

USE OF BEVACIZUMAB (AVASTIN) IN THE TREATMENT OF METASTATIC BREAST CANCER

A Technology Assessment

INTRODUCTION

In February 2008, the US Food and Drug Administration (FDA) gave accelerated approval of bevacizumab for the treatment of metastatic breast cancer when used with paclitaxel. This decision has been controversial because the pivotal clinical trial failed to demonstrate an improvement in overall survival for patients treated with bevacizumab. Furthermore, the Oncologic Drugs Advisory Committee at the FDA voted five to four against approval of bevacizumab for this indication in December 2007. In 1999, the same committee voted that delaying disease progression was not sufficient evidence for approval of a drug for first-line therapy in cancer. On the other hand, European regulators approved the use of bevacizumab for metastatic breast cancer in March 2007 and the FDA has approved both endocrine therapies and many chemotherapeutic agents based on improvements in progression-free survival alone.¹ In a New York Times interview, Dr. Richard Pazdur of the FDA stated that overall survival was favored as the standard for drug approval, but that the FDA “wanted to have the regulatory flexibility to approve effective drugs where there isn’t overall survival.”²

The California Technology Assessment Forum is requested to review the scientific evidence for the use of bevacizumab (Avastin) for treatment of metastatic breast cancer.

BACKGROUND

Breast cancer

Cancer of the breast is the most common form of cancer in women. Every American woman is estimated to have a one in nine chance of developing breast cancer at some time during her life. In 2008, there will be an estimated 184,450 new cases of invasive breast cancer in the United States and an estimated 40,930 deaths from this cancer. This represents approximately 31% of all new cancer cases in women and 15% of all cancer deaths in women.³

The staging system of the American Joint Committee on Cancer⁴ defines early stage (Stage I and Stage II) invasive breast cancer as tumors ≤ 5 cm in largest dimension and without distant metastasis or involvement

of the fixed axillary or internal mammary lymph nodes (T1-2, N0-1, M0). In the TNM (Tumor Node Metastasis) staging system for breast cancer, stage T1 refers to carcinomas 2.0 cm or less in greatest dimension; stage T2 refers to tumors more than 2.0 cm, but not more than 5.0 cm in greatest dimension; stage T3, to tumors more than 5.0 cm in greatest dimension; and stage T4, to tumors with direct extension to chest wall or skin. Stage N0 refers to tumors without regional lymph node metastasis and N1 to tumors with ipsilateral lymph nodes metastases that are not fixed or grouped. M0 refers to tumors without distant metastases. Advanced breast cancer is commonly used to refer to metastatic breast cancer (T any, N any, M1). The most common sites of breast cancer metastases include the bone, the liver, and the lungs.

Treatment of metastatic breast cancer

Current clinical trials have not established either single-agent chemotherapy or combination chemotherapy as the preferred approach in first-line treatment of metastatic breast cancer.⁵ Many agents have demonstrated activity against metastatic breast cancer, including doxorubicin, epirubicin, mitoxantrone, paclitaxel, docetaxel, cyclophosphamide, capecitabine, 5-fluorouracil, methotrexate, vinorelbine, vinblastine, vincristine, carboplatin, cisplatin, gemcitabine and mitomycin C. The rate of disease progression, the presence or absence of comorbid medical conditions, and physician/patient preference should guide the choice of therapy in individual patients. A Cochrane systematic review of 17 randomized trials concluded that the addition of one or more drugs to an established chemotherapy regimen in the attempt to intensify the treatment improved tumor response but had no effect on overall survival time or time to progression. The observed tumor response was associated with increased toxicity.⁶ Thus, most women with metastatic breast cancer are treated with single agent chemotherapy, with additional agents added sequentially rather than concurrently. Metastatic tumors that express the estrogen or progesterone receptors are usually treated with hormonal therapy based on their menopausal status and prior treatments. These treatments include ovarian suppression or ablation for premenopausal women and third generation aromatase inhibitors or tamoxifen for post-menopausal women. Women with breast cancer metastatic to the bone are usually treated with a bisphosphonate (pamidronate or zoledronic acid) in addition to other therapies. Overall survival in patients with metastatic breast cancer has improved somewhat over the past 20 years, but median survival in most studies is still less than two years.⁷⁻⁹

