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REVIEW

Efficacy of Bevacizumab-Capecitabine in Combination for the First-Line Treatment of Metastatic Breast Cancer

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Abstract: There is an ongoing need for development of new chemotherapeutic regimens for metastatic breast cancer [mBC], especially when tumors lack therapeutic targets such as the estrogen or progesterone receptor [ER/PR], or the human epidermal growth factor receptor-2 [HER2]. Capecitabine is an orally bioavailable fluoropyrimidine approved for monotherapy in mBC, and bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor which has shown to be active in mBC and tolerable in combination with other chemotherapeutics. The combination of these two agents has been explored in multiple phase II and III clinical studies, with improvements in progression-free survival and overall response rates noted as compared to capecitabine monotherapy. However, the use of bevacizumab in combination with capecitabine and other chemotherapy agents for mBC remains beset with controversy due to safety concerns, cost issues, and pending regulatory decisions.

Keywords: metastatic breast cancer, capecitabine, bevacizumab

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Introduction

Despite many recent advances in the therapy of metastatic breast cancer [mBC], the median survival of newly diagnosed patients remains at approximately 2 years.[1] Many of these advances have been achieved through the development of targeted therapies. The initial targeted therapies for breast cancer were endocrine-based therapies (ie, tamoxifen and subsequently the aromatase inhibitors), which suppress hormone-mediated growth signals to tumor cells that express estrogen and/or progesterone receptors [ER/PR].[2,3] More recently, the identification of a subset of breast cancers that overexpress the human epidermal growth factor receptor-2 [HER2], and subsequent development of the monoclonal antibody trastuzumab that targets the receptor, has resulted in meaningful gains in survival in patients with these tumors.[4] However, a significant proportion of patients are still diagnosed with breast cancers that either do not express one of these three therapeutic targets, such as the so-called "triple-negative" breast cancers [TNBC]; or tumors which have lost the ability to respond to the targeted agents, such as the endocrine resistant tumors. A new target that has been identified in the last few years is the vascular endothelial growth factor [VEGF], which is a key mediator for tumor growth by promoting angiogenesis and neovascularization. Blocking the VEGF ligand selectively has been shown to inhibit tumor angiogenesis and cell proliferation.[5] In addition, some investigators have suggested that inhibiting VEGF activity allows increased penetration of traditional cytotoxic agents into tumor tissue, enhancing the antitumor effect of these agents.[6] Therefore, utilizing combinations of VEGF targeted agents and traditional chemotherapy is an attractive option. In this work we will review the role of the bevacizumab-capecitabine combination as first-line treatment of metastatic breast cancer.

Bevacizumab and Capecitabine

Bevacizumab

There are a number of investigational antiangiogenic agents for the treatment of advanced or mBC.[7] Bevacizumab is a fully human monoclonal antibody against soluble VEGF-A which was initially approved by the United States Food and Drug Administration in 2004 for the treatment of metastatic colorectal cancer in combination with 5-FU based-chemotherapy.[8] It is currently approved for the treatment of several malignant disorders such as breast, colon, renal, brain (glioblastomas) and non-squamous non-small cell lung cancers, but is also being used in non-malignant conditions, such as ocular disorders due to neovascularization. Its use in mBC has been an area of active investigation for several years, initially as a single agent[9] and more recently as a part of multiple iterations of combination regimens.[10–12] In the landmark ECOG 2100 trial, adding bevacizumab to weekly paclitaxel, significantly prolonged median progression-free survival (PFS, 11.8 months versus 5.9 months; $P < 0.0001$) and almost doubled the objective response rate (ORR) (36.9% versus 21.2%; $P < 0.001$) over paclitaxel alone in previously untreated mBC.[10] However, overall survival was not improved.

