Intraperitoneal Therapy for Ovarian Cancer: Why Has It Not Become Standard?

By Karen Rowan

Three randomized, controlled trials have demonstrated substantial improvements in overall survival for patients with advanced ovarian cancer who received chemotherapy via the intraperitoneal (IP) route—Injected directly into the peritoneal cavity—compared with those who received it intravenously. Moreover, the National Cancer Institute has recommended that intraperitoneal treatment to be the standard of care. But according to those who treat ovarian cancer, only about half of the physicians in the field have accepted the technique.

Toxic effects, technical complications with the procedure, and concerns about study designs have all contributed to the lack of acceptance. And, as these phase III trials were under way, the drugs used to treat ovarian cancer evolved: paclitaxel replaced cyclophosphamide; carboplatin replaced cisplatin; and now, new targeted agents such as bevacizumab are being eyed for possible additions to current regimens.

Some physicians point to studies showing that patients may live more than a year longer if given intraperitoneal instead of intravenous treatments and express frustration that the technique is not more widely accepted. Others point to evolving drug regimens and say that the data are insufficient to support such acceptance.

“Even though the NCI suggested that intraperitoneal therapy be the standard of care, and even though we have three phase III trials, there are enough questions about efficacy and toxicity” to explain the split within the academic community, said J. Tate Thigpen, M.D., professor of oncology at the University of Mississippi Medical Center in Jackson. Thigpen used IP che-
motherapy as part of a randomized, controlled trial but said he would not recommend the treatment on the basis of the evidence gathered so far.

The idea that injecting drugs directly into the peritoneal cavity would kill cancer cells dates to the 1950s, said Maurie Markman, M.D., vice president for clinical research at the University of Texas M. D. Anderson Cancer Center in Houston. But there was no evidence that patients benefited, and the technique was abandoned. A key report in 1978 reawakened interest, leading to trials in the 1980s. Then, with growing acceptance of the effective but highly toxic cisplatin, intraperitoneal delivery gained favor because it promised to reduce systemic toxicity.

The theory behind the technique is that drugs delivered directly to the peritoneal cavity move slowly into the systemic circulation, allowing doses 18–20 times higher than what could be tolerated in the blood plasma. Because ovarian cancer metastasizes almost exclusively within the peritoneal cavity, the hope is that delivering the platinum drugs this way will kill residual cancer cells after surgery and delay recurrence. However, drugs present in the cavity cannot diffuse deeply into tumors, so intraperitoneal delivery is used only for women whose tumors have been optimally debulked by surgery (leaving tumors no larger than 1 cm).

The first of the phase III trials took place in the late 1980s and early 1990s, when intravenous cisplatin was the standard of care. Patients were randomized to receive either intraperitoneal or intravenous cisplatin, and both groups also received intravenous cyclophosphamide. The study, led by David Alberts, M.D., now director of the Arizona Cancer Center in Tucson, was published in the New England Journal of Medicine in 1996. It found that women given intraperitoneal cisplatin had a median overall survival of 49 months, compared with only 41 months for the control group—a statistically significant difference.

However, earlier that year, research published in the same journal showed that paclitaxel was more effective than cyclophosphamide when paired with cisplatin. That result prompted some to claim that if paclitaxel had been used instead of cyclophosphamide, the apparent benefits of the IP treatment would not have been significant.

A second phase III trial, led by Markman, compared patients receiving paclitaxel and cisplatin intravenously with patients receiving 4 weeks of intravenous carboplatin, followed by intravenous paclitaxel and IP cisplatin. The researchers found an improved overall survival (63 versus 52 months), but the difference was of borderline statistical significance and toxicity was greater in the IP group.

Most recently, the Gynecologic Oncology Group, led by Deborah Armstrong, M.D., associate professor of oncology at Johns Hopkins University in Baltimore, conducted a phase III trial in which patients received intravenous paclitaxel with either intravenous cisplatin or intraperitoneal cisplatin. The researchers again found a statistically significant difference in the median overall survival, which was 65.6 months in the IP group and 49.7 months in the intravenous group. As a result of the study, published in the New England Journal of Medicine in 2006, NCI issued guidelines recommending that IP chemotherapy be the standard of care. Since then, however, carboplatin has replaced cisplatin as the standard chemotherapy, which has led to calls for IP therapy to prove its worth once again.

Toxicity, Technical Challenges

One of the main problems with intraperitoneal chemotherapy is toxicity. Robert F. Ozols, M.D., Ph.D., a senior vice president at the Fox Chase Cancer Center in Philadelphia, pointed out that in the GOG study, only 42% of patients randomized to the IP regimen completed all six cycles, and 18% received only one cycle. Cisplatin causes nephropathy, neuropathy, and severe nausea and vomiting, among other side effects.

“The toxicity was very severe,” Ozols said. “Consequently, very few people are using it.” Proposed future trials are “not worth the effort,” he said. “I think we should move on.”