Trastuzumab (Herceptin)

One prior monoclonal antibody has been studied extensively in breast cancer. Trastuzumab (Herceptin) is a humanized monoclonal antibody that binds to the HER2/neu receptor. A randomized trial of trastuzumab in

addition to chemotherapy in women with metastatic breast cancer demonstrated greater overall survival (OS) for patients treated with trastuzumab plus chemotherapy compared with those receiving chemotherapy alone (25.1 months vs. 20.3 months, $P = .05$).¹⁰ Currently trastuzumab is used exclusively in patients with breast cancers that overexpress the HER2 receptor.

Bevacizumab (Avastin)

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), a potent stimulator of new blood vessel growth or angiogenesis. Bevacizumab binds to circulating VEGF and thus inhibits binding of VEGF to its receptors on the surface of endothelial cells; this in turn should reduce the development of the blood supply to tumors and thus limit their growth.

Angiogenesis is a finely regulated process to generate new blood vessels that are normally turned on briefly for growth, wound healing, and in the menstrual cycle. Judah Folkman hypothesized in 1971 that angiogenesis was necessary for tumors to grow beyond about 3 mm in size and that blocking this process might be a useful approach in the treatment of cancer.¹¹ Angiogenesis has now been shown to be important in the development and metastasis of solid tumors.^{12, 13} The FDA has approved bevacizumab for use in metastatic colon cancer and lung cancer based on randomized clinical trials demonstrating statistically significant improvements in overall survival.^{14, 15} In breast cancer, high microvascular density and higher levels of VEGF in tumors are associated with the transformation of premalignant tissue to cancer and with more aggressive tumors, including associations with significant reductions in overall survival.¹⁶⁻²⁴ The possible benefits of antiangiogenic therapy for breast cancer have been explored in an avalanche of recent review articles and opinion pieces.²⁵⁻⁵⁶

Adverse events associated with bevacizumab

The most serious adverse events reported in clinical trials of bevacizumab include gastrointestinal perforations, wound healing complications, hemorrhage, arterial thromboembolic events, hypertensive crisis, nephrotic syndrome, congestive heart failure, and neutropenic sepsis.⁵⁷ The most common bevacizumab adverse events include weakness, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

The FDA and Genentech have issued several drug warnings regarding bevacizumab.⁵⁷ There is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accidents,

myocardial infarctions, transient ischemic attacks, and angina related to bevacizumab. The risk of fatal arterial thrombotic events is also increased. In randomized trials conducted in patients with metastatic colorectal cancer, the risks of a serious arterial thrombotic event was approximately two-fold higher in patients receiving infusional 5-FU based chemotherapy plus bevacizumab, with an estimated overall rate of up to five percent. A second drug warning stated that there is evidence of an increased risk of reversible posterior leukoencephalopathy syndrome (RPLS), a rare brain-capillary leak syndrome associated with hypertension, fluid retention, and cytotoxic effects of immunosuppressive drugs on the vascular endothelium. The most recent drug warning stated that non-gastrointestinal fistula formation has been reported in patients treated with bevacizumab in clinical trials (incidence of < 0.3%), in some cases with fatal outcome. Fistulas involving the following areas have been reported: tracheo-esophageal, bronchopleural, biliary, vaginal, and bladder. Most events occurred within the first six months of bevacizumab therapy.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

On February 22, 2008, bevacizumab (Avastin) (Genentech, Inc., South San Francisco, CA) received FDA approval for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer. Marketing approval of this product was granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. As noted in the FDA approval letter, approval under these regulations requires, among other things, that adequate and well-controlled studies be conducted to further define the degree of clinical benefit to patients.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

We searched PUBMED, EMBASE, Cochrane clinical trials database, Cochrane reviews database, the Database of Abstracts of Reviews of Effects (DARE) and the International Pharmaceutical Abstracts (IPA) through May 15, 2007 using the key word *breast neoplasms*. This search was cross-referenced with the

keywords *bevacizumab* OR *Avastin*. We examined the reference lists of the clinical trials and review articles for additional trials. We then asked several experts to review our bibliography to ensure completeness of our list.

