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Bevacizumab and breast cancer: current therapeutic progress and future perspectives

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Abstract

Bevacizumab is a humanized monoclonal antibody to VEGF, and the incorporation of bevacizumab to chemotherapy is one of the rapidly evolving areas in the treatment of breast cancer. Bevacizumab in combination with chemotherapy versus chemotherapy alone improves progression-free survival and increases the response rate in first-line therapy for locally recurrent or metastatic breast cancer. This approach has been and is still being evaluated for early breast cancer in neoadjuvant and adjuvant settings. Bevacizumab is well tolerated and has an established tolerability profile. Both tumor- and host-related biomarkers of bevacizumab activity, response and benefit are emerging from Phase I, II and III clinical trials. The biomarkers of benefit will ultimately help identify the subgroups of patients who specifically benefit from anti-VEGF therapy with bevacizumab.

Keywords

bevacizumab; breast cancer; chemotherapy; clinical trials; first-line therapy; VEGF

VEGF-A & bevacizumab

For decades, it has been observed that tumors are unable to grow beyond a diameter of 2 mm in the absence of angiogenesis (angiogenic pheno-type) that supports their progressive growth [1]. As a result, tumors are in a hypoxic state without angiogenesis, the process of new blood-vessel growth. The normal cellular response to hypoxia is to produce growth factors, such as VEGF, TGF- β and PDGF, which stimulate neoangio-genesis. Hypoxia-inducible transcription factor (HIF)-1 regulates the production of these growth factors [2]. Furthermore, it has been shown that estradiol and progesterone enhance VEGF expression through the interaction of estradiol-bound estrogen receptor (ER) α with an estrogen response element in the VEGF promoter region [3,4]. In addition, HER2 activates multiple cellular signaling pathways that are involved in cell proliferation and survival, and increase VEGF protein synthesis. The latter is regulated via activation of the mTOR/p70S6K cap-dependent translation pathway in human breast cancer cells [5].

VEGF-A, generally referred to as VEGF, is a potent, selective endothelial cell growth factor that induces blood vessel permeability and regulates angiogenesis [6]. It plays an important role in a number of physiological processes, such as embryogenesis, skeletal growth and wound

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healing [7,8]. VEGF consists of four major splice variants yielding proteins of 121, 165, 189 and 206 amino acids [9]. VEGF₁₂₁ is a freely diffusible protein, whereas VEGF₁₈₉ and VEGF₂₀₆ are sequestered in the extracellular matrix. VEGF₁₆₅, the predominant isoform, is both secreted and cell bound [10,11]. The functions of VEGF are mediated by binding to the VEGF receptors (VEGFR1 or Flt-1, and VEGFR2 or KDR). VEGFR2 is believed to be the major receptor that mediates the angiogenic effects of VEGF [12–14].

VEGF is continuously expressed throughout the development of many tumor types and is the only angiogenic factor known to be present throughout the entire tumor life cycle [15]. It is expressed in a wide range of human tumors, including breast cancer [16,17]. High levels of VEGF in primary breast tumor tissue were associated with poor prognosis [18–20]. Moreover, VEGF levels were significantly predictive of both disease-free survival (DFS) and overall survival (OS) in patients with node-positive breast cancer treated with either adjuvant chemotherapy or hormone therapy [21]. Recently, a VEGF profile that consists of 13 genes has been shown to be highly expressed in metastatic breast tumors relative to primary breast tumors or regional metastasis [22]. Overall, VEGF plays an important role in the process of angiogenesis that is associated with the growth and metastasis of breast cancer, as well as with clinical outcome of breast cancer patients. Therefore, targeting the VEGF pathway represents a promising approach in the treatment of breast cancer.

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody developed from the murine anti-VEGF monoclonal antibody A4.6.1 and binds to all isoforms of VEGF (Avastin®, Genentech, Inc.) [23]. It prevents the interaction between VEGF and its receptor tyrosine kinases VEGFR1 and VEGFR2. Bevacizumab is intravenously administered and has a terminal half-life of 17–21 days. Sustained inhibition of VEGF with bevacizumab results in the regression of existing tumor micro-vasculature and normalization of surviving tumor vasculature as well as inhibition in the formation of new vasculature [24,25]. However, withdrawal of anti-VEGF therapy has led to the rapid regrowth of tumor vasculature in preclinical models [26]. This suggests that anti-VEGF treatment should be continued until disease progression or beyond.

