Small Reduction in Quality of Life Seen With Bevacizumab Maintenance in Patients With Ovarian Cancer

A recent report suggests that bevacizumab begets a small, but clinically significant, decrease in quality of life (QoL) compared with chemotherapy alone in patients with ovarian cancer (Lancet Oncol. 2013;14:236-243).

The report builds on the International Collaboration on Ovarian Neoplasms 7 (ICON7) study, a randomized phase 3 trial comparing a control arm of women who received standard chemotherapy with carboplatin and paclitaxel with an experimental arm of women treated with the same chemotherapy regimen plus concurrent and maintenance bevacizumab as upfront therapy after surgery. In the ICON7 study, chemotherapy was given over 18 weeks and the maintenance continued out to 54 weeks.

ICON7 outcomes have previously been reported, showing a significant increase in progression-free survival (PFS) but not in OS. This earlier report also demonstrated an improvement in QoL in both groups over time. However, near the end of chemotherapy, the QoL was better in the control group, although the difference was small and not considered to be clinically significant (N Engl J Med. 2011;365:2484-2496).

The difference in QoL was subsequently evaluated using newer, evidence-based guidelines (J Clin Oncol. 2011;29:89-96) to refine the interpretation of QoL data. Using this new method to examine ICON7 data, the recent Lancet Oncology article reports the QoL differences to be more important than originally believed.

“This further analysis captured a deficit in QoL in detail that the more general analysis for the main paper did not,” says Daniel Stark, MD, PhD, medical oncologist at the Leeds Institute of Molecular Medicine, University of Leeds, St. James’s University Hospital, Leeds, West Yorkshire, United Kingdom, and the report’s lead author. “It also explored potential reasons for that, although it didn’t identify any definitively.”

Study Results

In the study by Stark et al, baseline QoL data were collected just before treatment started and on the first day of each 3-week chemotherapy cycle for 4 months. Following that, data were collected every 6 weeks during the next 8 months, and every 3 months during year 2. The 58 items on the ovarian cancer module of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Ovarian Cancer Module (EORTC OV28 and Core 30) were used. Of note, QoL data were not collected at the time of disease progression, but there is a scheduled QoL survey for patients still alive at 3 years that will be reported in the future.

All 1528 women in the study were asked to fill out QoL questionnaires. At baseline, 90% of women in both arms provided completed data. Reasons for a missing questionnaire were recorded so it was known whether it was patient or investigator dependent. At 54 weeks, 388 women (51%) in the control arm and 502 women (66%) in the bevacizumab arm provided data (33% of women in the control arm and 19% of women in the bevacizumab arm had developed disease progression or died, and therefore no QoL data were obtained).

During the 18 weeks chemotherapy was administered, the mean global QoL of women in both groups improved by 7.2 points. At the end of chemotherapy, there was a difference of 5 points in the mean global QoL scores. At week 54, there was a difference of 6.4 points; both favored the control arm and both were significant (P < .0001). Furthermore, 66% of women in the control arm and 56% of women in the bevacizumab arm had at least a 10-point improvement in their global QoL score at 54 weeks (P = .001).

Clinical Significance

Dr. Stark points out that evidence-based guidelines for definitions of clinically meaningful changes in QoL are only

Women have reported a slight decrease in their overall quality of life after the drug bevacizumab was added to their chemotherapy regimen to treat ovarian cancer.
available for part of the data collected (EORTC Core 30), and more research is needed to better interpret QoL data.

Paul Sabbatini, MD, deputy physician-in-chief for clinical research and medical oncologist at Memorial Sloan-Kettering Cancer Center in New York City, adds, “The threshold for clinical significance in quality-of-life studies is always a challenge. It is equally true that determining the threshold for clinical significance is also challenging when considering PFS/OS benefits, as well as toxicity for agents in oncology.” He adds that the study points to the importance of including QOL as a study endpoint, particularly when the primary efficacy endpoints yield modest results.

“Placing patients on maintenance therapy, even with modest toxicity, carries a measurable detriment to QoL,” Dr. Stark notes. “This raises a pertinent question: if the gain seen is in length of cancer control, not in length of life, is this in the patient’s best interest?”

The findings by Dr. Stark and his colleagues are in contrast to the Gynecology Oncology Group (GOG) 218 Phase III Trial (Gynecol Oncol. 2013;128:573-578). GOG 218, which was also a study of adding bevacizumab to chemotherapy for the treatment of ovarian cancer, did not show any significant differences in QoL. The authors of the current study suggest that may have been because GOG 218 was a placebo-controlled trial, and therefore both groups had the same number of physician visits, whereas ICON7 was an open-label study, so the number of visits was much higher in the bevacizumab arm. However, definite reasons are not clear.

Stark et al believe the strengths of this analysis include the large representative sample from 263 international centers, a large amount of QoL data collected systematically, and the collection of reasons for missing data. Furthermore, the substudy was planned as part of the original study, not as a retrospective analysis, Dr. Stark noted. However, there are weaknesses, including the lack of data beyond disease progression, and that ICON7 was an open-label study, thereby potentially affecting QoL.

Future Implications
The findings of the study by Dr. Stark and his colleagues have clinicians asking whether the approximately 2-month increase in PFS noted with the addition of bevacizumab is offset by the potential detriment in QoL parameters. When data from the 36-month QoL survey are published, this may be easier to answer.

“I think the emerging data for bevacizumab definitely support a place for its use in the course of patients with ovarian cancer,” says Dr. Sabbatini. “At a minimum, available data suggests that the risk:benefit ratio for completely or optimally debulked patients does not support the routine use of bevacizumab as part of primary therapy. One can argue that a benefit exceeding risk starts to emerge in the more advanced patients, and there particularly appears to be a place for bevacizumab later in the disease course.”

“My bias is that it likely has more meaningful activity in the recurrent setting and this would be the preferred time to use it,” Dr. Sabbatini added. “This QoL study further shifts one away from the modest PFS advantage for most patients when bevacizumab is used up front.”

Dr. Stark contends that despite the advantage in PFS, not all patients should receive maintenance therapy, as it may produce inconvenience and disruption with a reduction in QoL. “Therapy needs to be individualized and the patient’s outlook taken into consideration,” he says. ■