Capecitabine

5-fluorouracil [5-FU] has long been incorporated into chemotherapy regimens both for adjuvant and metastatic disease, but its use has been complicated by adverse effects and difficulty with administration.[13] In the past decade, capecitabine, an oral fluoropyrimidine which is selectively converted to 5-FU in tumor cells,[14] has been studied in multiple tumor types, including breast cancer. Its ease of administration, relatively favorable toxicity profile, and lack of cross-resistance to other commonly used chemotherapeutic agents make it an attractive treatment option for metastatic breast cancer. Capecitabine was first explored in metastatic breast cancer by Blum et al in a phase II study in patients previously treated with two or three chemotherapy regimens.[15] 162 patients were treated with capecitabine 2500 mg/m^2/day in divided doses, with 27 (20%) complete or partial responses, and another 54 patients (40%) with stable disease. Median time to progression was approximately 3 months, and median survival was 12.8 months. As a result of this study, capecitabine was the first drug to be approved for use in metastatic breast cancer patients who were resistant to paclitaxel/anthracycline-containing regimens or resistant to paclitaxel and not a candidate for further anthracycline therapy. It was also approved

in combination with docetaxel for the treatment of mBC that has failed prior anthracycline-based therapy.[16]

Clinical studies of the combination of capecitabine plus bevacizumab in breast cancer

Several clinical trials have explored the use of capecitabine in combination with bevacizumab, and are summarized in Table 1. As is common with the development of most agents in oncology, the combination of capecitabine and bevacizumab (CAPE + BEV) was initially studied in previously treated patients with mBC (second/third line therapy). The seminal trial in this setting was the avf2119 g study.[17] This study randomized 462 patients to capecitabine 2500 mg/m^2 in two divided daily doses for two weeks followed by a week off, or the same dose and schedule of capecitabine plus bevacizumab 15 mg/kg every three weeks. Although an improvement in overall response rate was seen with the addition of bevacizumab (19.8% vs. 9.1%), it did not meet the primary end-point of improvement of PFS (4.17 vs. 4.86 months for CAPE vs. CAPE-BEV respectively; $P = 0.857$) and the OS was also the same in the two groups (14.5 vs. 15.1 months; $P = 0.63$). The authors felt that the addition of antiangiogenic therapy earlier in the course of disease was more likely to have clinical benefit.

The first study to evaluate the combination of capecitabine and bevacizumab (CAPE + BEV) in the first-line setting was the multi-center phase II study XCALIBr, initially reported at the 2007 annual meeting of the American Society of Clinical Oncology (ASCO).[18] The primary end-point was to evaluate time to progression (TTP) in chemotherapy-naive HER2 negative metastatic breast cancer patients. Secondary endpoints included overall survival, overall response rate, response duration, biomarkers, quality of life, time-to-failure and safety profile. One hundred and three patients were treated with capecitabine 1000 mg/m^2 twice a day for 14 days with seven days off in combination with bevacizumab at 15 mg/kg IV in three-week cycles until first progression or intolerance to treatment. Once progression was documented, patients were treated with second-line therapy of BEV in combination with either weekly paclitaxel or vinorelbine. The ORR was 38.5% (with an additional 42.9% achieving stable disease). Median PFS was 5.7 months (95% CI 4.9–8.4 months), with a median overall survival of 16 months. Women with advanced estrogen receptor positive breast cancer demonstrated an especially significant delay in disease progression, with a median delay of 8.9 months. The most common grade 3 adverse events were hand-foot syndrome (13%) and pain (10%). The most serious AE was pulmonary embolism (2%).

The above study supported the development of a larger phase III study evaluating the use of bevacizumab and capecitabine as first line treatment for mBC. The RIBBON-1 study was an international, multicenter, double-blinded, placebo-controlled, phase III trial designed to look at the addition of bevacizumab to multiple chemotherapeutic agents in 1,237 patients who did not receive previous chemotherapy for their HER2-negative locally recurrent or metastatic breast cancer. It was initially presented at the annual ASCO meeting in 2009 and recently published.[12] The chemotherapy backbone was preselected for each patient at the treating physician's and patient's discretion, and subsequently patients were randomized to chemotherapy plus placebo or chemotherapy plus bevacizumab. Patients were randomized in a 2:1 ratio to receive bevacizumab plus chemotherapy. One of the chemotherapy options was capecitabine (as opposed

Table 1. Key mBC trials utilizing the capecitabine-bevacizumab combination.

