneca, Tesaro, and Merck; and has received institutional research funding from Genentech/Roche, On Target Laboratories, Pfizer, AIVITA Biomedical, Tesaro, AstraZeneca, Merck, Akeso Biopharma, and the Spanish Ovarian Cancer Research Group (GEICO).

Suggested Readings

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