Rectovaginal Nodularity, Bowel Perforations Tied

BY JANE SALODOF MACNEIL

SAN ANTONIO — Rectovaginal nodularity turned out to be the only significant risk factor for bowel complications in a retrospective single-institution study of 112 women treated with bevacizumab for recurrent epithelial ovarian cancer.

Ten women (9%) developed bowel perforations in the study, and five died within 30 days—a mortality rate of 50% for this serious complication. Fistulas were diagnosed in two patients (1.8%): one enterocutaneous fistula and one fistula-in-ano.

To the investigators' surprise, a host of potential causes—among them, the number of previous bevacizumab (Avastin) regimens, carcinomatosis, bowel involvement on CT scan, and history of small bowel obstruction—produced no significant associations with bowel complications. Rectovaginal nodularity increased risk more than threefold (odds ratio 3.64, P = .04), however.

After hearing the data presented at the Society of Gynecologic Oncologists' annual meeting on women's cancer, an audience member asked Dr. Debra L. Richardson, the lead author, whether the 50% mortality rate she reported was excessive. Most of the patients were heavily pretreated, she responded, and three patients chose not to pursue any further interventions at a late stage in their disease.

Though potentially deadly, the risk of bevacizumab-related bowel complications should not preclude use of the agent in advanced ovarian cancer, Dr. Richardson added in an interview. If other treatment options are available, she might hold off introducing bevacizumab. If not, she would discuss the risk with the patient.

"If bevacizumab is the only treatment option, I think it still may be worthwhile as long as the patient is well counseled about this risk," she said.

Dr. Richardson and her coauthors at the Ohio State University in Columbus undertook the chart review because high rates of bowel complications have been seen when bevacizumab is used in patients with recurrent epithelial ovarian cancer. Bowel perforation and fistula have been reported in 0%-11% of patients given monotherapy, and 0%-9% of patients when bevacizumab is used in combination with other cytotoxic agents. Of particular concern, these rates are higher than with bevacizumab use in other cancers, including colorectal cancers.

Despite this toxicity, she noted, bevacizumab continues to be used because it has produced response rates of 10%-21% as monotherapy and 24%-78% when used in combination with other drugs for recurrent ovarian cancer.

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DR. RICHARDSON

The chart review looked at all patients treated with at least one dose of bevacizumab. Dr. Richardson reported that 112 patients (median age 60 years) who met study requirements received 160 different bevacizumab regimens. Nearly a third, 31%, had received more than one bevacizumab regimen. The most common cytotoxic combination was with weekly paclitaxel (34%) followed by combinations of bevacizumab with gemcitabine and carboplatin or cisplatin.

Patients had a median of four prior chemotherapy regimens, and they received a median of six cycles of bevacizumab with a median total dose of 8,313 mg. The population included 18 patients with a history of small bowel obstruction, 31 with rectovaginal nodularity, 78 with a CT scan prior to starting bevacizumab, 10 with a CT scan showing bowel involvement, and 21 with carcinomatosis.

The bowel perforations occurred 2-25 days (0.5-5 cycles) after starting bevacizumab, Dr. Richardson reported. Three of the patients who developed perforations had previously been treated with bevacizumab, and 30% of perforated patients died within 7 days. After the perforations were diagnosed, she continued, four patients opted for surgery and three of them survived 30 days as did two patients treated with intravenous antibiotics.

As for why rectovaginal nodularity turned out to be the only significant risk factor, Dr. Richardson cited the small size of the study as one possibility. Another is that only large-volume disease is associated with bevacizumab-related bowel perforation, she said, and yet another that current imaging is not large enough to detect bowel involvement.

Dr. Richardson disclosed no conflicts of interest. ■

Endometrial Ca: Progression-Free Interval Predicts Survival, 'Limited' Clinical Value

BY JANE SALODOF MACNEIL

SAN ANTONIO — The length of time between the starts of primary and secondary treatment for advanced or recurrent endometrial cancer is a statistically significant predictor of a woman's risk of death 6 months after resuming treatment, according to a review of phase III trials conducted over the last 20 years.

