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Bevacizumab Active in Ovarian Cancer, But Best for Which Patients?

BY ROBERT H. CARLSON

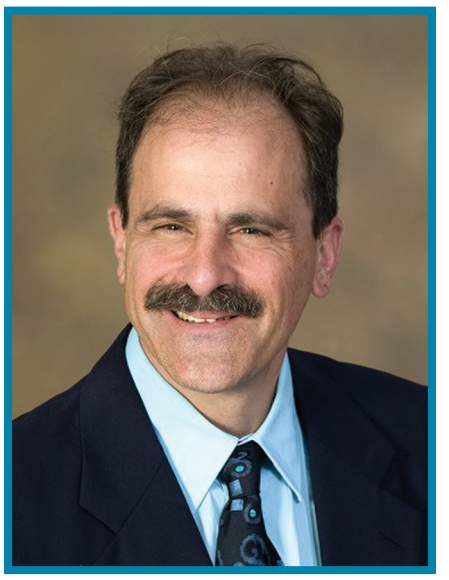
NEW YORK CITY—There is very compelling biology to indicate a role for vascular endothelial growth factor (VEGF) in normal ovarian function, as well as the growth and development of advanced-stage ovarian cancer, providing a rationale for targeting VEGF with agents such as bevacizumab.

"It's a given that VEGF is a biologically relevant target and that bevacizumab is an effective therapeutic agent with acceptable toxicity," said Michael A. Bookman, MD, Chief for Hematology/Oncology and Professor of Medicine at the University of Arizona Cancer Center, speaking here at the Chemotherapy Foundation Symposium. "It's just a question of who should be treated, and when, and with what compounds and combinations.

"What's missing from recent bevacizumab trials is that we haven't nailed down the optimal dose, timing, duration, and sequence of bevacizumab administration, and we still don't have predictive biomarkers to guide treatment interventions for bevacizumab."

Dr. Bookman noted that data from several recent trials with bevacizumab in ovarian cancer suggest that prolongation of progression-free survival appears greater in the front-line management of patients with large-volume disease, as well as in the setting of recurrent disease.

He said it appears that bevacizumab can be used for high-risk patients as maintenance post-chemotherapy or at the time of recurrence, either as a single agent or in combination with chemotherapy, although some people might certainly challenge these points.



MICHAEL A. BOOKMAN, MD, said he would like to see more early studies with small numbers of patients, to determine whether a bevacizumab-type drug is better than a tyrosine-kinase inhibitor or not, or whether to use them in combination, or use with an mTOR inhibitor, for example. "We could have answered those questions many years ago if we had done those small trials, but it's been hard to get the pharmaceutical industry to collaborate and sponsor these trials….We are jumping from small studies with new agents directly into Phase III trials that are costing $100 million."

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Best in Advanced, Recurrent Disease

Dr. Bookman said bevacizumab seems to be largely targeting the host or environment rather than directly targeting the tumor itself, as the tumor makes VEGF which triggers an angiogenic response from the host. "The implication is that bevacizumab will probably work better in patients who have ascites or large volume disease which have been associated with a high VEGF state. Treating someone [with bevacizumab] after optimal cytoreductive surgery and chemotherapy with only microscopic residual disease may not provide much benefit, because there's not much tumor-related VEGF in the body."

That's a hypothesis that could be tested, he said, but the data are showing consistently that larger volume disease, recurrent disease, and patients with ascites seem to have more immediate benefit from bevacizumab than people treated after chemotherapy and surgery in the front-line setting.

He said that ascites is the most well-recognized hallmark of VEGF production—"you can almost guarantee that is related to VEGF production in ovarian cancer, and if you treat with an anti-VEGF it will respond, perhaps not 100%, but the ability to control ascites is impressive."

In Recurrent Disease

Another speaker, William P. McGuire, MD, Director of the Weinberg Cancer Center and Professor of Medicine and Oncology at Georgetown University, agreed with Dr. Bookman on the use of bevacizumab in recurrent disease rather than in primary treatment of advanced ovarian cancer.

He said in the OCEANS trial with platinum-sensitive recurrent disease, the hazard ratios for progression-free and overall survival were significantly better (PFS HR 0.45) than in either trial of primary therapy, GOG218 (PFS HR 0.717) or ICON7 (PFS HR 0.81).

"This suggests that bevacizumab has a greater role in recurrent disease," he said.

The reason might be seen in early trials of neoadjuvant taxane therapy for ovarian cancer which showed that treatment actually increases microvessel density, as measured by CD31 and CD105.

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why this feedback loop is not operational in melanomas."

Dr. Bernards' presentation sparked an animated discussion, with numerous audience members asking for more details regarding the feedback loop, including the role of ligands and other proteins in the pathways. While Dr. Bernards seemed able to address all of the questions (and some audience members said they now needed to go back and reevaluate old experimental results), some people did not seem to be entirely convinced that Dr. Bernards' team has nailed down the details of the pathway.

Many of those in the audience, however, did seem to share Dr. Hahn's reaction that the results are strong enough to warrant a trial in these hard-to-treat colon cancer patients.

Dr. Bernards himself declined to answer specific questions in an email interview, because the work is unpublished. The group, however, does appear to be interested in moving forward with clinical trials if they can interest industry partners.