Study	Setting	Design	n	Median PFS (mos.)	ORR	Median OS (mos.)
Avf2119	Previously treated	Phase II, randomized	232	4.86	19.8%	15.1 mo.
XCALIBr	Newly diagnosed	Phase II, single arm	103	5.7	38.5%	16.0 mo.
RIBBON-1	Newly diagnosed	Phase III	409	8.9	35.4%	Not reached
ATHENA	Newly diagnosed	Open-label, observational	102	7.0*	36.3%	Not reached

Note: *reported as "time to progression".
Abbreviations: PFS, progression-free survival; OS, overall survival; mos., months.

to the other option of taxane- or anthracycline-based chemotherapy). In all, capecitabine was selected for 615 patients, 409 of whom were randomized to capecitabine plus bevacizumab [CAPE + BEV], and 206 of whom were randomized to capecitabine plus placebo [CAPE]. Capecitabine dose was 1000 mg/m^2 twice daily for 14 days followed by 7 days off, while bevacizumab was given 15 mg/kg every three weeks. The two groups were evenly matched with respect to baseline characteristics.

The primary endpoint of the RIBBON-1 study was progression free survival, with overall response rate, overall survival, 1 year survival, and duration of response listed as secondary endpoints. Median progression free survival was significantly longer in the CAPE + BEV group, 8.9 months as opposed to 5.7 months in the CAPE group (HR 0.69 (0.52–0.80); $P < 0.001$). Kaplan Meier curves demonstrated a separation in the PFS curves at about 3 months, with convergence of the curves seen at approximately 18 months, suggesting some possible dilution of therapeutic effect due to crossover and second-line therapies. Overall response rate was significantly higher in the CAPE + BEV group (35.4% vs. 23.6%, $P = 0.0097$), but there was no statistically significant overall survival difference or in the 1-year survival rate. Taken with similar results seen for the taxane and anthracycline cohorts, the authors of the study concluded that the study provides rationale for adding bevacizumab to chemotherapy.

In addition to the above randomized trial looking at capecitabine and bevacizumab, there was a large single-arm, open label study of bevacizumab in combination with chemotherapy in the first-line setting, known as ATHENA, which primarily sought to examine safety endpoints in a setting that was thought to better represent a "real-world" scenario.[19] The vast majority of the 2251 patients in this study received a taxane-based therapy, but 102, or 4.5% of patients, received capecitabine as a chemotherapy backbone, and subgroup analyses for each regimen were reported for efficacy and safety endpoints. Median time to progression for CAPE + BEV was 7.0 months (95% CI 5.8–8.6), slightly lower than that observed in the RIBBON-1 study, but the overall response rate of 36.3% was fairly comparable. Additionally, 42.0% of patients achieved stabilization of their disease. No new safety signals for bevacizumab were observed in the study. Grade ≥ 3 hypertension was seen in 4.4% of patients and grade ≥ 3 bleeding occurred in 1.4% of patients.

Attempts have also been made to build on the efficacy of capecitabine and bevacizumab combination. A small phase II study by the North Central Cancer treatment Group (NCCTG), the N0432 trial, looked at the use of docetaxel in combination with capecitabine and bevacizumab in the first line mBC setting.[20] 45 patients were enrolled, and efficacy results were encouraging with a 49% ORR and median PFS 11.1 months. However, despite reducing the starting dose of capecitabine to 825 mg/m^2 BID, 98% of patients had at least one grade 3 or 4 adverse event, resulting in multiple dose reductions and delays. Hematologic toxicities were common including 78% of patients with grade 3 or 4 neutropenia.