Bevacizumab was approved by the US FDA as first-line treatment for metastatic colorectal cancer in February 2004 [27], and subsequently as second-line treatment in June 2006 [28]. The OS was significantly longer in patients receiving irinotecan, fluorouracil and leucovorin (IFL) plus bevacizumab versus those receiving IFL plus placebo; and in those receiving oxaliplatin, fluoro uracil and leucovorin (FOLFOX4) with bevacizumab compared with those receiving FOLFOX4 alone. In October 2006, the FDA approved bevacizumab, administered in combination with carbo platin and paclitaxel, for first-line treatment of patients with unresectable locally advanced, recurrent or meta-static, non-squamous, non-small-cell lung cancer [29]. This was based on a statistically significant improvement in OS in patients who received bevacizumab in combination with carboplatin plus paclitaxel compared with those who received carboplatin and paclitaxel alone. In February 2008, the FDA granted accelerated approval for bevacizumab in combination with paclitaxel as first-line treatment in patients with metastatic HER2-negative breast cancer [30]. Progression-free survival (PFS), but not OS, was significantly improved in patients who received bevacizumab plus paclitaxel compared with those who received paclitaxel alone. Recently, in May 2009, bevacizumab was approved for use as a single agent for patients with recurrent glioblastoma with progressive disease following prior therapy, since durable objective response rates (ORRs) were demonstrated from two single-arm trials, AVF3708g and NCI 06-C-0064E [31,32]. More recently, in July 2009, based on significantly improved PFS by bevacizumab plus interferon versus interferon alone, bevacizumab was approved as first-line therapy in metastatic renal cell carcinoma [101].

Bevacizumab in the treatment of metastatic breast cancer

Second-line therapy

The first randomized Phase III trial compared the efficacy and safety of capecitabine with or without bevacizumab in 462 patients with metastatic breast cancer previously treated with an anthracycline and a taxane [33]. Patients were randomly assigned to receive capecitabine (2500 mg/m²/day) twice daily on day 1 through to 14 every 3 weeks, alone or in combination with bevacizumab (15 mg/kg every 3 weeks) on day 1. The primary end point was PFS as determined by an independent review facility (IRF). The addition of bevacizumab to capecitabine produced a significant increase in response rates (19.8 vs 9.1%; $p = 0.001$), but did not demonstrate an improvement in PFS (4.86 vs 4.17 months; hazard ratio [HR]: 0.98) or OS (15.1 vs 14.5 months). That this trial did not meet its primary end point was ascribed to redundant angiogenic pathways caused by multiple angiogenic factors in patients with previously treated, highly refractory disease and this underscores the need to target VEGF-associated angiogenesis early in the disease process [34]. Of note, the results are in contrast to bevacizumab plus chemotherapy as second-line treatment in metastatic colorectal cancer, in which the addition of bevacizumab to FOLFOX4 significantly improved survival duration [28]. This raises the question of whether angiogenesis status or genomic make-up of tumors that have originated from different organ sites might be a factor in response to second-line bevacizumab plus chemotherapy. In addition, previous chemotherapy for the management of metastatic disease may have altered VEGF-associated angiogenic phenotype in metastatic breast cancer since chemotherapy agents, such as docetaxel and paclitaxel, have anti-angiogenic properties [35, 36].

First-line therapy

As VEGF plays an important role in tumor growth and metastasis, and limited angiogenesis pathways are active early in the metastatic disease process [37], it is compelling to target the VEGF-associated angiogenesis for initial treatment. In an open-label Phase III trial (E2100) of paclitaxel plus bevacizumab versus paclitaxel alone as first-line therapy of metastatic breast cancer, 722 patients were randomly assigned to receive paclitaxel alone or with bevacizumab [30]. The primary end point of this trial was PFS assessed by the investigators, and OS was the secondary end point (Table 1). The addition of bevacizumab significantly improved median PFS (11.8 vs 5.9 months; $p < 0.0001$) and nearly doubled the ORR (36.9 vs 21.2%; $p < 0.001$). However, OS was similar in two treatment arms (26.7 vs 25.2 months; $p = 0.16$). Nonetheless, this is a landmark study that first demonstrated benefit from the addition of bevacizumab to conventional chemotherapy in patients with metastatic breast cancer. Recently, the PFS benefit assessed by the investigators was confirmed by IRF [38]. In this analysis, nonprotocol therapy was censored. HRs for PFS (0.48; 95% CI: 0.385–0.607; $p < 0.0001$) and ORR (48.9 vs 22.2%; $p < 0.0001$) were significantly higher in patients treated with paclitaxel and bevacizumab.