The initial search identified 105 articles. We limited the review to published clinical trials of bevacizumab in women with metastatic breast cancer. We excluded clinical trials reported only as abstracts. There were three uncontrolled clinical trials⁵⁸⁻⁶⁰, one retrospective case series⁶¹, and two larger randomized clinical trials.^{62, 63} This review will primarily focus on the randomized trials. We will separately focus the review on studies evaluating bevacizumab as initial therapy for advanced breast cancer and those evaluating use of bevacizumab in patients who have received prior chemotherapy for metastatic disease.

Level of Evidence: 1, 2, 5

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

The most important outcome in trials of therapies for metastatic breast cancer is overall survival and it remains the endpoint of choice in assessing the efficacy of new treatments. The use of overall survival as the primary endpoint has been criticized because it requires long-term follow-up of all patients in a study and effects on overall survival may be diluted by the use of second and third line therapies once a patient progresses on first line therapy. Thus, much work has gone into the evaluation of other endpoints, such as tumor response rates, progression free survival, and time to progression as surrogate endpoints for overall survival.⁶⁴ The primary group working on this problem recently reported that progression free survival is a good surrogate for overall survival in randomized trials of therapies for advanced colorectal cancer^{65, 66}, but the same relationship did not hold for evaluating therapies for advanced breast cancer.⁶⁷

Metastatic breast cancer is not yet a curable disease, but there is hope of turning it into a chronic disease with good quality of life. Thus, an important secondary outcome is quality of life. A therapy that does not extend life, but does improve quality of life would be welcomed as long as toxicities are reasonable. A common tool used to assess quality of life in breast cancer trials is the Functional Assessment of Cancer Treatment – Breast (FACT-B) questionnaire.⁶⁸ This instrument consists of four general subscales evaluating

well-being (Physical, Social/Family, Emotional, and Functional) and one focusing on breast cancer, the Breast Cancer Specific Subscale. It has been validated in both early stage and advanced breast cancer and has been shown to be sensitive to important changes in breast cancer patients' quality of life.⁶⁸

Toxicities in cancer clinical trials are usually assessed using the National Cancer Institute (NCI) Common Toxicity Criteria.⁶⁹ Adverse events are classified into one of six grades on a scale from 0 through 5. Grade 0 represents no adverse event or a value within normal limits, grade 1 a mild event, grade 2 a moderate event, grade 3 a severe and undesirable event and grade 4 a life-threatening or disabling event. Grade 5 is reserved for deaths due to adverse events. The grades for each type of adverse event are explicitly defined in guidelines available on the NCI website (<http://ctep.cancer.gov/reporting/ctc.html>). Grades 3 and higher are usually considered severe enough to include in the assessment of net health outcomes in cancer treatment.

Retrospective cohort

Link and colleagues reported the outcomes of forty women treated with at least two courses of combination therapy with paclitaxel and bevacizumab at a community based breast oncology group in Long Beach, CA.⁶¹ They retrospectively reviewed the records of all women treated with albumin bound paclitaxel and bevacizumab (10 mg/kg every 14 days) between March 2005 and December 2006. The median age of the women was 46 years and 85% had been treated with at least three prior rounds of chemotherapy. The 12 women (30%) who had HER2/neu+ tumors were treated concurrently with trastuzumab. Among the 33 women with measurable disease, the objective response rate (ORR) was 48.5% (16/33). The time to progression was 128 days (4.2 months) for the 16 responders. The authors do not present the data on time to progression for the full 40 women in the cohort. Three women had grade 3 pain, two had grade 3 anemia, and one had grade 3 neuropathy. Two women had their treatment discontinued because of possible hemorrhage into a metastatic brain lesion. Because this was not a prospective trial with standard data collection, it is not clear that all adverse events were captured. For instance, it is remarkable that no grade 3 or 4 hypertension events were noted as these are commonly reported in larger trials. However, the trial did suggest potential benefit using the combination of paclitaxel and bevacizumab in women who had already received heavy pretreatment for metastatic breast cancer.