The use of the combination of bevacizumab and capecitabine is an area of ongoing research interest, and there are currently several pending clinical trials which are awaiting results or completion of accrual. The TURANDOT trial from the Central European Cooperative Oncology Group is a randomized phase III trial comparing capecitabine and bevacizumab to paclitaxel and bevacizumab in the first line mBC setting. It is currently closed after completing accrual.[21] Safety data was reported for 80 patients in the CAPE + BEV arm (174 patients total enrolled) at the ASCO 2010 annual meeting; efficacy data has not yet been reported.[22] The CARIN trial from Germany has completed randomization of 400 patients to CAPE + BEV or CAPE + BEV + vinorelbine. Preliminary safety data was reported at the ASCO 2011 annual meeting; efficacy data has yet to be published.[23] The South Eastern European Research Oncology Group is also currently recruiting participants for a single-arm phase II study of capecitabine and bevacizumab as first line therapy in women over the age of 70 with mBC.[24]

Safety of the combination of capecitabine plus bevacizumab in breast cancer

Of course, despite positive efficacy results in phase II and III clinical trials, the safety of the addition of bevacizumab to capecitabine is of the utmost concern. The adverse event (AE) profiles of the two drugs have been well described as monotherapy, with capecitabine most notably causing hand-foot

syndrome, myelosuppression and GI adverse events such as diarrhea,[15] and bevacizumab causing hypertension, proteinuria, bleeding and thromboembolic events.[8,9] Fortunately, there is little overlap between these two toxicity profiles, but nevertheless, it has been important to ensure that the AEs seen with monotherapies are not potentiated by the two-drug combination. Taken as a whole, there is now a moderate amount of safety data available for the evaluation of the capecitabine-bevacizumab regimen in MBC, which is summarized in Table 2.

Early studies utilizing the CAPE + BEV regimen provided initial reassurance that the two drugs, when combined, were tolerable for patients. The avf2119-study from Miller et al[17] reported that capecitabine toxicities were similar with or without bevacizumab—for example, rates of grade 3 hand-foot syndrome were 24.2% for monotherapy vs. 27.5% for the combination regimen, and rates of grade 3 diarrhea were 10.7% for monotherapy vs. 11.8% for combination therapy. Dose reductions were very common in both groups, 65% in the CAPE group and 79% in the CAPE + BEV group (the starting dose of capecitabine was 2500 mg/m^2 cumulative daily dose, which was subsequently lowered in later studies). Rates of therapy discontinuation were virtually identical between the groups. Hypertension and minor mucosal bleeding was more common in the CAPE + BEV group, but rates of thromboembolic events were infrequent. Seven patients on the CAPE + BEV arm developed grade 3 or 4 congestive heart failure or cardiomyopathy, against only 2 patients on capecitabine alone. However, it warrants mention that all patients on both arms were pretreated with anthracyclines.

The RIBBON-1 trial provided the largest data set for safety analysis in the combination regimen of bevacizumab and capecitabine.[12] Overall, there were higher rates of AEs reported in the combination arms than in the arms containing chemotherapy without bevacizumab. Specifically for the combination of bevacizumab and capecitabine, hypertension and proteinuria were increased, as expected. Venous thromboembolism was noted in 20 out of 404 patients (5.0%) in the combination arm, and 7 out of 201 patients (3.5%) on capecitabine monotherapy. There were also trends noted toward higher incidence of sensory neuropathy (12 patients on CAPE + BEV, 1 patient on CAPE alone), as well as left ventricular dysfunction (6 patients on CAPE + BEV, 1 patient on CAPE alone); however, statistical significance was not reported for the safety analyses within this subgroup. Fatal AEs were low in both groups, 5 on capecitabine alone and 6 on the combination arm. An equal number of patients in both arms, 11.9%, had an AE leading to drug discontinuation. The authors concluded that the addition of bevacizumab to chemotherapy did not significantly alter the toxicities of these agents or result in an increased number of fatal toxicities.

