ASCO: Avastin Improves Survival in Advanced Cervical Cancer

By Anne Landry | 7 de junio de 2013
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At the plenary session of the 2013 meeting of the American Society of Clinical Oncology (ASCO) in Chicago on June 2, results from the phase III Gynecology Oncology Group (GOG) 240 trial showed addition of bevacizumab (Avastin) to standard chemotherapy improved overall survival (OS) by nearly 4 months in women with advanced or relapsed cervical cancer (ASCO abstract 3). Administering bevacizumab with chemotherapy also yielded a 12% improvement in tumor response rate compared with chemotherapy alone. Median progression-free survival (PFS) and overall response rate were also notably improved, and benefit with the addition of bevacizumab to treatment was seen even in women who had received pelvic irradiation. Importantly, these benefits were realized without significantly impacting health-related quality of life.

GOG 240 investigators noted that the findings mark bevacizumab as the first molecularly targeted agent to improve overall survival in a gynecologic cancer.

Krishnansu S. Tewari, MD, FACOG, FACS, professor, department of obstetrics and gynecology, and director, division of gynecologic oncology at the Chao Family Cancer Center, University of California at Irvine, Orange, California, presented the findings from this trial, which involved 452 patients with primary stage IVB recurrent/persistent cervical cancer.

A Significant Health Problem

Cervical cancer is a significant health problem around the world. It is the second most common cancer among women worldwide and the second most common cause of cancer mortality in women globally. It has a worldwide incidence of 500,000, with 250,000 cervical cancer–related deaths each year. In the United States, the incidence of cervical cancer is 12,000, with 4,000 deaths from the disease annually. The average age of patients is 47 years.
Efforts at screening and prevention have made inroads into reducing mortality from cervical cancer. Tools in the armamentarium include targeted educational strategies; male and female condoms; the Papanicolaou (Pap) screening test; vaccines against the causative agent, human papillomavirus (HPV); and, more recently, a promising new acetic acid (vinegar) test that was also reported on June 2 in the 2013 ASCO plenary session (ASCO abstract 2; presented by Surendra S. Shastri, MD, of Tata Memorial Hospital, Mumbai. The vinegar test for cervical cancer was studied over a 15-year period in India in more than 150,000 women; it reduced cervical cancer mortality by 31% and could potentially prevent 72,000 deaths in low-resource countries annually.)

**New Options Are Needed for Advanced or Relapsed Disease**

Unfortunately, as Dr. Tewari noted, while surgery (in early-stage disease) or chemoradiation therapy (in later-stage disease) can be effective, “there are very limited treatment options for patients with advanced stages of cervical cancer and for those whose cancer relapses after initial treatment,” and drug resistance “is one very big problem with this disease.” He said that, “unlike some other solid cancers, cervical cancer doesn’t really respond to different chemotherapies. In fact, the standard regimen [cisplatin plus paclitaxel] probably extends survival by about 12 months or less—and then, once patients don’t respond to this regimen, they die.”

Following a clinical alert by the National Cancer Institute (NCI) in 1999, he explained, “the majority of women with recurrent cervical cancer have received primary treatment with cisplatin-based chemoradiation for locally advanced disease. We were concerned that, with widespread adoption of chemoradiation protocols, platin-based therapies at recurrence would be less effective due to acquired drug resistance.” In fact, in 2009, GOG 204, a phase III trial of four platinum-based chemotherapy doublets in recurrent cervical cancer, was closed for futility; it was discovered that many of the women had platinum-resistant disease because they had received platinum as part of their prior chemoradiation therapy.

The four-arm GOG 240 study investigated new therapeutic options for women with cervical cancer, comparing efficacy of topotecan as an alternative to cisplatin in the chemotherapy regimen; two of the arms also included the monoclonal antibody bevacizumab, which binds to vascular endothelial growth factor (VEGF) to inhibit angiogenesis. Explaining the clinical rationale for including bevacizumab in the study, Dr. Tewari said that, besides the fact that VEGF inhibition has shown benefit in a number of solid tumors, angiogenesis is very active in cervical cancer and “is a hallmark” of invasive disease.