The bevacizumab plus docetaxel trial (Avastin plus Docetaxel [AVADO]) has confirmed the benefit of adding bevacizumab to first-line taxane therapy for metastatic breast cancer [39]. This double-blind, randomized, placebo-controlled Phase III study compared docetaxel plus placebo ($n = 241$) with docetaxel plus low-dose bevacizumab (7.5 mg/kg; $n = 248$) or high-dose bevacizumab (15 mg/kg; $n = 247$). The primary end point was PFS, and secondary end points were OS, time to treatment failure, best overall response, duration of response and safety. The addition of bevacizumab significantly improved PFS and increased ORR in both the 7.5 and 15 mg/kg treatment arms (Table 1). OS was not ready to be reported due to a short follow-up. Higher bevacizumab dose appeared to be better than the lower dose although the study was not powered to detect a difference between the two bevacizumab arms. More recently, another Phase III trial (RIBBON-1) evaluated chemotherapy with or without bevacizumab for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer [40]. Patients

were randomized in a 2:1 ratio to receive bevacizumab plus chemotherapy or placebo plus chemotherapy (Table 1). Bevacizumab was administered every 3 weeks until disease progression. Secondary end points included ORR, 1-year survival rate and OS at the time of PFS analysis. Bevacizumab plus capecitabine (n = 409) compared with placebo plus capecitabine (n = 216), and bevacizumab plus taxane or anthracycline (n = 415) versus placebo plus a taxane or anthracycline (n = 207) significantly improved PFS and increased ORR.

As summarized in Table 1, the results from all three Phase III trials demonstrated adding bevacizumab (either 10 mg/kg every 2 weeks or 7.5 mg/kg or 15 mg/kg every 3 weeks) to commonly used chemotherapy agents (paclitaxel, docetaxel, capecitabine, taxane or anthracycline) significantly improves PFS as first-line therapy for metastatic breast cancer. The duration in median PFS gained varied from 0.7 to 5.9 months. On the other hand, thus far an improvement in OS has not been demonstrated from these Phase III trials. These data suggest that the benefit from the addition of bevacizumab to chemotherapy is modest and consistent in unselected patients with metastatic breast cancer.

At present, more trials of bevacizumab in combination with chemotherapy and/or with other biological agents are being conducted in patients with metastatic breast cancer. Table 2 lists some of the ongoing Phase III trials of bevacizumab in combination with chemotherapy, hormone therapy or anti-HER2 therapy. The rationale for combining bevacizumab with hormone therapy (CALGB 40503) is that hormone therapy with tamoxifen or letrozole blocks the effect of estrogen on the growth of breast tumors, and bevacizumab may inhibit tumor growth through blocking blood supply to the tumor. Besides, it has been shown that estradiol enhances VEGF expression through estradiol-bound ER with an estrogen response element in the VEGF promoter region. It is postulated that combining hormone therapy with bevacizumab may be more effective in women with hormone receptor-positive advanced breast cancer. Another promising regimen (E1105) is to combine bevacizumab plus chemotherapy with trastuzumab in the treatment of metastatic breast cancer. Overexpression of HER2 has been shown to associate with the increased angiogenesis and expression of VEGF in tumor cells, thus promoting metastasis of tumor cells. Trastuzumab inhibits tumor cell growth and VEGF expression in preclinical studies [41]. E1105 is testing whether first-line chemotherapy plus trastuzumab is more effective with or without bevacizumab in patients with metastatic breast cancer that overexpresses HER-2.

Bevacizumab in the treatment of early breast cancer or previously untreated advanced breast cancer

Adjuvant setting

Anti-angiogenic therapy using bevacizumab in combination with chemotherapy versus chemotherapy alone or plus another biologic agent in early breast cancer is being evaluated in the adjuvant setting. Table 3 lists some of the ongoing adjuvant bevacizumab-containing Phase III trials, the results of which will be available within 5 years. Of note, ABCDE is a randomized Phase III study of adjuvant bevacizumab, metronomic chemotherapy, diet and exercise in patients with pathologic residual disease in the breast or lymph nodes removed after neoadjuvant chemotherapy (Table 3). The trial is to determine if additional treatment after preoperative chemotherapy and surgery with bevacizumab and metronomic chemotherapy would reduce recurrence compared with the standard of care, by observation alone.

Neoadjuvant setting

Trials evaluating the clinical and biological activities of neoadjuvant bevacizumab in combination with chemotherapy in locally advanced and inflammatory breast cancer have shown promising results. In a pilot Phase II trial, 20 patients with previously untreated