Because of the small signal of left ventricular dysfunction noted in these and other trials, a meta-analysis was undertaken to examine the incidence of CHF in patients treated with bevacizumab for mBC.[25] The study included 5 large randomized trials, including avf2119 g, RIBBON-1 and RIBBON-2, among others. The study demonstrated a significantly increased risk of congestive heart failure in patients treated with bevacizumab (1.6% vs. 0.4%, RR 4.74, $P = 0.001$). Important caveats include the fact that the extent of the interaction with other therapies such as anthracyclines is unknown, and the absolute incidence is small, less than 2%.

The ATHENA study reported safety analyses for the 102 patients in the capecitabine subgroup.[19] 45.1% had at least 1 grade 3 or higher AE, with 21.6% of patients having a serious event. Absolute numbers of specific grade 3 AEs were small, including 5.9% hypertension, 1.0% proteinuria, 4.9% arterial

Table 2. Key safety endpoints for published capecitabine-bevacizumab trials in percentage of patients.

Study	n	Hypertension	Thromboembolic events	Hand-foot syndrome	Proteinuria	GI perforation	CHF
Avf2119*	229	23.6 (17.9)	7.4 (5.7)	69.9 (27.5)	22.3 (0.9)	Not reported	2.2 (2.2)
RIBBON-1†	404	10.1	5.0	Not reported	2.2	0	1.5
ATHENA‡	102	5.9	4.9	Not reported	1.0	0	0

Notes: *All AEs (grade 3 and 4 AEs in parentheses). †Grade 2 and above AEs. ‡Grade 3 and above AEs.
Abbreviation: CHF, congestive heart failure.

or venous thromboembolism, and 1% hemorrhage. No patients with grade 3 CHF were reported in the capecitabine subgroup.

Interim safety analyses have been reported in some ongoing trials as well. The TURANDOT study has not yet reported efficacy results, but preliminary safety data has been performed.[22] Eighty patients receiving CAPE + BEV were evaluated at a pre-specified interim analysis: 80% of patients had at least one AE; 31% had grade 3 AEs, with 10% of patients experiencing a serious AE. The most common grade 3 or 4 AE reported was diarrhea, at a frequency of 8.8%. The CARIN trial comparing CAPE + BEV with or without vinorelbine also has reported interim safety data,[23] with grade 3 hypertension or thromboembolic events reported uncommonly (1 patient in each arm). Neutropenia was frequently seen, but almost exclusively in the vinorelbine group.

Although the dosing of capecitabine 1000 mg/m^2 BID for 14 days of a 21 day cycle has been used most commonly, several different dosing schedules have been employed in an attempt to find the most efficacious schedule while minimizing toxicity. Gajria et al from the Memorial Sloan Kettering Cancer Center reported a single arm, phase II trial[26] that used a flat capecitabine dose of 2000 mg BID for 7 days, followed by 7 days off, along with bevacizumab 10 mg/kg every two weeks. Prior chemotherapy was allowed, and a total of 41 patients were enrolled. Efficacy data was similar to other reported studies of capecitabine plus bevacizumab, with median PFS of about 8 months, ORR of 20% and 35% stable disease. However, dose reduction or delay of capecitabine was still needed in 32 of 41 patients (78%), with 9 patients discontinuing study medication due to adverse effects. Gastrointestinal side effects were lessened, but hand-foot syndrome was still present in numbers similar to other schedules of capecitabine and bevacizumab. Seven patients required dose reduction of bevacizumab due to hypertension, and 2 patients had a thromboembolic event. No patients died while on study.

In summary, although there is a discernible increase in toxicities with the addition of bevacizumab to capecitabine, the toxicities are generally tolerable. Serious adverse events include thromboembolism and congestive heart failure, although fortunately these are quite uncommon.