**The GOG 240 Trial: Protocol and Results**

The GOG 240 schema involved randomization of 452 patients with primary stage IVB recurrent or persistent cervical cancer, measureable disease, GOG performance status 0–1, and no prior chemotherapy for recurrence. Patients were matched in the chemotherapy and chemotherapy-plus-bevacizumab groups for age, race, histology, stage of disease, performance status, and presence of pelvic disease in the previously irradiated pelvis. “Importantly, more than 70% of the entire study population had received a prior platinum as chemotherapy with their radiation, and this was also evenly distributed between the two groups,” Dr. Tewari said.

This NCI–funded trial was activated on April 6, 2009 and closed to accrual on January 3, 2012. Multiple cancer centers in the United States and Spain participated. Patients were randomized to one of four treatment arms, with treatment every 21 days to disease progression, unacceptable toxicity, or complete response.

Arms I and III randomized the women to chemotherapy alone. Arm I was paclitaxel at 135 mg/m² IV or 175 mg/m² IV plus cisplatin at 50 mg/m² IV and arm III was paclitaxel at 175 mg/m² IV plus topotecan at 0.75 mg/m² on days 1–3 (with topotecan selected based on laboratory data showing synergy with microtubule-interfering agents, and phase II clinical data showing efficacy of topotecan plus paclitaxel in...
cervical cancer). Arms II and IV used the same chemotherapy doublets used in arms I and III, respectively, but with the addition of bevacizumab at 15 mg/kg IV. The median number of treatment cycles was 6 in the two chemotherapy arms and 7 in the two chemotherapy-plus-bevacizumab arms.

In a preplanned interim analysis, OS was assessed in February 2012, after a total of 174 events (deaths). Secondary endpoints were PFS and objective tumor response rate (evaluated by RESIST-1). Exploratory endpoints assessed included quality of life, a pooled analysis of prognostic markers identified in phase III trials, the prevalence and effect of nicotine dependence on survival in this population, and novel translational endpoints involving circulating tumor cells and VEGF isoform expression, Dr. Tewari said.

Addition of paclitaxel to the cisplatin was previously shown (in GOG 204) to improve survival by about 12 months, and in GOG 240, in the 225 patients who received chemotherapy alone, median OS was comparable, at 13.3 months. (There was no significant difference between median survival with cisplatin/paclitaxel vs topotecan/paclitaxel [15 months vs 12.5 months, respectively; \( P = .880 \)). “If we could increase survival [even further with bevacizumab] by about 4 months, to [an OS of] about 16 months, that’s what we felt would be clinically meaningful,” Dr. Tewari said. Indeed, in the 227 patients in GOG 240 who received bevacizumab with their chemotherapy, median OS was about 17 months (HR = 0.71; 97.6% CI, 0.54–0.94; \( P = .0035 \)).

“We were very delighted to report that the overall survival improved significantly in patients who were given the anti-angiogenesis drugs,” he said. The OS improvement was 3.7 months, “which we feel is clinically meaningful in a population of patients that doesn’t respond to chemotherapy very well.”

The response rate in patients treated with chemotherapy alone was 36% (with 14 complete responses), compared with a 48% response rate (with 28 complete responses) in patients treated with chemotherapy plus bevacizumab (\( P = .00807 \)).

Assessment of Adverse Events and Quality of Life

Median follow-up of the patients was 20.8 months. “There were fatal adverse events in four patients in each group [the two chemo arms combined vs the two chemo plus bevacizumab arms combined], so there was not a significantly increased number of fatal adverse events with bevacizumab,” Dr. Tewari said. Known side effects associated with bevacizumab were seen: The incidence of grade 4 neutropenia was higher with bevacizumab (35% vs 26% without it), and grade 2 or higher hypertension was 25% with bevacizumab (vs 2% with just chemotherapy), but no patients discontinued treatment because of hypertension. The rate of grade 3 or higher thromboembolic events in patients treated with bevacizumab was 3%, compared with a 1% incidence with chemotherapy alone. The incidence of grade 3 or higher gastrointestinal (GI) or genitourinary fistula was nearly 6% in women who received bevacizumab plus chemotherapy (compared with only one genitourinary fistula [< 1%] seen among patients receiving chemotherapy alone), which Dr. Tewari said is “relatively low” (ie, below 10%).