Prospective cohort – no comparison

Cobleigh and colleagues published the earliest clinical trial results for the use of bevacizumab in women with previously treated metastatic breast cancer.⁵⁸ They treated 75 women with increasing doses of bevacizumab ranging from 3 mg/kg up to 20 mg/kg. The women had a mean age of 48 years and were on average 1.6 years from the diagnosis of metastatic breast cancer. They had received a median of two prior rounds of chemotherapy for metastatic disease. The authors reported an objective response rate of 9.3% with a median duration of confirmed response of 5.5 months. An additional 16% of the women (12/75) had stable disease at the final assessment on day 154 (five months). The most common grade 3 or 4 toxicities were hypertension (14/75, 19%), shortness of breath (8/75, 11%), and weakness (7/75, 9%). Significant proteinuria developed in six patients (8%) with two developing nephrotic syndrome. Because there was no comparison group, it is unclear what proportion of these significant adverse events (AE's) are due to bevacizumab and which are due to progression of the underlying breast cancer. However, hypertension and proteinuria are known side effects of bevacizumab and are not commonly seen in the progression of breast cancer. Bleeding events, which were seen in clinical trials of bevacizumab for non-small cell lung cancer, were common (25%), but all were grade 1.

Finally, Ramaswamy and colleagues reported the results of a phase II trial of bevacizumab with docetaxel in 27 women with metastatic breast cancer.⁵⁹ While the majority of these women had received prior adjuvant therapy (78%), the same percentage (78%) had never received chemotherapy for metastatic disease. The objective response rate was 52% and the median progression-free survival was 7.5 months. Overall survival was not reported. The most common grade 3 and 4 toxicities were leucopenia (26%) and neutropenia (19%), most likely related to the docetaxel therapy. Only one episode of grade 3 hypertension was documented (4%)

Non-metastatic breast cancer

For completeness and for comparison, we report the results of a pilot study of bevacizumab in women without metastatic disease. Wedam and colleagues reported on 21 patients with locally advanced inflammatory breast cancer (Stages IIB through IIIC) who had not previously been treated with chemotherapy.⁶⁰ Women were initially treated with bevacizumab (15 mg/kg) followed by six cycles of bevacizumab with doxorubicin and docetaxel. The investigators compared biopsy results before and after initial bevacizumab treatment. After bevacizumab therapy alone, there was a median 67% decrease in phosphorylated tumor VEGFR2 levels and a 129% increase in tumor apoptosis. However, there were no

significant changes in microvessel density or VEGF expression. The investigators also reported that three magnetic resonance imaging (MRI) measures of vascular permeability and flow decreased with treatment, although these measures could not separate responders from non-responders. The objective response rate among the 21 women was 67%. The median progression-free survival time was 25.3 months and median overall survival time was not reached in 27 months follow-up. The one and two-year overall survival rates were 90% and 80% respectively. These outcomes are better than those seen in the trials of bevacizumab described earlier, likely reflecting the early stage breast cancers in the women included in this trial. The most common grade 3 or 4 toxicities included neutropenia (86%), hypertension (38%), diarrhea (19%), and fatigue (19%). No grade 3 or 4 proteinuria was reported. Delayed wound healing was also reported in 24% of patients (39% of patients undergoing surgery), which is likely to be due to the anti-angiogenic effects of bevacizumab.

Randomized clinical trials

The first large randomized trial (Miller 2005) compared bevacizumab and capecitabine to capecitabine alone in women with previously treated metastatic breast cancer.⁶³ The quality of the study (Table 1) was good, using the Jadad rating system, although neither the investigators nor the patients were blinded. This can significantly impact subjective outcomes, but has been shown to have less impact on more objective assessments such as disease progression or overall survival.⁷⁰ The primary outcomes were adjudicated by a blinded, independent review committee; the committee assessed disease progression differently from the investigators for 103 participants (23%). The results presented in this review will all reflect the adjudication by the independent committee. The investigators enrolled 462 women with metastatic breast cancer who had received either one or two prior chemotherapy regimens for metastatic breast cancer and who had been treated with both an anthracycline and a taxane. Patients with HER2+ cancers were required to have progressed after treatment with trastuzumab. Patients were also required to have at least one measurable tumor greater than or equal to 2 cm and to have high functional (Eastern Cooperative Oncology Group performance status of 0 or 1: fully active or only limited in strenuous physical activity). Patients were excluded if they had impaired renal, hepatic or hematologic function, if they had central nervous system (CNS) metastases, recent surgery, non-healing wounds, infections requiring parenteral antibiotics, other cancers within the past five years, or clinically significant cardiovascular disease. Women were randomized to standard dose capecitabine with or without bevacizumab (15 mg/kg). The primary outcome was progression-free survival.