A progression-free interval lasting more than 6 months reduced the risk of death by 30% in the Gynecologic Oncology Group (GOG) studies. The finding was statistically significant with a *P* value of .0001, but investigators concluded it had "limited" clinical value. Compared with women whose disease progressed within 6 months or less, patients gained about 3 months of life when they went longer before restarting treatment. Moreover, platinum sensitivity did not make much difference in the impact of second-line treatments on survival.

"Ten months versus 7 months—that's not a very useful prognostic indication," lead investigator Kathleen M. Moore said in an interview, referring to the median probability of survival after second-line treatment with the longer progression-free interval versus a shorter span. "For endometrial cancer, it really doesn't change what you are going to do for that patient. It doesn't change how you are going to counsel that patient about progression."

Dr. Moore of the University of Oklahoma, Oklahoma City, presented the results at the annual meeting of the Society of Gynecologic Oncologists.

The ancillary data analysis compared outcomes relative to progression-free intervals among 586 women who participated in GOG protocols 107, 122, 139, 163, and 177, which tested a variety of chemotherapy regimens. The women had a median age of 64 years, and nearly two-thirds had recurrent disease in this first part of the study. Most received platinum-based regimens as first-line therapy; their median progression-free interval was 6.7 months.

Investigators also reviewed treatment-free intervals from completion of the first regimen to progression for 275 women in the GOG protocol 129 series of trials. This group's median age was 66 years, and 89% of the women had been given platinum-based regimens as first-line therapy.

The women in this part of the study had a median treatment-free interval of 2.9 months. A treatment-free interval greater than 3 months was associated with a 25% reduction in risk of death (*P* = .014), but the investigators again saw little clinical value. Median survival from the start of therapy was 10.22 months with the longer treatment-free interval and 7.39 months for those who stayed off treatment for less than 3 months.

The findings were "very disappointing," Dr. Moore said. Investigators had hoped to see a difference comparable to ovarian cancer, a disease in which some women gain 2 years of life, with median survival improving from 12 months to 36 months, if they remained progression free for more than 6 months after first-line treatment. She attributed the differences in predictive value of progression-free interval in part to underlying differences in response to first-line therapy. Women with ovarian cancer are typically in remission after completing their first chemotherapy, she said. This is not the case in women with endometrial cancer: "Only 15% had a complete clinical response—the majority finished their first chemotherapy with measurable disease."

Moreover, the second-line treatments that can significantly prolong survival in ovarian cancer are lacking in endometrial cancer, she said, describing continued drug development as key to improving survival. Dr. Moore disclosed no conflicts of interest. ■

Obesity Negates OC Protection Against Endometrial Cancer

DENVER — Even long-term use of oral contraceptives can't nullify the substantially increased risk of endometrial cancer conferred by obesity, results of a case-control study show.

"These results highlight the importance of weight reduction in the primary prevention of endometrial cancer," Dr. Linda S. Cook observed at the annual meeting of the American Association for Cancer Research.

She presented a study of OC use in 542 endometrial cancer patients enrolled in the population-based Alberta,Canada, cancer registry during a recent 3-year period, as well as in 1,032 randomly selected age-matched controls.

As other studies have shown, OC use protected against endometrial cancer. The benefit was duration dependent. Women who used OCs for less than 5 years had an adjusted 26% reduction in endometrial cancer risk relative to never-users, and women with a history of 5 years or more of OC use had a 43% risk reduction after adjustment for age, body mass index (BMI), parity, menopausal status, and urban versus rural residence, reported Dr. Cook of the University of New Mexico, Albuquerque.

What's new in this study are the findings on how a history of OC use interacts with parity and BMI to affect endometrial cancer risk. Increasing parity and OC use reduced risk in what appeared to be additive fashion. For example, women with a parity of three or more plus a history of at least 5 years on OCs had an 83% reduction in risk of endometrial cancer compared with nulliparous non–OC users. On the other hand, endometrial cancer risk climbed with increasing BMI. Overweight women had a greater risk than normal-weight women, and obese women had a higher risk than overweight ones. Even with a history of at least 5 years of OC use, obese women still had a 2.8-fold greater risk of the malignancy than normal-weight non–OC users.

—Bruce Jancin

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