inflammatory breast cancer and one with locally advanced breast cancer (stage III and IV) received one cycle of bevacizumab (15 mg/kg) followed by six cycles of bevacizumab plus docetaxel (75 mg/m²) and doxorubicin (50 mg/m²) on day 1 every 3 weeks prior to surgery. A total of 14 patients (67%; 95% CI: 43–85.4%) had partial response [42]. Of the 21 patients evaluated for toxicities, 38% of patients had grade 3 hyper tension and 24% had wound-healing complications after surgery. In another Phase II trial, 30 patients with locally advanced breast cancer with unfavorable prognostic features were given neoadjuvant chemotherapy (epirubicin 25 mg/m², cisplatin 60 mg/m² and fluorouracil 200 mg/m²) followed by weekly paclitaxel plus bevacizumab (10 mg/kg) [43]. In total, 26 (87%) patients had ORR (95% CI: 69–96%) and ten (33%) achieved pathological complete response (pCR). pCR was defined as no evidence of invasive tumors in the final surgical specimens. Moreover, in another study, 18 patients with HER2-negative and nonmeta-static breast cancer received six cycles of neoadjuvant bevacizumab (15 mg/kg), docetaxel (75 mg/m²) and capecitabine (950 mg/m²) before surgery [44]. This treatment resulted in a 72% ORR and a 22% pCR rate. Together, these early neoadjuvant trials indicate that the addition of bevacizumab to chemotherapy is feasible. Whether bevacizumab plus neoadjuvant chemotherapy versus chemotherapy alone increases pCR rate will not be known until the results of randomized Phase II or III trials.

NSABP-B-40 (NCT00408408) is an ongoing randomized Phase III trial of neoadjuvant therapy in patients with palpable and operable breast cancer (stage I, II or IIIA), evaluating the effect of adding capecitabine or gemcitabine to docetaxel on pCR rate when administered before doxorubicin plus cyclophosphamide with or without bevacizumab plus correlative science study. The latter is set to identify predictors of high likelihood for pCR rate. Total projected patient accrual is 1200 and the results are expected in 2012 [102].

GBG 44 or GeparQuinto (NCT00567554) is another Phase III trial exploring the integration of bevacizumab, everolimus (RAD001) and lapatinib into current neoadjuvant chemotherapy regimens for primary breast cancer. One of the primary objectives of this trial is to compare pCR rates of neoadjuvant treatment of epirubicin plus cyclophosphamide followed by docetaxel (EC-T) with or without bevacizumab (EC-T vs ECB-TB) in patients with HER2-negative primary breast cancer. The targeted enrollment of this trial is 2547 patients with an estimated primary completion in 2010 [103].

Safety of bevacizumab

A Phase I/II trial of bevacizumab (AVF0776g) as a single agent was conducted in patients with previously treated metastatic breast cancer [45]. A total of 75 women were administered bevacizumab with either 3 mg/kg (n = 18), 10 mg/kg (n = 41) or 20 mg/kg (n = 16) every 2 weeks. Grade 3–4 hypertension occurred at all three dose levels with similar frequencies (22% [4 out of 18], 18% [18 out of 41] and 19% [3 out of 16]). The other serious adverse events (AEs) included 4% thrombotic events and 2.7% congestive heart failure (CHF) in patients who previously had received anthracycline. The only dose-limiting toxicity was headache associated with nausea and vomiting in four (25%) patients in the 20 mg/kg arm. Based on the results from this trial, a bevacizumab dose of 10 mg/kg every 2 weeks was selected for use for further trials in metastatic breast cancer.

Bevacizumab at a dose of 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks (similar dose density) was generally well tolerated and AEs were manageable. The most common adverse event is hypertension (Table 4). It is readily managed with antihypertensive therapy [33,45]. Other less frequent serious AEs include proteinuria, headaches, bleeding events, cardiac toxicity, gastrointestinal perforation or wound-healing complications. As shown in Table 4, toxicities associated with bevacizumab across the trials have been consistent, although chemotherapy toxicities differ. Bevacizumab appears to increase the frequencies of

chemotherapy-related AEs at varying degrees (Table 4). In the RIBBON-1 trial, grade 3–4 AEs occurred at least 2% more frequently in patients who received bevacizumab plus chemotherapy versus chemotherapy alone (Table 4) [104]. Noticeably, both low- and high-dose bevacizumab arms in the AVADO trial did not increase the incidences of grade 3–4 arterial thromboembolic events, CHF and gastrointestinal perforation. There were some degrees of increase in grade 3–4 febrile neutropenia in both bevacizumab arms and hypertension in the high-dose bevacizumab arm (Table 4).

Currently, a large ongoing open-label Phase IV trial (MO19391) is assessing the safety profile of bevacizumab when combined with taxane-based chemotherapy as first-line treatment for patients with locally recurrent or metastatic breast cancer. Bevacizumab was administered at either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks plus a taxane by physician's choice. Treatment with bevacizumab continued until disease progression or unacceptable toxicity occurred. From September 2006 to June 2008, 2027 patients from 37 countries were enrolled. The most commonly observed grade 3–4 side effects were hypertension (2.2%), proteinuria (0.7%), pulmonary embolism (0.5%) and epistaxis (0.4%) [46].