The investigators randomized 232 patients to capecitabine plus bevacizumab and 230 patients to capecitabine alone. Unfortunately, 93 patients (20%) were later found to not meet at least one of the inclusion or exclusion criteria. Including or excluding these patients did not change the results, so the investigators preserved the intention-to-treat principle by including all patients in the primary analyses. The patients were on average about 51 years old. The sample included about 80% white women and 12% black women. Characteristics of the patients tumors are described in Table 2. The authors reported no significant differences between the two groups at baseline. The main outcomes and toxicities are summarized in Table 3. The objective response rate was higher in the bevacizumab arm of the trial (19.8% vs. 9.1%, $p=0.001$). Progression-free survival did not differ between the two groups (hazard ratio (HR) 0.98, 95% CI 0.77-1.25, $p=0.86$). The median time to progression was 4.9 months for the bevacizumab arm and 4.2 months for the control arm. Overall survival (15.1 vs. 14.5 months) and quality of life as assessed by the FACT-B questionnaire (2.9 months to deterioration in both arms) were similar in the two arms of the trial.

Capecitabine toxicities were similar in the two groups, although significantly more patients in the arm receiving bevacizumab required dose reduction (79% vs. 65%, $p = 0.001$ by my calculation). The bevacizumab arm had significantly more grade 3 and 4 toxicities known to be associated with bevacizumab (Table 3). By far the most common was hypertension (17.9% vs. 0.5%, $p < 0.001$ by my calculation). Two patients in the bevacizumab arm developed grade 3 proteinuria, one of whom went on to develop nephrotic syndrome. Minor bleeding was more common in the bevacizumab arm (18.4% vs. 10.7%), but there were no differences in serious bleeding rates. Grade 3 or 4 congestive heart failure developed in seven patients in the bevacizumab arm compared with two in the control arm.

The second large randomized trial (Miller 2007) compared bevacizumab and paclitaxel to paclitaxel alone in women with metastatic breast cancer who had never received treatment for metastatic disease.⁶² The quality of the study (Table 1) was good, using the Jadad rating system, although again, neither the investigators nor the patients were blinded. In this trial, the authors do not report adjudication of the primary outcomes by a blinded, independent review committee. The investigators enrolled 722 women with metastatic breast cancer who had not received cytotoxic therapy for metastatic breast cancer. Patients with HER2+ cancers were only eligible if they had already received treatment with trastuzumab. Patients were also required to have high functional (Eastern Cooperative Oncology Group performance status of 0 or 1). Patients were excluded if they had impaired renal, hepatic or hematologic function, if they had CNS metastases, recent surgery, non-healing wounds, infections requiring parenteral antibiotics, other cancers

within the past five years, or clinically significant cardiovascular disease. Women were randomized to standard dose paclitaxel with or without bevacizumab (10 mg/kg). The primary outcome was progression-free survival.

The investigators randomized 368 patients to paclitaxel plus bevacizumab and 354 patients to paclitaxel alone. Unfortunately, 21 patients (5.7%) in the bevacizumab arm and 28 patients (7.9%) in the control arm were later found to not meet at least one of the inclusion or exclusion criteria. In this study, the investigators decided to exclude these patients from the primary outcome analyses, but included them in the toxicity analyses. The patients analyzed for outcomes were on average about 56 years old and the characteristics of the patients tumors are described in Table 2. Of note, that patients in the bevacizumab arm had less visceral disease (79.5% vs. 87.1%, $p=0.009$) and less measurable disease (68.6% vs. 77.9%, $p=0.007$). There was also slightly less extensive disease in the bevacizumab arm (42.9% vs. 46.3% with ≥ 3 sites, p NS). Later multivariable analyses demonstrated that both measurable disease and extent of disease were significant predictors ($p<0.05$) of progression-free survival, independent of treatment assignment, estrogen receptor status, age of the patient, the interaction between age and treatment assignment, and the interaction between treatment assignment and time. The main outcomes and toxicities are summarized in Table 3. The objective response rate was higher in the bevacizumab arm of the trial (36.9% vs. 21.2%, $p<0.001$). Progression-free survival was significantly longer in the bevacizumab arm (11.8 vs. 5.9 months, HR 0.60, $p<0.001$). However, this effect decreased significantly with time (p for treatment x time interaction < 0.001). Median overall survival was similar in the two arms (26.7 vs. 25.2 months, HR 0.88, $p = 0.16$), but the one-year survival rate was higher in the bevacizumab arm (81.2% vs. 73.4%, $p=0.01$). Quality of life as assessed by the FACT-B questionnaire did not differ between the two arms of the trial at 17 weeks and 33 weeks, although follow-up data was incomplete (77% and 58% of the 631 women who completed the questionnaire at baseline).

