Monitoring Ovarian Cancer: CA125 Trial Stirs Controversy

By Radha Chitale

Monitoring ovarian cancer with regular blood tests for the CA125 biomarker is a firmly embedded practice in oncology, the theory being that rising CA125 levels may indicate a recurrence, which can be treated effectively upon early detection.

But results from a new randomized, controlled trial presented at the annual meeting of the American Association of Clinical Oncology (ASCO) earlier this year challenge current practice. The trial found that women treated for a recurrence detected through the CA125 biomarker had no better outcomes than those who waited to be treated until after the patient began to show clinical and quality of life than delaying treatment, whereas the other received chemotherapy only after they began to show clinical signs of tumor recurrence—a median of 5 months after therapy was initiated in the immediate group. At 2 years' follow-up, the overall survival between the groups was virtually the same.

Also, women who received delayed treatments reported a higher quality of life than those who were treated early. Using the Global Health Score questionnaire to measure quality of life, the researchers found that patients in the delayed-treatment group had a median of 9.2 months with a "good" score versus 7.1 months for the early-treatment group.

"For the first time, women can be offered informed choices [about CA125 monitoring] after they finish their first-line chemotherapy."

"On the basis of the evidence we have, we don’t have to monitor [CA125] so closely," said Maurie Markman, M.D., vice president of clinical research at the University of Texas M. D. Anderson Cancer Center in Houston, who was not involved with the study. “We have evidence that watching you less aggressively is just as good.”

Limitations and Critics

But critics said that there were enough problems with the study that the results are not likely to instigate broad changes in how CA125 levels are monitored. Robert Bast, M.D., vice president of translational research at M. D. Anderson, said that one of the major failings of the study was not performing a computed tomography scan before CA125 monitoring was initiated. Computed tomography scans can show how much residual cancer remains after primary surgery and chemotherapy, which is a factor in overall survival. More patients with residual cancer could have been randomized to the CA125 arm by chance, he said.

"Everybody agrees that the amount of disease left after the first surgery is a prognostic factor," Bast said. “This study didn’t take that into account. ... If more disease was left behind in the first place in the CA125 arm, that arm would have a worse outcome. If that in fact occurred, even if starting chemotherapy earlier had helped, it would cancel out.”

Another limitation of the trial was that patients did not receive the same treatments after recurrence. Only one-third received a combination of carboplatin and paclitaxel, which improves survival in recurrent disease compared with platinum therapy alone. Consequently, therapy for recurrent disease was not optimal by today’s standards for most patients, said Bast, who discovered the CA125 biomarker and receives royalties on use of the assay.

Also, Beth Karlan, M.D., director of the Women’s Cancer Research Institute at Cedars-Sinai Medical Center in Los Angeles, noted that patients were not considered for a second cytoreductive, or debulking, surgery along with their chemotherapy treatments to remove tumor masses. This approach could have affected overall survival, although it may not have had enough effect to alter the findings, said Karlan, who discussed the findings at ASCO’s plenary session.
Both the criticism of the study design and the overall conclusions cause concern among some patient groups. “Most women know they will have at least one recurrence, and 75% of women do,” said Cara Tenenbaum, senior policy director for the Ovarian Cancer National Alliance, an advocacy and education organization. “[CA125] is not always the best marker, but sometimes it’s useful.” Relying only on symptoms makes her wary, she said.

But Rustin said the study does not suggest that patients rely solely on symptoms to signal a recurrence, nor does it propose discarding the CA125 biomarker. Rather, the study supports the notion that treating a number is not the best way to treat a patient.

“The standard thing done is to do [CA125 testing] every 3 months. Or we can do it every 6 months. Or we can not do it at all. We now have the leeway to say all of these are fine,” Markman said. “I don’t think it changes anything one should have been doing all along. One now just has data to support it.”

Ursula Matulonis, M.D., director of the gynecological oncology program at the Dana–Farber Cancer Institute in Boston, agreed. “There is no definitive study that says you have to check [CA125] levels every 3 months,” she said. “I think everyone has this similar worry that we and our patients are too wedded to CA125 and we need to change our thinking a little bit.”

The strong focus on CA125 levels may subtly lead doctors and patients to consider cancer recurrence a numbers game, when it is far more complex, Matulonis said. “Some physicians will treat [a patient] solely on an elevated CA125 with chemotherapy when patients are upset. That’s something that could change.”
Matulonis is the writing committee member for the ovarian cancer guidelines panel of the National Comprehensive Cancer Network. She said that the panel plans to meet in the fall to discuss updates to the ovarian cancer guidelines, and one topic will be how to use information gleaned from CA125 tests and how often to monitor them. “We’ll definitely discuss it,” Matulonis said. “[The study] presents some very interesting points, but also some pieces of information need to be filled in.”

**Control or Anxiety?**

Some dialogue about the trial results focused on the value that patients place on knowing their CA125 status. “It lets [people] know what is going on in places [they] can’t see or feel in the body,” Tenenbaum said. “There’s no easy way to tell if you have ovarian cancer. … Like any other tool we have in our medical belt, we need to use that.”

Knowing their CA125 levels can be an empowering way for some women with ovarian cancer to have a sense of control about or knowledge over their bodies, Karlan said. But she also noted that constantly awaiting the results of a blood test can be a source of anxiety; some women begin to put so much emphasis on their next CA125 test that their quality of life is affected.

For women who worry about their CA125 levels, the study’s results could decrease anxiety. “I don’t think we should stop doing [CA125 testing]. I don’t think this trial says that,” Karlan said. “But I’m not sure we need to do it every 3 months because it won’t tell about outcomes. … The idea is that a woman can manage her life, understanding that there may be episodes where she needs to go back on treatment, but she may have some power in deciding exactly when.”

One immediate reaction to the trial from some cancer patients and doctors was worry over whether insurance companies would stop paying for CA125 tests if they were deemed unnecessary for monitoring recurrence. But insurance companies are not likely to stop reimbursing patients for it, according to Andrew Berchuck, M.D., director of gynecologic oncology at the Duke University Medical Center in Durham, N.C.

“When you’re managing any kind of chronic disease with a marker, the marker is valuable even if it doesn’t predict survival,” Berchuck said.

The most important clinical outcome of this study may be that doctors and patients should discuss in greater detail how to monitor ovarian cancer for recurrence and what to do with the information, according to Karlan. These types of discussions are especially important in light of the current focus on health care costs and how best to invest our research dollars, she said.

“The validity of this large, randomized trial cannot be swept under the carpet. We need to be sober and realistic in how we look at these findings moving forward.”

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