AURELIA Analysis Shows Benefits of Bevacizumab as Add-on Therapy in Ovarian Cancer

Written by ***Phil Vinall***

In patients with ovarian cancer, progression-free survival (PFS) and overall response rate (ORR) are significantly improved with the addition of bevacizumab to chemotherapy in front-line [Burger RA et al. *N Engl J Med* 2011] and platinum-sensitive recurrent [Aghajanian C et al. *J Clin Oncol* 2012] settings, and as shown in the Phase 3 AURELIA: A Study of Avastin (Bevacizumab) Added to Chemotherapy in Patients with Platinum-Resistant Ovarian Cancer [AURELIA; NCT00976911] trial [Pujade-Lauraine E et al. *J Clin Oncol* 2012].

Andrés Poveda, MD, Fundación Instituto Valenciano de Oncología (IVO), Valencia, Spain, presented the results from a subanalysis of AURELIA that showed that the benefits of bevacizumab as add-on therapy are observed regardless of the choice of chemotherapy.

AURELIA, the first trial to compare bevacizumab plus chemotherapy versus chemotherapy alone in platinum-resistant ovarian cancer patients (epithelial ovarian, fallopian tube, or primary peritoneal cancer), was a multicenter, open-label, randomized, 2-arm trial. Patients with platinum-resistant ovarian cancer that had progressed <6 months after 4 cycles of platinum-based therapy were randomly assigned in 1:1 ratio to either chemotherapy alone or chemotherapy plus bevacizumab (15 mg/kg every 3 weeks) and treated until disease progression, unacceptable toxicity, or withdrawal of consent. Chemotherapy regimen was chosen by the investigator prior to randomization and included standard regimens of paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD). Stratification factors were the chemotherapy selected, prior antiangiogenic therapy, and treatment-free interval (<3 vs 3 to 6 months from previous platinum to subsequent progressive disease).

The primary objective was to compare PFS with chemotherapy alone versus chemotherapy plus bevacizumab according to Response Evaluation Criteria in Solid Tumors (RECIST v1.0) guidelines. Secondary objectives included ORR, overall survival, quality of life, safety, and tolerability.

Subjects were median ~60 years of age. Approximately 25% had a progression-free interval of less than 3 months. More patients in the paclitaxel cohort had received 2 prior chemotherapy regimens compared with the PLD and topotecan cohorts.

In the patients with platinum-resistant ovarian cancer, the addition of bevacizumab to single-agent chemotherapy was associated with improvements in median PFS (Table 1) and ORR across all chemotherapy cohorts.

Table 1. Median Progression-Free Survival.

Population	CT Alone Months (95% CI)	CT + BEV Months (95% CI)	HR (95% CI)	p Value
Overall population	3.4 (2.2–3.7)	6.7 (5.7–7.9)	0.48 (0.38–0.60	<0.001
Paclitaxel cohort	3.9 (3.5–5.6)	10.4 (7.9–11.9)	0.46 (0.30–0.71)	
PLD cohort	3.5 (1.9–3.9)	5.4 (3.9–6.6)	0.57 (0.39–0.83)	
Topotecan cohort	2.1 (1.9–3.3)	5.8 (5.3–7.5)	0.32 (0.21–0.49)	

BEV=bevacizumab; CT=chemotherapy; PLD=pegylated liposomal doxorubicin.

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The bevacizumab plus chemotherapy arm was associated with a higher incidence of grade ≥2 peripheral sensory neuropathy and grade ≥3 neutropenia in the paclitaxel cohort, and grade ≥2 hand-foot syndrome and grade ≥3 hypertension in the PLD cohort. Incidence rates of grade ≥3 neutropenia and leucopenia were higher in the chemotherapy-alone arm.

The effects of bevacizumab on PFS within the individual chemotherapy cohorts were consistent with the results in the overall population. Increased chemotherapy exposure associated with prolonged PFS accounted for some increase in cumulative chemotherapy toxicity. However, overall, there was no indication that bevacizumab exacerbates chemotherapy-related adverse events. The authors concluded that bevacizumab plus chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer.