In this study, only grade 3 and 4 toxicities were reported. Known paclitaxel toxicities were generally similar in the two groups except for neuropathy (23.6% vs. 17.6%, $p=0.03$), infection (9.3% vs. 2.9%, $p<0.001$), and fatigue (8.5% vs. 4.9%, $p=0.04$). Additionally, more patients in the arm receiving bevacizumab discontinued paclitaxel at least three weeks prior to disease progression (51.3% vs. 35.9%, $p < 0.001$ by my calculation). However, patients in the bevacizumab arm had a longer median duration of paclitaxel treatment (7.1 vs. 5.1 months). The bevacizumab arm also had significantly more grade 3 and 4 toxicities known to be associated with bevacizumab (Table 3). By far the most common was hypertension (14.8% vs. 0%, $p < 0.001$), although

there were also more strokes (1.9% vs. 0%, $p=0.02$) and proteinuria (3.6% vs. 0%, $p<0.001$). There were no important differences in bleeding and thromboembolic disease other than the strokes reported above.

Table 1. Summary of Study Design Strengths and Weaknesses of the randomized trials of bevacizumab in advanced breast cancer

| Study | Randomization | Allocation concealment | Comparable groups at baseline | Loss to follow-up equivalent | Blinded outcome assessment | Patient blinding | Co-interventions equivalent | ITT analysis | Quality * |
|-------------|---------------|------------------------|-------------------------------|------------------------------|----------------------------|------------------|-----------------------------|--------------|-----------|
| Miller 2005 | Yes | No | Yes | Yes | Yes | No | Yes | Yes | 4 |
| Miller 2007 | Yes | No | No | No | No | No | No | +/- | 3 |

ITT: intention to treat; NR: Not reported.

* Jadad score (0-2 poor, 3-4 good, 5 excellent)

Table 2. Study Characteristics of the randomized trials comparing single agent chemotherapy to the same agent plus bevacizumab in advanced breast cancer

| Author Year | Location, Indication | Study group | Number randomized | Losses following randomization | Mean Age, years | ER+, % | | Extent of disease ≥ 3 sites | Measurable disease | Visceral disease |
|-------------|--|-------------|-------------------|--------------------------------|-----------------|--------|-----|-----------------------------|--------------------|------------------|
| | | | | | | | | | | |
| Miller 2005 | Multi-center, second-line treatment for advanced breast cancer | C + B | 232 | 0 | 51 | 42 | 49% | 100% | 78% | |
| | | C | 230 | 0 | 52 | 52 | 50% | 100% | 80% | |
| Miller 2007 | Multi-center Initial treatment for advanced breast cancer | P + B | 368 | 39 | 56 | 60 | 43% | 69% | 80% | |
| | | P | 354 | 41 | 55 | 63 | 46% | 78%* | 87%* | |

C: capecitabine; B: bevacizumab; P: paclitaxel.