Biomarkers of bevacizumab activity, response or benefit

As bevacizumab and other anti-angiogenic agents are increasingly integrated into standard practice, biomarkers of benefit for appropriate selection of patients have become a major focus of interest in preclinical and clinical research. However, VEGF-associated angiogenic phenotype may differ from primary to metastatic tumors [22], and to previously treated metastatic breast tumors. Chemotherapy and/or biological therapy might alter VEGF-associated angiogenic phenotype. In addition, the mechanisms of action of anti-angiogenic agents, including bevacizumab, are not fully understood [47]. All of these pose challenges for the identification of consistent biomarkers of anti-VEGF therapy. Nonetheless, biomarkers of bevacizumab activity, response or benefit are emerging from Phase I, II and III clinical trials.

Biomarkers of bevacizumab in early breast cancer or previously untreated advanced breast cancer

Currently, biomarker data of bevacizumab therapy in early breast cancer are limited since data are only available from a few trials. In an early pilot Phase II trial, 21 patients with inflammatory and locally advanced breast cancer received neoadjuvant bevacizumab followed by bevacizumab plus doxorubicin–docetaxel [42]. Baseline CD31 levels (clone JC70, DAKO Corp., CA, USA) but not intratumoral microvessel density (MVD) in the tumor vasculature was significantly associated with response ($p < 0.001$); so was expression of PDGF receptor (PDGFR)- β ($p = 0.01$; Cell Signaling Technology, Inc., MA, USA) and tumor VEGF ($p = 0.04$; clone JH121, AngioBio Corp, CA, USA). These findings at protein level were confirmed at gene transcriptional level. Representative significant gene ontology (GO) classes identified in association with response included spindle (11 genes; $p = 0.001$) that probably related to docetaxel response, VEGFR activity, including PDGFR- β (five genes; $p = 0.002$), and cell motility that comprised CD31 (80 genes; $p = 0.005$). The latter two GOs are probably relevant to bevacizumab response. This study demonstrated that patients with higher levels of tumor VEGF-A, and CD31 as well as PDGFR- β in the tumor vasculature were more likely to respond to bevacizumab plus doxorubicin–docetaxel therapy [48]. However, baseline plasma VEGF (ELISA kit, R&D Systems, MN, USA) and serum VCAM-1 (R&D Systems) were not associated with response. VCAM-1 was significantly increased after one cycle of bevacizumab treatment alone or in combination with chemotherapy [49]. Interestingly, VEGFR2 was found to be expressed in breast tumor cells in this study. VEGFR2 activity examined by immunohistochemistry and angiogenesis assessed by dynamic contrast-enhanced (DEC)-MRI were significantly reduced by one cycle of bevacizumab or in combination with chemotherapy

[42]. These results indicate that bevacizumab has an inhibitory effect on key VEGF receptor activation and vascular permeability.

In a randomized Phase II trial, 49 patients with inoperable breast cancer were randomized to receive either two cycles of preoperative docetaxel or docetaxel with bevacizumab 10 mg/kg every other week [50]. There was no difference in overall clinical response, PFS or OS between the two treatment arms; this trial was not powered to detect the difference in treatment outcome. Baseline levels of VCAM-1 and E-selectin, a cell-adhesion molecule expressed only on endothelial cells, were correlated with clinical response by univariate analysis. DCE-MRI showed a greater decrease in tumor perfusion by the combination treatment versus docetaxel alone. A greater increase in circulating VEGF and VCAM-1 were observed by combination treatment compared with docetaxel alone. These data suggest that VCAM-1 and E-selectin may represent important surrogates for response. Treatment with bevacizumab plus docetaxel modulates the levels of circulating angiogenic factors; so does docetaxel alone but to a lesser degree.

In another trial of preoperative bevacizumab combined with chemotherapy plus letrozole in locally advanced breast cancer, a clinical response rate of 86% (95% CI: 70–95) and no pCR were reported [51]. Higher baseline levels of circulating endothelial progenitor cells (CEPs), but not circulating endothelial cells (CECs), were correlated with clinical response ($p = 0.026$). This probably related to the roles of CEPs on the angiogenic switch in tumor growth and metastatic progression [52]. CEP is defined as positive if expressing CD133; whereas CEC is regarded as positive if they are positive for the endothelial markers CD31 and CD146, and negative for the hematopoietic marker CD45 and progenitor marker CD133.