Place in Therapy

Despite a growing body of evidence with the use of these agents, efficacy and safety results do not tell the complete story with bevacizumab as combination therapy. Perhaps no other oncologic drug in recent memory has caused as much controversy as bevacizumab. In July 2010, the Oncologic Drugs Advisory Committee (ODAC) of the United States Food and Drug Administration (FDA) voted 12-1 to recommend withdrawal of the conditional approval of bevacizumab as front-line therapy for HER2 negative mBC based on their concerns of the potential serious adverse events with this agent, the lack of confirmation of the magnitude of benefit seen in the E2100 trial (comparing paclitaxel with and without bevacizumab[10]) in the RIBBON-1 trial, as well as the AVADO trial, another seminal trial examining docetaxel with or without bevacizumab[11] and the lack of improvement in OS in all those trials. On December 15, 2010, the FDA's Center for Drug Evaluation and Research recommended to initiate the process of withdrawal of the approval of the breast cancer indication for bevacizumab.[27] Subsequently, Europe's regulatory body, the European Medicine Agency, released a statement that bevacizumab would remain as an option for metastatic breast cancer, but only when used in combination with paclitaxel.[28] On June 27th–28th, 2011, the FDA conducted a hearing with the Center for Drug Evaluation and Research and the manufacturer of bevacizumab, Genentech, which further explored the approval of bevacizumab for treatment of metastatic breast cancer.[29] Following this meeting the Centers for Medicare & Medicaid Services made a public statement that they will continue to pay for bevacizumab when it's used to treat metastatic breast cancer, even if the FDA decides to remove that indication from the drug.[30] Also the National Comprehensive Cancer Network (NCCN), has voted overwhelmingly in favor of maintaining its recommendation that bevacizumab should continue to be available as an option to treat mBC.[31] A final ruling from Dr. Margaret Hamburg, commissioner of the FDA, was still pending at the time of submission of this manuscript. Although bevacizumab is in no danger of removal from the market because of its current indications in other tumor types, the removal of the breast cancer indication from the labeling of

bevacizumab would likely result in decreased ability of researchers and providers to use this medication in mBC.

It is also impossible to have a meaningful discussion regarding the use of bevacizumab in breast cancer without mentioning the concerns over cost of therapy. A study from Switzerland utilized the data from the avf2119, E2100, and AVADO studies to determine the cost-effectiveness of the addition of bevacizumab therapy in MBC.[32] The conclusion of this study, conducted under the constraints of the Swiss health system, was that addition of bevacizumab to weekly paclitaxel was estimated to cost 40,369 euros (approximately $58,000 US dollars) for the gain of 0.22 quality adjusted life years, equaling an incremental cost-effectiveness ratio of 189,427 euros ($272,812 USD) per QALY gained. Of course, the improvement in survival needed to justify the use of a particular agent is subjective, but the authors point out that bevacizumab is expensive compared to common willingness-to-pay thresholds.

Conclusions

At this time, there remain many unanswered questions regarding the use of capecitabine and bevacizumab in the first line setting for metastatic breast cancer. Based on the results from well conducted large clinical trials, taxanes and anthracyclines are likely to remain the standard first line therapy for patients who are able to tolerate and willing to receive these agents. However, the relatively favorable toxicity profile and the ease of orally administered therapy make capecitabine an attractive option for patients and providers. The additive benefits of bevacizumab, however, do seem to extend not only to taxanes but also to capecitabine therapy, and for patients with contraindications to taxane-based therapy, combination treatment with these two agents is relatively safe and tolerable.

Perhaps the most important question remaining is, "How much benefit is enough?" The benchmark of overall survival has been difficult to achieve by these large trials, hypothetically because of the availability of several additional therapies that can prolong survival and dilute the therapeutic effect of the study agents after they are discontinued[33] and possibly also because the aforementioned trials were not powered enough to demonstrate statistically significant improvement in overall survival. Therefore, the use of progression free survival as a meaningful surrogate has dramatic implications for the use of drugs like bevacizumab. The RIBBON-1, E2100 and AVADO trials all demonstrated an advantage for PFS when bevacizumab was added to chemotherapy; although these differences were statistically significant, were they clinically significant? The answer may vary between providers, payors, and regulatory bodies, creating an undercurrent of tension that is not easily resolved.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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