* p<0.01

Table 3. Primary outcomes of the randomized trials of bevacizumab in women with metastatic breast cancer

| Study | Study group | N analyzed | Objective response rate | Progression free survival, months | Overall survival, months | Hypertension | Infection | Fatigue | Stroke |
|-------------|-------------|------------|-------------------------|-----------------------------------|--------------------------|--------------|-----------|---------|--------|
| Miller 2005 | C + B | 232 | 19.8% | 4.9 | 15.1 | 17.9% | 0.9% | 7.4% | NR |
| | C | 230 | 9.1% | 4.2 | 14.5 | 0.5% | 0.5% | 6.6% | |
| | | | P=0.001 | P=0.86 | P NS | P NR | P NR | P NR | |
| Miller 2007 | P + B | 347 | 37% | 11.8 | 26.7 | 14.8% | 9.3% | 9.1% | 1.9% |
| | P | 326 | 21% | 5.9 | 25.2 | 0% | 2.9% | 4.7% | 0% |
| | | | P=0.001 | P<0.001 | P=0.16 | P<0.001 | P<0.001 | P=0.04 | P=0.02 |

C: capecitabine; B: bevacizumab; P: paclitaxel; NR: not reported; S: standard dosing arm.

Summary

The three small cases series of bevacizumab in women with metastatic disease and the pilot study in women with inflammatory breast cancer suggested that bevacizumab has activity in breast cancer as predicted by earlier work on VEGF and angiogenesis in breast cancer. However, much more useful information is available in the large, phase III randomized trials. The first, in women who had received prior treatment for metastatic breast cancer, unequivocally demonstrated that breast tumors respond to bevacizumab therapy through the greater objective response rate in patients treated with the combination of bevacizumab and capecitabine than that observed in patients treated with capecitabine alone ($p=0.001$). However, this tumor response did not translate into improved progression-free survival, overall survival, or patient quality of life. Furthermore, it was associated with a modest increase in patients requiring treatment for hypertension. Outcomes were somewhat better in the second randomized trial in which bevacizumab was added to paclitaxel as initial treatment for metastatic breast cancer. In addition to a greater percentage of patients with an objective response to treatment, patients receiving bevacizumab had significantly longer time to progression and a larger proportion were alive at the 12 month follow-up, though this did not translate into longer overall survival. There were more methodologic issues in the second trial (lack of blinding, baseline imbalances in predictors of the primary outcome, lack of intention to treat analysis), but the authors tried to address them with multivariable analyses and sensitivity analyses. The improvement in progression-free survival would potentially be meaningful if it also led to better quality of life. However, the trial failed to demonstrate any differences in quality of life between the two treatment arms and those patients receiving bevacizumab suffered more grade 3 and 4 toxicities including more strokes, headaches, fatigue, and hypertension requiring treatment. Thus, it is not clear that the longer period of progression free survival in women with known metastatic breast cancer translates into health outcomes that are meaningful for the patient. Additionally, there are significant harms associated with adding bevacizumab to paclitaxel. Thus, it is not clear that net health outcomes are improved with paclitaxel, even limiting consideration to initial therapy for metastatic disease in combination with paclitaxel.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The choice of agents to use as the initial or second line treatment for metastatic breast cancer is not straightforward. The decision depends, in part, on prior therapies used by the patient; the patient's other medical conditions, the presence of hormone receptor and HER2 expression, tumor burden, visceral organ involvement, the patient's functional status, and patient preference. Both capecitabine and paclitaxel are considered first-line chemotherapeutic options according to the National Comprehensive Cancer Network guidelines⁷¹ for the treatment of metastatic breast cancer and thus were reasonable alternatives for comparison. The lack of clinical benefits in the randomized trial of women who had received prior treatment for metastatic disease clearly demonstrated that the combination of capecitabine and bevacizumab should not be used for this indication. When used as initial therapy for metastatic disease in combination with paclitaxel, bevacizumab improved progression-free survival, but not overall survival or quality of life. Given the context of a prior trial demonstrating no benefit in metastatic disease and the equivocal benefits seen in the second trial with clear associated harms, it is not clear that the addition of bevacizumab offers any important benefits over established therapies.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

There are no technical or clinical complexities associated with the use of bevacizumab beyond those that oncologists are used to managing with infusion of other monoclonal antibodies or chemotherapeutic agents or when using bevacizumab for indications with clear evidence of improvements in clinical outcomes, such as the treatment of advanced colon cancer. However, the clinical utility of bevacizumab for metastatic breast cancer has not yet been demonstrated in the investigational setting, so no conclusions can be reached about the potential effectiveness of this drug in a community setting.

