CED-CCO Special Advice Report #12

The Use of Bevacizumab in Metastatic Breast Cancer

R. Dent, A.E. Haynes, K. Enright, C. Hamm, M. Trudeau, and A. Eisen

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SUMMARY

QUESTION

Does bevacizumab (alone or in combination with other systemic therapies) improve outcomes in women with locally advanced or metastatic breast cancer compared to the same therapy without bevacizumab? Outcomes of interest include overall survival, progression-free survival, objective response rate, quality of life, and adverse events.

TARGET POPULATION

This evidence-based series applies to adult women with locally advanced (stage IIIb) or metastatic (stage IV) breast cancer.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- **For women with metastatic or locally advanced breast cancer receiving taxane-based chemotherapy as first-line therapy, the addition of bevacizumab could be offered to improve progression-free survival.**

- **The addition of bevacizumab to chemotherapy is not recommended for patients with metastatic breast cancer receiving second-line therapy or greater.**

QUALIFYING STATEMENTS

- Bevacizumab should not be administered to patients with cerebral metastases, uncontrolled hypertension, severe proteinuria, advanced atherosclerotic disease, bleeding diatheses, or with non-healing wounds, recent surgery, or trauma (i.e., within the previous 28 days), as those patients were excluded from enrolment in clinical trials using bevacizumab.
- The addition of bevacizumab to paclitaxel chemotherapy is associated with significant but manageable toxicity, specifically hypertension, proteinuria, neuropathy, fatigue, and infection. In the most recent randomized study of bevacizumab and docetaxel chemotherapy, the toxicities were much less frequent than in the study of bevacizumab and paclitaxel.

KEY EVIDENCE

Three phase III randomized controlled trials (RCTs) (1-3) comparing a chemotherapy regimen to the same regimen plus bevacizumab were included in this report. Two of the clinical trials studied bevacizumab in combination with a taxane-based chemotherapy in the first-line treatment of metastatic breast cancer (1,2). The remaining trial studied bevacizumab in combination with capecitabine for second-line or greater treatment (3).

First-line Treatment of Metastatic Breast Cancer

Bevacizumab with Weekly Paclitaxel Chemotherapy

Miller et al (1) randomized patients to receive weekly paclitaxel and 10 mg/kg of bevacizumab every two weeks or to weekly paclitaxel alone. Patients receiving weekly paclitaxel with bevacizumab did not have a statistically significant improvement in overall survival (26.7 versus [vs.] 25.2 months; hazard ratio [HR]=0.88, p=0.16) compared to weekly paclitaxel alone. There was a statistically significant increase in median progression-free survival (11.8 vs. 5.9 months; HR=0.60, p<0.001) and overall response rate (36.9% vs. 21.2%; p<0.001) in the cohort receiving bevacizumab with paclitaxel versus paclitaxel alone. The predominant grade 3/4 toxicities observed in the combination arm versus standard arm included hypertension (14.8% vs. 0%, p <0.001), proteinuria (3.6% vs. 0%, p<0.001), headache (2.2% vs 0.0%, p=0.008), and cerebrovascular ischemia (1.9 vs. 0.0%, p=0.02).

Bevacizumab with Docetaxel Chemotherapy

A phase III RCT by Miles et al (2) randomized patients to one of three arms of docetaxel combined with either bevacizumab 15 mg/kg or 7.5 mg/kg, or placebo given every three weeks. The median overall survival has not yet been reached in any arm. Patients receiving docetaxel in combination with bevacizumab 15 mg/kg and 7.5 mg/kg had a small but statistically significant increase in median progression-free survival compared to docetaxel alone (8.8 vs. 8.0 months; HR=0.72, p=0.0099) and (8.7 vs. 8.0 months; HR 0.79, p=0.0318). There was a significant increase in overall response rate in patients receiving bevacizumab 15 mg/kg (63.1% vs. 44.4%, p=0.0001) and 7.5 mg/kg (55.2% vs. 44.4%, p=0.0295) compared to docetaxel alone. Grade3/4 toxicities seen in earlier studies were observed less frequently than in previous studies. For example, there did not appear to be a significant increase in the rate of grade 3/4 hypertension in patients receiving bevacizumab 15 mg/kg (3.2% vs. 1.3%, p=not reported) and 7.5 mg/kg (0.4 vs. 1.3%, p=not reported). Further details of toxicity are expected in the final publication of the study.

Meta-Analysis

A meta-analysis of reported hazard ratios for progression-free survival from the two RCTs with first-line taxane-based therapy was performed. This indicated a significant benefit in progression-free survival for the addition of bevacizumab to taxane-based chemotherapy compared to taxane-based therapy alone (HR=0.64; 95% confidence interval, 0.54 to 0.77, p<0.00001).

Second-line or Greater Treatment of Metastatic Breast Cancer

Bevacizumab with Capecitabine Chemotherapy

Miller et al (3) randomized patients who had received previously treatment for metastatic breast cancer to bevacizumab 15 mg/kg combined with capecitabine every three weeks or to capecitabine alone. No significant differences in overall survival or progression-free survival were detected between the two arms.

FUTURE RESEARCH

The RIBBON-1 study is a double-blind, placebo-controlled phase III study in first-line metastatic HER2-negative breast cancer investigating bevacizumab in combination with either taxane-based, anthracycline-based, or Xeloda (capecitabine) chemotherapies compared to the same therapy with placebo. The RIBBON-2 study is a placebo-controlled phase III trial enrolling patients who have received only one prior chemotherapy regimen. Patients are randomized to receive either bevacizumab or placebo in combination with taxane-based, gemcitabine, vinorelbine, or Xeloda (capecitabine) chemotherapy. The data will likely be presented at the American Society of Clinical Oncology meeting in June 2009. Randomized phase III trials evaluating the benefit of adding bevacizumab to chemotherapy in high-risk individuals in adjuvant setting are currently underway.

IMPLICATIONS FOR POLICY

In February 2008, the Food and Drug Administration (FDA) in the United States approved the use of bevacizumab in conjunction with paclitaxel for the treatment of patients who have not received chemotherapy for their metastatic breast cancer. In February 2009, Health Canada approved the use of bevacizumab in combination with paclitaxel for the treatment of patients with HER2 negative metastatic breast cancer.

In Ontario, it is estimated that 8500 new cases of breast cancer were diagnosed in 2008 (4). Each year, about 25% of breast cancer patients, or 2000 women, die of metastatic disease. Over two thirds of these women have HER2-negative disease, and a significant proportion of those patients would be expected to be eligible to receive chemotherapy treatment, including the option of treatment in combination with bevacizumab.

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Evidence-based Series

- #1-12: *The Role of Gemcitabine in the Management of Metastatic Breast Cancer.* Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34178.

Practice Guideline Reports

- #1-3 Version 2.2003: *The Role of the Taxanes in the Management of Metastatic Breast Cancer.* Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34140.
- #1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer.* Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34174.
- #1-11 Version 2.2002: *Use of Bisphosphonates in Women with Breast Cancer.* Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34182.
- #1-16 Version 2.2003: *Capecitabine in Stage IV Breast Cancer.* Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13874.

Evidence Summary Reports

- #1-4: *Vinorelbine in Stage IV Breast Cancer.* Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34144.

For further information about this special advice report, please contact:
Dr. Maureen Trudeau; Co-Chair, Breast Cancer Disease Site Group; Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Ave, Toronto ON, M4N 3M5;

Telephone 416-480-5145; FAX 416-217-1338;
E-mail: maureen.trudeau@sunnybrook.ca

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