Taken together, the correlative biomarkers of response to bevacizumab therapy identified in these studies are hypothesis generating and require confirmation by larger studies. Further studies in early breast cancer or previously untreated advanced breast cancer should continue to focus on investigating baseline tumor VEGF and circulating VCAM-1, E-selectin and CEPs in relation to response or benefit. The evaluation of these markers in the adjuvant setting is warranted. The increase in circulating VEGF and VCAM-1, and the decrease in vascular permeability by bevacizumab alone or in combination with chemotherapy as biomarkers of drug activity hold promise for the determination of optimal biological dose.

Correlative biomarkers in metastatic breast cancer

Bevacizumab has been widely incorporated to the treatment regimens for the management of metastatic disease, and the correlative biomarker data are emerging. In E2100 Phase III trial, by the pharmacogenomic approach, *VEGF*-2578 AA genotype (AA vs CA plus CC) and the *VEGF*-1154 AA genotype (AA vs GA vs GG) predicted a favorable median OS ($p = 0.023$ and $p = 0.001$) for patients in the paclitaxel plus bevacizumab arm [53]. These genotypes did not predict an improved OS for patients in the paclitaxel arm nor did predict PFS or ORR for either arm. There was a trend for an association between the *VEGF*-2578 AA and *VEGF*-1154 AA genotypes and lower VEGF expression in the tumors, which is considered hypothesis generating [53]. Furthermore, tumor VEGF (clone VG1; Lab Vision, CA, USA) and VEGFR2 (clone 55B11; Cell Signaling Technology, Inc.) were not associated with outcome. Another interesting finding of this study was that the *VEGF*-634 CC and *VEGF*-1498 TT genotypes were correlated with less grade 3–4 hypertension (14.8 vs 0 or 8%, respectively). These results are encouraging but need independent confirmation by prospective studies.

In a Phase II study of bevacizumab plus vinorelbine chemotherapy in patients with advanced breast cancer, 56 women that were treated on protocol received bevacizumab 10 mg/kg and vinorelbine each week until progression or unacceptable toxicity occurred. This combination yielded a 34% response rate (95% CI: 22–48%) and median time to progression of 5.5 months.

Lower levels of baseline plasma VEGF were associated with longer time to progression, but not with response [54].

In another Phase II trial of bevacizumab in combination with docetaxel in patients with previously untreated metastatic breast cancer, 28 patients received bevacizumab at 10 mg/kg on days 1 and 15 in combination with docetaxel on days 1, 8 and 15 of a 28-day cycle. The ORR was 52% (95% CI: 32–71%). Higher plasma levels of E-selectin and soluble ICAM-1, one of the ICAM family members that is expressed in leukocytes and endothelial cells, at baseline and their decreases after one cycle of treatment were significantly associated with response in univariate analysis [55].

In summary, further steps should be taken towards standardizing methodologies for measuring tumor and plasma VEGF, circulating E-selectin, ICAM-1, or VCAM-1 in early and metastatic breast cancer. VEGF genotypes as potential biomarkers of benefit and toxicities need to be tested in prospective clinical trials. In addition, other tumor markers with known functions in angiogenesis, such as HER2, ER, p53 or HIF-1, in relation to benefit or response should be investigated in future studies or in the context of specific trial design. The information is required to determine which subset population of patients would benefit from bevacizumab therapy. All together, these may facilitate accelerating discovery, validation and establishment of biomarkers of anti-VEGF therapy.

Expert commentary

The activity of bevacizumab in combination with chemotherapy agents have been demonstrated by clinical trials in the management of metastatic breast cancer as first-line treatment, which has resulted in the incorporation of bevacizumab into day-to-day practice. Results from these trials are expected to guide clinical practice over the next 5 years and beyond. The incorporation of bevacizumab or other anti-angiogenesis agents to chemotherapy has certainly increased the options for the management of metastatic disease. However, the increased treatment options have raised questions regarding how to use these agents to achieve or maximize patient benefit. First, who should receive bevacizumab in order to gain survival benefit remains elusive in breast cancer. This underscores an urgent need for the validation and establishment of tumor- and host-related biomarkers of benefit. Second, risk–benefit for individual patients is another important aspect for the selection of anti-VEGF therapy. Third, cost–benefit relationship would be another factor for considering treatment options. Finally, the mechanisms of action of how bevacizumab in synergy with various chemotherapy agents in the context of treatment regimens are warranted in further preclinical and clinical studies.

Five-year view

The role of anti-VEGF therapy with bevacizumab in early breast cancer is yet to be demonstrated. The validation and establishment of biomarkers of benefit such as VEGF genotype will identify the subgroups of patients with locally recurrent and metastatic breast cancer as well as early breast cancer who will benefit from the addition of bevacizumab. The identification and validation of new biomarkers of bevacizumab or other anti-angiogenic agents will be likely. The use of established biomarkers to select patients to receive bevacizumab will substantially reduce the cost of cancer care. Bevacizumab plus chemotherapy in combination with other biologic agents such as letrozole, tamoxifen or trastuzumab will hold promise for the applications of more effective treatment regimens in both early and metastatic breast cancer.