All of the drugs tested in the preclinical work are already approved, which could speed the translation of the findings into clinical care. "I think René's findings should stimulate a clinical trial," said William C. Hahn, MD, PhD.

→BEVACIZUMAB

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Pro-angiogenic factors from bone marrow may also be involved during recovery from previous chemotherapy, Dr. McGuire said. That would make antiangiogenic therapies have a proportionally greater effect following prior cytotoxic therapy.

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Smaller Trials Needed

Dr. Bookman said the most important question researchers should ask, with bevacizumab or any new agent, is how to use an investigational drug at the point in time and optimal clinical-biologic setting when it can provide the most benefit, "and not just run them in a large Phase III front-line trial designed to achieve FDA approval."

"I'm being critical, but I have shared these thoughts with industry," he said. "We need to do more small, intelligent, randomized, exploratory studies to figure out what's important.

"Eventually you have to do the large Phase III randomized trials to establish a new standard of care, and to achieve FDA registration, but at least you would be conducting these trials in the right population at the right time. Current Phase III trials involve millions of dollars and substantial clinical resources. Many of these large trials are negative, in part, due to unrealistic and untested expectations."

Dr. Bookman said it's necessary, with industry collaboration, to develop comparative and combinatorial data for targeting angiogenesis and associated pathways using selective randomized Phase II trials.

"The pharmaceutical industry and academic laboratories have shifted their priorities, and are not creating new cytotoxic chemotherapy drugs, but are, instead, concentrating on newer molecular targeted agents. So now we are [in a way] putting chemotherapy aside, and have to switch paradigms and focus on molecular targeted approaches, growth factors, antiangiogenesis, and intracellular signal transduction cascade."

This is challenging, he said, because it involves a network, and when one element is perturbed it causes feedback responses, corrective responses, or escape responses in other pathways. This calls for a new paradigm in testing, Dr. Bookman said.

"Taking one drug, testing it in the old fashioned way and saying it is good or not may not be the preferred strategy," he said, in an interview. "It may be more appropriate to test drugs in combination so you knock out multiple arms of the same pathway or related pathways."

He said companies may be slow to engage in research to evaluate and compare these agents, and may not feel comfortable sharing intellectual property, until they have at least one primary FDA approved indication for their drug.

"Once FDA approval is obtained, it is easier to do combination and comparative studies, but while it is still an investigational drug and not approved, it is very hard unless you have a neutral broker in the middle like the National Cancer Institute or something similar."

He said he would like to see more early studies with small numbers of patients, to determine whether a bevacizumab-type drug is better than a tyrosine-kinase inhibitor or not, or whether to use them in combination, or use with an mTOR inhibitor (for example).

"We could have answered those questions many years ago if we had done those small trials, but it's been hard to get the pharmaceutical industry to collaborate and sponsor these trials.

"What we need are more intelligent, smaller studies, such as randomized Phase II trials, to tell us what the Phase III trials should be," he said. "We are jumping from small studies with new agents directly into Phase III trials that are costing $100 million."

WILLIAM P. MCGUIRE, MD, ended his presentation by asking whether society can afford bevacizumab as it is used now, noting that the literature in general shows that new therapies costing less than $100,000 per life year saved are considered economically rational—for example, when paclitaxel was added to platinum in the GOG 111 study in the mid-1990s, the incremental cost effectiveness ratio was about $30,000, but comparing maintenance paclitaxel in the GOG178 study with maintenance bevacizumab in GOG218, those were $13,000 and $327,000, respectively—"certainly not a great buy."

shows that new therapies costing less than $100,000 per life year saved are considered economically rational. For example, he said, when paclitaxel was added to platinum in the GOG 111 study in the mid-1990s, the incremental cost effectiveness ration (ICER) was about $30,000 (though obviously less now that paclitaxel is generic).

> "What's missing from recent bevacizumab trials is that we haven't nailed down the optimal dose, timing, duration, and sequence of bevacizumab administration, and we still don't have predictive biomarkers to guide treatment interventions for bevacizumab."

Our current clinical trials infrastructure is complex, with substantial administrative and regulatory overhead. In that context, larger studies are actually easier to conduct, he said. As a result, we are compelled to launch several large trials, but they are studying one drug at a time, primarily to seek a pathway toward regulatory approval, rather than looking at the science and biology and figuring out how to do the very best for our patients. In addition, running large Phase III trials obligates our centers to focus clinical resources and enroll patients into these studies, making it harder to address the scientific and clinical questions we have."

Can We Afford Bevacizumab?

Dr. McGuire ended his presentation asking whether society can afford bevacizumab as it is used now. He said the literature in general

But comparing maintenance paclitaxel in the GOG178 study with maintenance bevacizumab in GOG218, the ICERs were $13,000 and $327,000 respectively—"certainly not a great buy," he said.

And a study comparing the three arms of GOG218 revealed ICERs of $480,000 for concurrent paclitaxel-carboplatin-bevacizumab, and $401,000 for paclitaxel-carboplatin-bevacizumab followed by maintenance bevacizumab (***Lesnock: Gynecol Oncol 2011 Sep;122[3]:473-478***), making consolidation paclitaxel far more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer.

"No one has done an analysis from the OCEANS trial yet, but clearly with a better hazard ratio for bevacizumab in that study it will certainly be a better buy than in GOG218," he said.