Antiangiogenics in Ovarian Cancer: Where Are We Now?

Written by ***Emma Hitt, PhD***

Vascular Endothelial Growth Factor (VEGF) promotes ascites and effusions in ovarian cancer [Byrne AT et al. *Clin Cancer Res* 2003], and it is an independent adverse predictor of patient prognosis [Shen GH et al. *Br J Cancer* 2000]. Bevacizumab, a humanized monoclonal antibody that targets VEGF, has shown single-agent activity in Phase 2 epithelial ovarian cancer trials [Burger RA et al. *N Engl J Med* 2011]. Elizabeth A. Eisenhauer, MD, Queen's University, Kingston, Ontario, Canada, provided an update on the data available from Phase 3 bevacizumab ovarian cancer trials.

The Carboplatin and Paclitaxel with or Without Bevacizumab in Treating Patients with Stage III or Stage IV Ovarian Epithelial, Primary Peritoneal Cancer, or Fallopian Tube Cancer [Gynecologic Oncology Group (GOG)-0218; NCT00262847] trial was the first reported randomized study of bevacizumab in ovarian cancer. Patients with newly diagnosed stage III or IV epithelial ovarian, primary peritoneal (PP), or fallopian tube (FT) cancer who had undergone debulking surgery were randomized to the placebo group, bevacizumab-initiation group, or bevacizumab-throughout group [Burger RA et al. *N Engl J Med* 2011]. All patients received paclitaxel and carboplatin. Progression-free survival (PFS) improved by approximately 4 months in the bevacizumab throughout group with a hazard ratio (HR) of 0.717 compared with an HR of 0.908 in the control group ($p<0.001$).

In addition to GOG-0218, six other Phase 3 trials have been undertaken to evaluate the addition of an angiogenesis inhibitor to chemotherapy in epithelial ovarian cancer. Three of these have presented initial results (Table 1). In the International Collaborative Ovarian Neoplasm 7 [ICON7; NCT00483782] trial, women with newly diagnosed epithelial ovarian, PP, or FT cancer were randomized to either chemotherapy alone or concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab [Perren TJ et al. *Ann Oncol* 2010]. While the dose of bevacizumab in this trial was half the dose used in the GOG-0218 trial, a significant improvement in PFS was observed.

Table 1. Phase 3 Trials Evaluating the Addition of an Angiogenesis Inhibitor in Epithelial OVCA.

Agent	Trial ID	n	Line of Therapy	Chemo	PEE	Status
BEV	GOG0218	1873	First	TC	PFS	Published
	ICON7	1528	First	TC	PFS and OS	Published
	OCEANS	484	Recurrent - p *sens*	GC	PFS	Published
	AURELIA	361	Recurrent - p *res*	T or Topo or liposomal doxorubicin	PFS	Presented (ESMO 2012)
BIBF	AGO-OVAR 12	1300	First	TC	PFS	Closed
CED	ICON6 (GCIG study)	2000	Recurrent - p *sens*	TC	PFS and OS	Closed
PAZ	AGO-OVAR 16	900	First (maintenance only)	TC (BEV allowed)	PFS	Active

BEV=bevacizumab; BIBF=nintedanib; CED=cediranib; ; GC=gemcitabine/carboplatin; OS=overall survival; PAZ=pazopanib; PEE=primary efficacy endpoint; PFS=progression-free survival; TC=docetaxel/cyclophosphamide; Topo=topotecan; T=paclitaxel.

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In the Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease [OCEANS; NCT00434642] trial, patients with platinum-sensitive recurrent ovarian cancer who had not previously received chemotherapy were randomized to either bevacizumab with gemcitabine plus carboplatin, or gemcitabine and carboplatin alone [Aghajanian C et al. *J Clin Oncol* 2012]. Dr. Eisenhauer said that bevacizumab resulted in "a striking PFS increase in this trial."

The AURELIA [NCT00976911] trial, included patients with platinum-resistant ovarian cancer who had received 2 or less prior cancer therapies [Poveda A et al. ESMO 2012. Abstract LBA26]. All patients received 1 of 3 chemotherapy options chosen by the investigator and were randomized to receive either bevacizumab plus chemotherapy or chemotherapy alone. To date, data from this trial have indicated a PFS advantage for bevacizumab regardless of which chemotherapy regimen was chosen.