Results and Subgroup Analyses of the PETACC-8 Trial

Written by ***Toni Rizzo***

FOLFOX4 (leucovorin, 5-fluorouracil, and oxaliplatin) has been the standard adjuvant therapy for resected stage III colon cancer since 2004, producing 3-year disease-free survival (DFS) rates of ~70%. The aim of the Combination Chemotherapy with or Without Cetuximab in Treating Patients with Stage III Colon Cancer That Was Completely Removed by Surgery [PETACC-8; NCT00265811] trial presented by Julien Taïeb, MD, PhD, Hôpital Européen Georges Pompidou, Paris, France, was to assess the potential benefit of adding cetuximab to standard treatment for colon cancer.

Patients with fully resected stage III colon cancer were randomized to FOLFOX4 every 2 weeks, with or without cetuximab (initial dose, 400 mg/m^2; 250 mg/m^2 weekly; Days 1 and 8), for 12 cycles. The primary endpoint was DFS in patients with KRAS wild-type (WT) tumors. The secondary endpoints were overall survival (OS), and treatment compliance and toxicity. A preplanned subgroup analysis focused on demographic, oncologic, and molecular data. An interim analysis was planned after 65% of planned events occurred.

At interim analysis, 2559 patients were enrolled, 62.5% of whom had KRAS WT tumors. A total of 1602 patients of these patients were randomized. The median follow-up for DFS was 3.33 years in the FOLFOX4 plus cetuximab arm and 3.30 years in the FOLFOX4 alone arm. Baseline characteristics were similar in both arms.

The 3-year DFS rate was 75.1% with FOLFOX4 plus cetuximab versus 78.0% with FOLFOX4 alone (HR, 1.047; 95% CI, 0.853 to 1.286; p=0.6562). The OS rate was 88.3% with FOLFOX4 plus cetuximab versus 90.5% with FOLFOX4 alone (HR, 1.092; 95% CI, 0.813 to 1.466; p=0.5583). Grade 3/4 adverse events occurred in 80.9% of patients treated with FOLFOX4 plus cetuximab versus 66.2% of those treated with FOLFOX4 alone. Patients with KRAS/BRAF WT tumors treated with FOLFOX4 plus cetuximab (n=492) versus FOLFOX4 alone (n=492) had no significant differences in DFS (115 vs 108 events; HR, 0.985; 95% CI, 0.755 to 1.284; p=0.9117) or OS (55 vs 52 events; HR, 0.981; 95% CI, 0.669 to 1.438; p=0.9236).

Worse DFS outcomes in patients treated with FOLFOX4 plus cetuximab versus FOLFOX4 alone were observed in females (adjusted HR, 1.45; 95% CI, 1.03 to 2.03; p=0.031), patients aged >70 years (adjusted HR, 1.97; 95% CI, 0.99 to 3.93; p=0.051), and patients with right-sided tumors (adjusted HR, 1.40; 95% CI, 1.01 to 1.94; p=0.043). Patients with pT4N2 tumors treated with FOLFOX4 plus cetuximab (n=79) versus FOLFOX4 alone (n=67) had significantly better DFS (32 vs 41 events; HR, 0.555; 95% CI, 0.348 to 0.885; p=0.0122).

Adding cetuximab to FOLFOX4 offered no DFS or OS benefit to patients with resected stage III KRAS WT or KRAS/BRAF WT colon cancer. Subgroup analyses suggested that patients with pT4N2 tumors may benefit from treatment with cetuximab, while females, patients aged >70 years, and patients with right-sided colon cancer may have worse outcomes with cetuximab—results that, according to Prof. Taïeb, suggest stage III and IV colon cancers have a different biology. Microsatellite instability status is being determined to explore interaction with poor outcomes in the 3 latter subgroups.

Single-Agent Doxorubicin Versus Doxorubicin plus Ifosfamide in Advanced Soft Tissue Sarcoma

Written by ***Toni Rizzo***

Patients with locally advanced unresectable or metastatic soft tissue sarcoma have poor outcomes. Palliative chemotherapy is standard treatment for these patients, but it generally results in considerable toxicity. Previous studies have compared single-agent doxorubicin with doxorubicin plus ifosfamide, but the optimal doses remain unclear. The European Organisation for Research and Treatment of Cancer (EORTC) 62012 Phase 3 study [NCT00061984] presented by Winette van der Graaf, MD, PhD, Radboud