TA Criterion 5 is not met.

CONCLUSION

Overall survival is the endpoint of choice when evaluating the effectiveness of new therapies for metastatic cancer. Trastuzumab, another monoclonal antibody used in breast cancer treatment, improved overall

survival in randomized trials. Similarly, randomized trials of bevacizumab for metastatic colon cancer demonstrated improvements in overall survival. Clinical trials of bevacizumab for metastatic breast cancer have not demonstrated any benefit as second line therapy and no significant improvement in overall survival as initial therapy. The essential issue in the debate about the role of bevacizumab in metastatic breast cancer is whether a 5.5 month increase in median progression free survival and no improvement in overall survival is of sufficient benefit to outweigh the toxicities of bevacizumab given no difference in patients' overall quality of life.

The package insert for bevacizumab states this explicitly: "Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Avastin in breast cancer." It is clear that bevacizumab is active against breast tumors, however the evidence suggests that there are no net improvements in health outcomes of importance to patients. There may be a subset of patients who benefit clinically from bevacizumab, but, unlike HER2 for trastuzumab, there is currently no biomarker identified that predicts which patients are likely to have a clinically significant response to bevacizumab. Targeted therapy is much more likely to be effective therapy. The fact that bevacizumab had a significantly greater effect on progression-free survival when used as part of the initial treatment for metastatic breast cancer compared to its effect in patients who had received prior treatment suggests that the therapy may be more effective when used prior to the diagnosis of metastatic disease. There are many ongoing clinical trials evaluating bevacizumab for breast cancer in women with metastatic disease and in the adjuvant setting. These trials have the potential to define a clinically meaningful role for bevacizumab in the treatment of breast cancer.

DRAFT RECOMMENDATION

It is recommended that the use of bevacizumab as initial or second-line treatment for metastatic breast cancer does not meet Technology Assessment Criteria 3 through 5 for safety, effectiveness and improvement in health outcomes.

June 18, 2008

RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)

The BCBSA Technology Evaluation Center (TEC) conducted a review of *Off-Label Uses of Bevacizumab: Breast and Lung Cancer Indications* and determined that bevacizumab does not meet the TEC criteria as second-line therapy for advanced or metastatic breast or lung cancers or as a component of adjuvant therapy for either of these malignancies. (www.bcbs.com/betterknowledge/tec/vols/21/21_08.html)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Anti-cancer chemotherapeutic agents are eligible for coverage when used in accordance with FDA approved labeling.

ASSOCIATION OF NORTHERN CALIFORNIA ONCOLOGISTS (ANCO)

ANCO provided a statement regarding Bevacizumab noting “With respect to bevacizumab as a treatment for metastatic breast cancer, ANCO observes that bevacizumab has been FDA-approved as a beneficial treatment for metastatic breast cancer and should be covered by health insurance for this use.”. A representative of ANCO will not be attending the meeting.

MEDICAL ONCOLOGISTS ASSOCIATION OF SOUTHERN CALIFORNIA (MOASC)

MOASC has been invited to provide an opinion regarding this technology and to participate at the meeting.

AMERICAN CANCER SOCIETY (ACS)

ACS has been invited to provide an opinion regarding this technology and to participate at the meeting.

AMERICAN SOCIETY OF BREAST SURGEONS (ASBS)

ASBS has been invited to provide an opinion regarding this technology and to participate at the meeting.

ABBREVIATIONS USED IN THIS REVIEW

| | |
|--------|---|
| FDA | U.S. Food and Drug Administration |
| TNM | Tumor node metastasis |
| OS | Overall survival |
| VEGF | Vascular endothelial growth factor |
| RPLS | Reversible posterior leukoencephalopathy syndrome |
| DARE | Database of Abstracts of Reviews of Effects |
| IPA | International Pharmaceutical Abstracts |
| FACT-B | Functional Assessment of Cancer Treatment-Breast |
| NCI | National Cancer Institute |
| ORR | Objective response rate |
| AE's | Adverse effects |
| MRI | Magnetic resonance imaging |
| CNS | Central nervous system |
| HR | Hazard ration |
| ITT | Intention to treat |
| NR | Not reported |

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