Quality of life was assessed using the FACT-Cx TOI (Functional Assessment of Cancer Therapy–Cervix Trial Outcome Index scale) to assess physical and functional well-being specific to cervical cancer, where a between-group overall score difference of 5 or more would indicate a clinically significant detriment to quality of life. “In this study,” Dr. Tewari said, “the [FACT-Cx score] difference between patients receiving chemotherapy alone and patients receiving chemotherapy plus bevacizumab was only 1.2 points, indicating that the increased survival with bevacizumab did not come at a cost of decreased quality of life.”

GOG 240 Impact and Implications for Future Studies

In conclusion, Dr. Tewari called the GOG 240 study results a “triple-header,” since improvements were seen in OS, PFS, and response rate, and the adverse events seen with addition of bevacizumab were all known side effects and their incidence was under 10%. He noted that the NCI’s data monitoring committee voted to
release GOG 240’s topotecan/paclitaxel analysis into the public domain, and they were presented in March 2013 at the 44th Annual Meeting of the Society of Gynecologic Oncology (SGO); in March 2013 ASCO voted to release the anti-VEGF data from GOG 240 into the public domain, and in May of this year, he said, the National Comprehensive Cancer Network (NCCN) was considering listing cisplatin/paclitaxel/bevacizumab in their cervical cancer practice update guidelines.

To provide the greatest benefit, Dr. Tewari said, “[t]he discovery of survival gains such as that concurred by anti-VEGF therapy needs to be followed by cost-effectiveness studies to best determine how to balance the societal burden and, at the same time, provide these therapies to those who are in the greatest need.”

Moving forward, based on the GOG 240 results “the incorporation of anti-VEGF therapy into primary treatment for locally advanced disease should be considered,” Dr. Tewari said. “With respect to the GOG 240 population of patients with recurrent disease,” he added, “these data open up the doors to study other classes of anti-angiogenesis agents, both VEGF-dependent molecules, as well as non–VEGF-dependent molecules. In addition, vascular disrupting agents, Wee-1 checkpoint inhibitors, and NOTCH gamma secretase inhibitors may also be considered, with the latter being an evolutionarily conserved binary cell-fate decision switch that’s operative in cervical cancer angiogenesis.”

**Discussant of the GOG 240 Findings: Dr. Gottfried Konecny**

The ASCO Discussant for this study was Gottfried E. Konecny, MD, Associate Professor of Medicine at the David Geffen School of Medicine at the University of California, Los Angeles. He said GOG 240 can be seen as practice-changing, with “data that compares very favorably to what bevacizumab has achieved in other cancers in the first-line setting.” He commented that targeting VEGF in the setting of cervical cancer is “an extraordinarily good rationale … based on the pathophysiological role of HPV infections.” He outlined strengths of the study, including the fact that it was placebo-controlled; random assignments were “extremely well balanced” due to stratification for important prognostic factors, which he said “is particularly important in cervical cancer, because small differences—such performance status, presence of pelvic disease, a short disease-free interval, African American race, and primary platinum treatment—can adversely affect outcome”; the prespecified $P$ values all were adjusted for multiple testing; and there was no crossover, which he said enabled the investigators “to get the purest survival data.” In addition, he noted that “the control arm did not underperform,” so cisplatin plus paclitaxel remains the chemotherapy standard of care in this setting.

While noting that the incidences of neutropenia, hypertension, and thromboembolic complications in GOG 240 compare favorably with results of studies assessing first-line bevacizumab use in colon/abdominal tumors, Dr. Konecny cautioned that “we do need address special attention to the fistula formation and possibly GI perforations; this could be related to the fact that these patients generally have undergone prior radiation therapy.” Also, since less than one-fifth (17%) of the women in GOG 240 had metastatic disease, he emphasized that “it is incredibly important to move bevacizumab into [studies investigating] earlier disease stages” in the cervical cancer setting.