Key issues

- Progression-free survival benefit from the addition of bevacizumab at 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks to conventionally used chemotherapy

agents as first-line therapy is modest and consistent in unselected patients with metastatic breast cancer.

- The conduct of meta-analysis of randomized Phase III trials will help demonstrate whether or not there is an overall survival benefit from the addition of bevacizumab to chemotherapy as first-line therapy in unselected patient population with metastatic breast cancer.
- Bevacizumab was administered until disease progression; a benefit from the use of bevacizumab beyond progression remains unproven.
- The role of anti-VEGF therapy with bevacizumab is yet to be demonstrated in adjuvant and neoadjuvant settings in early breast cancer.
- Biomarkers of benefit will ultimately help select the subsets of patients who specifically benefit from the addition of bevacizumab and substantially reduce the cost of healthcare.

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- of considerable interest

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Table 1

Phase III trials comparing bevacizumab plus chemotherapy with chemotherapy alone in locally recurrent or metastatic breast cancer.

Trial	Therapy regimens	Arms	ORR (%); p-value	PFS		OS		Ref.
				HR (95% CI)	Median (months); p-value	HR (95% CI)	Median (months); p-value	
E2100	90 mg/m ² paclitaxel on days 1, 8, and 15 every 4 weeks, either alone or with 10 mg/kg bev every 3 weeks	Paclitaxel vs bev + paclitaxel	21.2 vs 36.9; <0.001	0.60 (0.51–0.70)	5.9 vs 11.8; <0.001	0.88 (NR)	25.2 vs 26.7; 0.16	[30]
AVADO	100 mg/m ² docetaxel every 3 weeks, either with placebo or with 7.5 mg/kg or 15 mg/kg bev every 3 weeks	Docetaxel + placebo vs 7.5 mg/kg bev + docetaxel Docetaxel + placebo vs 15 mg/kg bev + docetaxel	44 vs 55.2; 0.03 44 vs 63.1; <0.001	0.69 (0.54–0.89) [*] 0.61 (0.48–0.78) [*]	8.0 vs 8.7; 0.04 8.0 vs 8.8; 0.01	0.92 (NR) [*] 0.86 (NR) [*]	NR NR	[39]
RIBBON-1	2000 mg/m ² × 14 days of cap, taxane (nab-paclitaxel [260 mg/m ²] or docetaxel [75 or 100 mg/m ²]) or ant every 3 weeks, either with placebo or with 15 mg/kg bev every 3 weeks	Capecitabine + placebo vs bev + capecitabine Taxane or anthracycline + placebo vs bev plus taxane or anthracycline	23.6 vs 35.4; 0.001 37.9 vs 51.3; 0.005	0.69 (0.56–0.84) [*] 0.64 (0.52–0.80) [*]	5.7 vs 8.6; >0.001 8.0 vs 9.2; <0.001	0.85 (0.63–1.14) [*] 1.03 (0.77–1.38) [*]	21.2 vs 29.0; 0.27 23.8 vs 25.2; 0.83	[40]

Ant: Anthracycline; Bev: Bevacizumab; HR: Hazard ratio; NR: Not reported; ORR: Objective response rate.

* Stratified analysis with censoring for nonprotocol therapy that started prior to disease progression.

Table 2

Ongoing Phase III trials for locally recurrent or metastatic breast cancer.

Trial	Trial design	Primary end point(s)	Estimated enrolment; primary completion date	Treatment; population	Ref.
RIBBON-2	Chemotherapy vs bev + chemotherapy	PFS	650; April 2010	Second-line	[105]
CALGB40502	Bev + paclitaxel vs bev + Nab-paclitaxel vs bev + ixabepilone	PFS	900; October 2010	First-line	[106]
E1105	Trastuzumab + paclitaxel ± carboplatin + placebo vs bev + trastuzumab + paclitaxel ± carboplatin	PFS	489; November 2011	First-line; HER2 ⁺	[107]
CALGB-40503	Tamoxifen or letrozole + placebo vs bev + tamoxifen or letrozole	PFS	502; February 2009	First-line; ER ⁺ and/or PR ⁺	[108]
CECOG	Bev + paclitaxel vs bev + capecitabine	Comparison of OS	560; November 2012	First-line; HER2 ⁻	[109]
MO22223	Bev alone vs bev + capecitabine	PFS	360; May 2014	Maintenance therapy	[110]
MO19391	Bev + taxane-based chemotherapy	Incidence of AEs, serious AEs	2300; March 2011	Safety/efficacy study	
BO20231	Trastuzumab + docetaxel vs bev + trastuzumab + docetaxel	PFS	410; December 2011	First-line; HER2 ⁺	[111]
GEICAM/2006-11	Letrozole alone vs bev + letrozole	PFS	378; December 2011	First-line; postmenopausal, HER2 ⁻	[112]

AE: Adverse event; bev: Bevacizumab; HR: Hazard ratio; Nab: Nanoparticle albumin bound; OS: Overall survival; PFS: Progression-free survival.

