Intraperitoneal Chemotherapy Underused in Ovarian Cancer

BY ED SUSMAN

CHICAGO—Intraperitoneal chemotherapy—a proven life-extending treatment for women with Stage 3 ovarian cancer—appears to be underused. That is the conclusion of a study presented here at the American Society of Clinical Oncology Annual Meeting (***Abstract 5576***).

As shown in the poster study by Alexi A. Wright, MD, MPH, Assistant Professor of Medicine at Susan F. Smith Center for Women's Cancers at Dana-Farber Cancer Institute/Harvard Medical School, fewer than half of the women eligible for the treatment at six National Comprehensive Cancer Network institutions received it, despite an alert issued in 2006 by the National Cancer Institute recommending its use.

Of 613 women diagnosed with non-metastatic ovarian cancer from 2006 to 2013, intravenous chemotherapy was used in 334, while 269 received intraperitoneal.

The Gynecology Oncology Group (GOG)-172 study found a 16-month survival advantage with the intraperitoneal approach, and a 2013 follow-up confirmed that the benefit persisted.

The study reported at the ASCO meeting showed that at five years, 62.5 percent of the women treated with intraperitoneal chemotherapy were alive compared with 45 percent of those treated with intravenous chemotherapy—a 31 percent relative risk reduction, which was statistically significant.

"Notably, despite practice variation, intraperitoneal [IP] chemotherapy was associated with significantly improved survival in clinical practice, suggesting that the mechanism of chemotherapy delivery matters," Wright said.

Although the NCCN member institutions emphasize evidence-based medicine, when it comes to IP chemotherapy for ovarian cancer, controversy rages, she said. "Whether to give intraperitoneal chemotherapy has become a very polarized issue and often people are for or against it for various reasons. People will say, 'I don't believe in intraperitoneal therapy.' It is a very controversial issue within gynecologic oncology."

But, she said, data support intraperitoneal delivery. Although the GOG-172 protocol was fairly toxic to the patients, "we saw from these data that the regimens can be tolerable with fewer side effects than we originally thought. We have seen fewer side effects with intraperitoneal chemotherapy, and that may be because we are giving these patients extra fluids, more anti-nausea medications. This is a feasible treatment, and it has persistent, Phase 4 evidence that it is effective."

> "The findings suggest that physicians' preferences or institutional biases may have decided what care patients were offered—a troubling finding since this treatment is associated with a major survival benefit."

Barriers: Inconvenience and Cost

Asked for his opinion for this article, Paul Haluska, Jr., MD, PhD, Associate Professor of Oncology at the Mayo Clinic, noted that inconvenience has been a barrier: "You have to be admitted to the hospital, and you have to stay overnight. There are also cost and reimbursement issues, and there is some concern about side effects."

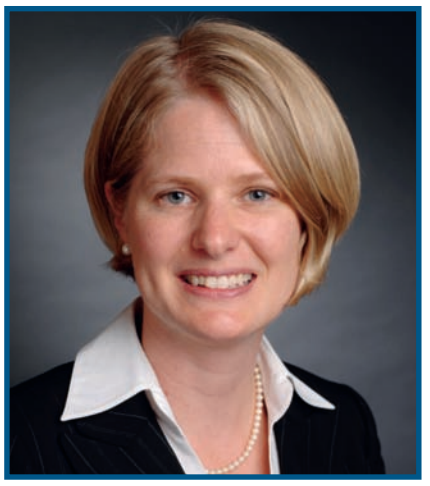
But the bottom line, he said: "I prefer it because it gives us a better chance to cure this disease. I tell my patients, especially those who are young and otherwise healthy, that this gives the woman a better chance of survival. We do get better outcomes with intraperitoneal administration of the anticancer therapies in ovarian cancer."

> "This is a feasible treatment, and it has persistent, Phase 4 evidence that it is effective."

Wright and her colleagues scrutinized data from Dana-Farber Cancer Institute; Fox Chase Cancer Center; MD Anderson Cancer Center; Ohio State University; the University of Michigan; and City of Hope. (Mayo Clinic is an NCCN member, but ovarian cancer patients from Mayo were not included in the study.)

Surprised by Results

Wright said she was surprised by the results and that use of IP chemotherapy was not higher: "The rates seemed to peak around 2006 and 2007 and then just really fell off," she said. In 2007, about 50 percent of women were receiving some form of intraperitoneal therapy, but by 2012, that percentage had dropped to about 30 percent. She speculated that increased use of dose-dense chemotherapy and neoadjuvant chemotherapy in ovarian cancer may have reduced the numbers of patients getting post-surgery chemotherapy.



ALEXI A. WRIGHT, MD, MPH: "Notably, despite practice variation, intraperitoneal chemotherapy was associated with significantly improved survival in clinical practice, suggesting that the mechanism of chemotherapy delivery matters."

"It is surprising in the era of evidence-based medicine that in one institution only 16 percent of women who were eligible received intraperitoneal chemotherapy while in another center 71 percent of patients got it," she said.

At Dana-Farber, doctors do follow the GOG-172 protocol, she said. On Day 1 patients are treated with intravenous paclitaxel; on Day 2 they receive cisplatin into the abdomen. Patients are physically rotated to make sure that the cancer drugs cover all the intestinal surfaces because that is where the disease typically comes back, she explained. On Day 8 paclitaxel is delivered directly into the abdomen.

'The Greater the Exposure to IP, the Better the Outcome'

In the study, although patients were scheduled to receive six cycles of treatment, the median number of cycles received was only four, Wright noted. Patients who could no longer tolerate IP chemotherapy were switched over to IV administration, but "the greater the exposure to intraperitoneal chemotherapy the better the outcomes."

Wright said her team delivers paclitaxel in a three- rather than 24-hour infusion because studies have shown

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little difference in outcomes or adverse side effects with the shorter delivery time. The intraperitoneal regimen allows physicians to deliver higher doses of chemotherapy than could be given intravenously.

Wright reported that in every way the results were analyzed, the outcome was the same for patients treated on clinical trial regimens and for women treated off trial and off protocol—IP patients achieved a risk reduction in favor of survival from 30 to 40 percent. In the full multivariate analysis the relative risk of mortality was reduced 40 percent for all 613 patients in the study in the period 2006 to 2012; for the 498 patients who were not on a clinical trial protocol, the reduction in mortality was 43 percent, also in favor of intraperitoneal chemotherapy.

"I think it is time to reconsider intraperitoneal chemotherapy," Wright said. "We should at least give our patients the information to make informed decisions. As doctors we have more responsibility to think clearly in an evidence-based way for our patients to make sure we are giving them the best treatment.

"Future studies should examine whether variations in intraperitoneal chemotherapy use reflect patients' informed preferences or physician-level and institution-level factors."

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