For all four Phase 3 bevacizumab trials, toxicity was greater in the bevacizumab arms and the cost of bevacizumab is considerable compared with chemotherapy. In addition, although these trials showed an impact of treatment on PFS, no trial has shown significant overall survival data in the analyses performed to date; however, with this observation it must be noted that the overall survival data are not yet mature for any of these trials. The investigators also need to analyze available data to clarify whether delay in progression is associated with freedom from symptoms for patients with ovarian cancer.

Dr. Eisenhauer said that "great progress in completion of Phase 3 trials of angiogenesis inhibitors has been made in ovarian cancer over the past 2 to 3 years," and these trials have shown clear evidence of a biological effect for bevacizumab through improvement in PFS; nonetheless, it will be the final overall survival data that will determine whether bevacizumab is truly paradigm changing for ovarian cancer management. She argued that validated selection biomarkers are urgently needed to identify patient subsets that are truly benefiting from angiogenesis inhibition—this knowledge may reveal those who do experience survival gains and reduce unnecessary treatment of those who do not, improving both therapeutic index and cost-effectiveness. Many of the studies discussed in the presentation included tissue, blood, and other sample collections that may serve as valuable resources for addressing these questions.

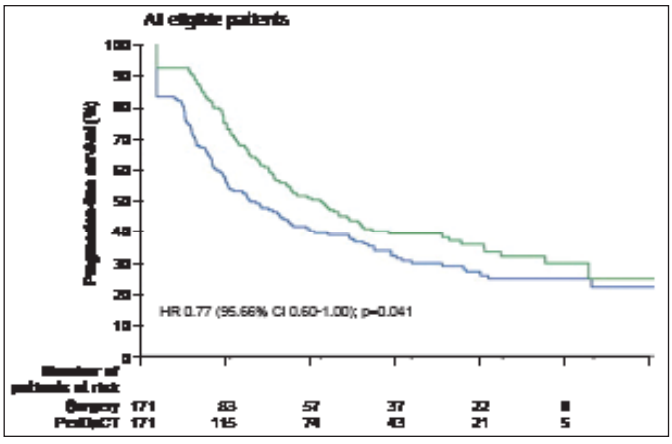
Pursuing the No Evidence of Disease Condition in Advanced Colorectal Cancer

Written by ***Toni Rizzo***

The clinical value of achieving no evidence of disease (NED) in patients with advanced colorectal cancer (CRC) depends on the balance between the duration of the NED state and the toxicity of the treatments to achieve it, particularly with multimodal interventions. Alberto Sobrero, MD, Hospital San Martino, Genova, Italy, discussed the rationale for pursuing the NED state and factors to consider in the decision to pursue this goal.

The chance of achieving NED is marginal with systemic therapy alone but substantial with local approaches. However, local approaches can be toxic and the addition of adjuvant chemotherapy after local treatment is not as effective as it should be. Results of a pooled analysis from two trials of 278 patients with advanced CRC showed that patients treated with surgery and adjuvant 5-fluorouracil (5-FU) chemotherapy had a 7% higher progression-free survival (PFS) rate than those treated with surgery alone (p=0.058) [Mitry E et al. *J Clin Oncol* 2008]. Nordlinger et al. [*Lancet* 2008] reported an 8.1% improvement in PFS at 3 years in patients with advanced CRC treated with surgery and perioperative chemotherapy versus surgery alone (HR, 0.77; 95% CI, 0.60 to 1.00; p=0.041; Figure 1). Another study found no significant difference in disease-free survival between patients treated with 5-FU/folinic acid (LV5FU) alone versus LV5FU plus irinotecan (HR, 0.89; 95% CI, 0.66 to 1.19) [Ychou M et al. ASCO 2008. Abstract LBA4013].

Figure 1. PFS at 3 Years: All Eligible Patients.



Reprinted from Nordlinger B et al. Perioperative Chemotherapy with FOLFOX4 and Surgery Versus Surgery Alone for Resectable Liver Metastases from Colorectal Cancer (EORTC Intergroup Trial 40983): A Randomised Controlled Trial. *The Lancet*;371(9617):1007-16. Copyright 2008, with permission from Elsevier.