Table 3
Ongoing Phase III trials of adjuvant bevacizumab plus chemotherapy for early breast cancer.

Clinical trial	Trial design	Primary end points	Estimated enrolment; primary completion date	Population	Ref.
E5103	AC → paclitaxel vs bev + AC → paclitaxel	DFS	4950; November 2013	Node positive, high-risk node negative	[113]
BETH/NSABP B-44I	Chemotherapy + trastuzumab vs bev + chemotherapy + trastuzumab	IDFS	3500; August 2012	HER2 ⁺ , node positive or high-risk node negative	[114]
NSABP B-46-I	TC or TAC vs bev + TC	IDFS	3900; November 2014	HER2 ⁻ , node positive or high-risk node negative	[115]
BEATRICE	Chemotherapy alone vs bev + chemotherapy	IDFS	2992; July 2014	ER ⁻ /PR ⁻ /HER2 ⁻	[116]
ABCDE	Bev + CM + diet + exercise vs bev + CM + diet vs diet + exercise vs diet	RFS	660; June 2011	HER2 ⁻	[117]

AC: Doxorubicin plus cyclophosphamide; bev: Bevacizumab; CM: Metronomic chemotherapy; DFS: Disease-free survival; IDFS: Invasive disease-free survival; ER: Estrogen receptor; RFS: Recurrence-free survival; TAC: Docetaxel plus doxorubicin plus cyclophosphamide; TC: Docetaxel plus cyclophosphamide.

Table 4

Adverse events (grade ≥ 3) observed in key bevacizumab plus chemotherapy trials in locally recurrent or metastatic breast cancer.

Adverse event	Incidence (%)	AVADO; Phase III [39]										RIBBON-1; Phase III; 15 mg/kg [40]				MO19391; n = 2027; Phase IV; 10 mg/kg or 15 mg/kg [46]
		AVF0776g; Phase I/II; 3 mg/10 mg/20 mg/kg [45]					E2100; Phase III; 10 mg/kg [30]									
		Cap+Bev	Cap	P+Bev	P	D+PL	7.5 mg/kg	15 mg/kg	Cap+Bev	Cap	T+Bev	T	Ant + Bev	Ant		
Hypertension	18.7	17.9	0.5	14.8	0	1.3	0.4	3.2	9.0	1.0	9.0	2.0	11.0	0	2.2	
Proteinuria	2.7	0.9	0	3.5	0	NR	NR	NR	2.0	0	3.0	0	3.0	0	0.7	
Thrombosis/embolism	4	6.9	4.2	2.1	0	0.4	0	0	NR	NR	NR	NR	3.0	1.0	0.5	
Bleeding events	NR	0.4	0.5	0.5	0	NR	NR	NR	NR	NR	5.0	0	NR	NR	0.4	
CHF/ cardiomyopathy	2.7	3.0	1.0	0	0	0	0.8	0	NR	NR	NR	NR	NR	NR	NR	
Nausea	0	2.6	1.9	3.3	1.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.6	
Neuropathy	0	NR	NR	23.5	17.7	NR	NR	NR	3.0	<1%	NR	NR	NR	NR	0.9	
Fatigue	NR	NR	NR	10.7	4.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.0	
Neutropenia	NR	NR	NR	0	0.3	NR	NR	NR	NR	NR	9.0	5.0	NR	NR	8.0	
Any grade decreased LVEF	NR	12.2	14.9	0.8	0.3	NR	NR	NR	NR	NR	3.0	0	NR	NR	NR	
Febrile neutropenia	NR	NR	NR	0.8	0	12	15.2	16.6	NR	NR	8.0	2.0	NR	NR	NR	
GI perforation	NR	NR	NR	0.5	0	0.9	0.4	0.4	NR	NR	NR	NR	NR	NR	NR	
Headache	6.7	1.7	0.5	2.2	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	

Ant: Anthracycline; Bev: Bevacizumab; Cap: Capecitabine; CHF: Congestive heart failure; D: Docetaxel; GI: Gastrointestinal; LVEF: Left ventricular ejection fraction; NR: Not reported; P: Paclitaxel; PL: Placebo; T: Taxane.