The importance of angiogenesis in cancer biology has been recognized for decades. One of the first angiogenesis-stimulating factors identified was the vascular endothelial growth factor (VEGF). Bevacizumab, a monoclonal antibody, inhibits the activity of VEGF. At the 2005 ASCO meeting, Dr Kathy Miller reported the results from ECOG-E2100, a Phase III randomized trial evaluating the addition of bevacizumab to paclitaxel as first-line therapy in women with metastatic breast cancer. The addition of bevacizumab was found to not only improve the response rate and progression-free survival but also overall survival. These findings have led to the incorporation of bevacizumab in multiple clinical trials, both in the adjuvant and metastatic settings. An update of this important study will be presented at this meeting.

ECOG-E2100: Paclitaxel Alone or with Bevacizumab

Overview of bevacizumab: A new cancer therapeutic strategy

Bevacizumab = 10 mg/kg q2wk; 
† Metastatic, first line 47 Docetaxel + capecitabine + bevacizumab

INCORPORATION OF BEVACIZUMAB INTO TREATMENT OF BREAST CANCER: A SURVEY OF US ONCOLOGISTS, SEPTEMBER 2005 (N = 50)

IMPLICATIONS OF E2100

I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would use it in a first-line setting, optimally in combination with paclitaxel as administered in the study. I doubt that the interaction is specific between paclitaxel and bevacizumab, although I’m well aware that when given with capcitabine in more advanced disease, bevacizumab seemed to be less active. However, I believe that’s probably related to the setting rather than the drug.

NEW CLINICAL TRIALS OF BEVACIZUMAB

An ECOG pilot trial of adjuvant bevacizumab, which will be primarily evaluating safety issues, will involve over 200 patients and will open within the next few months. Our belief is that given adequate safety data in the adjuvant setting — which we hope to have within 12 to 18 months — we’ll be able to go directly to a large Phase III trial comparing chemotherapy to chemotherapy plus bevacizumab. Of course, many questions can be added in the adjuvant setting with bevacizumab — which combination chemotherapy or what duration of therapy — and these may require more than one trial to answer. We will also need more than one trial because we’ll have to evaluate both HER2-negative and HER2-positive disease.

ECOG-E2100: Paclitaxel with or without Bevacizumab as First-line Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Protocol

ECOG-E2100* Single Agent Paclitaxel (n=312) Paclitaxel (n=338) Paclitaxel + bevacizumab (n=342) Paclitaxel + bevacizumab + metronomic cyclophosphamide/methotrexate (n=310) Response rate All patients 20.2% 14.2% <0.0001

Dose-dense AC q2wk x 4 + bevacizumab + paclitaxel q2wk x 4 + bevacizumab q2wk x 4 + bevacizumab q2wk x 4

ECOG-E2100: Phase III randomized trial of Paclitaxel with or without Bevacizumab as first-line therapy in patients with Locally Recurrent or Metastatic Breast Cancer

Protocol

ECOG-E2100-Trial with only 92 patients, so it will not be easy to assess the effect of bevacizumab in this setting.

ECOG-E2100 SAFETY ENDPOINTS

ECOG-E2100 SAFETY RESULTS

Dose-dense AC q2wk x 4 + bevacizumab + paclitaxel q2wk x 4 + bevacizumab q2wk x 4 + bevacizumab q2wk x 4

Overall survival Hazard ratio = 0.674 (CI: 0.495-0.917) 0.01

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ECOG-E2100: Paclitaxel with or without Bevacizumab as first-line therapy

...In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and increases the objective response rate with minimal increases in toxicity. Future studies in this area should begin to explore the role of bevacizumab in the adjuvant setting and continue to investigate methods to identify those patients who are most likely to benefit from VEGF-targeted therapies. The next step in this process will activate soon in a trial known as E2104. This adjuvant pilot trial will investigate the safety and feasibility of incorporating bevacizumab into standard adjuvant chemotherapy, using the dose-dense regimen, as followed by paclitaxel regimen, as used in previous CALGB-9411 trial.

— Kathy D Miller, MD et al. Presentation. ASCO 2005.

ECOG-E2100: SAFETY

As a result of the previous toxicity seen in the lung cancer trial, we had very stringent criteria for down-staging E2100 if we saw an excess number of patients developing Grade IV hypertension or bleeding. When the trial was initiated, the National Cancer Institute had significant concerns about patient safety as a result of the initial experience with bevacizumab in lung cancer. Fortunately, early analyses demonstrated that was not an issue in breast cancer. The side effects were relatively minimal. Predominantly, we saw mild to moderate increases in blood pressure, which is readily handled from a clinical standpoint. Of course, we’ll have to be careful with the hypertension as we move bevacizumab into the adjuvant setting. We also saw a few incidence of serious bleeding. Overall, bevacizumab was a nontoxic addition to chemotherapy.

— George W Stedje Jr, MD, Breast Cancer Update 2005 (6)

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— Eric P Winer, MD, Breast Cancer Update 2005 (7)

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The XCalib trial will start very soon. This trial will evaluate newly diagnosed patients — essentially the same group as in the E2100 trial — who need chemotherapy but use capcitabine in combination with bevacizumab. This trial allows but does not require patients to continue bevacizumab after initial progression either with sunitinib or paclitaxel, at the patients’ and investigators’ choice. This is a fairly small Phase II trial with only 92 patients, so it will not be definitive. Randomization to continuing bevacizumab or not is not included. That is an open question we need to address quickly.

— Kathy D Miller, MD, Breast Cancer Update 2005 (7)