One reason that the IP treatments may not work as theorized, Ozols said, is that tumors are covered with layers of fibrin, and this tough covering impedes a drug’s ability to get into a cell mass. Very little gets through the outermost layers, he said, so the best way to deliver drugs is through the intravenous route, which allows the drug to enter the microcirculation. He also said that there are sites of disease, such as the lymph nodes, that a drug in the peritoneal cavity can’t reach.

On the other side of the debate, experts point to outcomes. “There are a lot of concerns about cisplatin because of the side effects, but the survival advantage of intraperitoneal therapy is without a doubt,” said Carol Aghajanian, M.D., chief of the gynecologic medical oncology service at Memorial Sloan–Kettering Cancer Center in New York.

Aghajanian said that the long-term side effects of the cisplatin treatment may not be as bad as originally feared. She pointed to a quality-of-life study done along with the GOG trial. It found that after 1 year there were no statistically significant differences in side effects except for neuropathy. She is optimistic that trials using intraperitoneal carboplatin will show fewer side effects.

There are already indications this prediction may be so, according to Amy Tiersten, M.D., associate professor of medical oncology at New York University. Tiersten recently led a phase II study in which patients were given intravenous paclitaxel and carboplatin before surgery and then a regimen of intravenous paclitaxel, intraperitoneal carboplatin, and intraperitoneal paclitaxel after surgery. Of the patients whose tumors were optimally debulked, 70% completed the intraperitoneal regimen.

“Carboplatin can be safely administered via the intraperitoneal route and has a similar
pharmacokinetic advantage to cisplatin,” said Tiersten. Carboplatin, she said, may have accounted for the better tolerability in her study compared with previous research using cisplatin. It also may have helped, she said, that her chemotherapy regimen was based on a 28-day cycle instead of the 21-day cycle used elsewhere.

But others say that carboplatin’s effectiveness is the very reason IP therapy will not prove to offer a significant survival advantage in future studies. The University of Mississippi’s Thigpen pointed out that in the GOG trial, the 58% of patients in the IP group who could not complete all cycles of chemotherapy were put on a regimen including carboplatin instead of cisplatin. “They finished up with carboplatin, and that could have accounted for the difference that you see,” he said.

Aside from the toxicity of the drugs, the intraperitoneal route, which uses a catheter, presents unique challenges. “Any time you put a catheter in, you have the potential for problems,” said Armstrong, who led the GOG trial. “There are issues with patient selection, timing, and the experience and dedication of the person putting it in.” The comfort level of the nurses in dealing with catheters is also a factor, she said. “It is a situation where the more experienced the institution, the less likely it is that there will be problems.”

Armstrong said that the logistics of IP therapy require communication and cooperation between surgeons and the oncologists. The field of gynecologic oncology is unique in that gynecological surgeons are trained in giving chemotherapy, whereas other surgical oncologists are not. “The best candidates for intraperitoneal chemotherapy are those who’ve had optimal surgery, and that almost by definition requires a gynecological specialist,” she said. Patients who have been diagnosed “all want to have their surgery yesterday, but it may be better to wait a week and have the right doctor do the surgery.”

Carolyn Krasner, M.D., a medical oncologist at Massachusetts General Hospital in Boston, agrees with Armstrong. “For technical reasons, there’s been a failure to adopt [intraperitoneal therapy],” she said. Many medical oncologists don’t practice side by side with gynecological surgeons, and the need to train nurses compounds the difficulties. Krasner believes that fewer than half of gynecological oncologists have adopted intraperitoneal therapy as their standard of practice.

“I am hopeful that [the upcoming GOG trial] will answer the question of does intraperitoneal therapy add benefit above intravenous chemotherapy,” she said. That trial will give carboplatin to patients with paclitaxel and bevacizumab. Led by Joan Walker, M.D. at the University of Oklahoma, Oklahoma City, it will begin accruing later this year.

But M. D. Anderson’s Markman is not convinced that the new GOG trial will fix what he sees as a larger problem: getting information to physicians and making it more feasible for them to learn the technique. The biggest issue, he said, is that doctors may see only a few cases of ovarian cancer every year and may find it difficult to learn the technique and train their nurses to deal with the catheters.

When a new drug comes out, “pharmaceutical companies have meetings, they write letters, they present at [the American Society of Clinical Oncology], they hold dinners to present the evidence-based data. That’s the way you get data in front of practitioners. There is no such thing for intraperitoneal therapy,” he said. “This is not a drug; it’s a technique.”

Markman said he does not expect that all doctors will learn how to administer intraperitoneal therapy, but he would like to see more doctors informing patients that the treatment is an option and, for patients who would like to pursue it, being willing to refer them to institutions where the treatment can be done by practitioners with knowledge and experience. The negatives can be daunting. “It takes more time, more effort, and it’s toxic,” he said. “But people live longer.”

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