

The Intriguing Role of Bevacizumab in Advanced Breast Cancer – The Search Continues

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Abstract

Angiogenesis plays an important role in the biology of tumour progression and therapies that target the vascular endothelial growth factor (VEGF) pathways – ligands, receptors and co-receptors – have become an important treatment for many types of cancer. Bevacizumab, a monoclonal antibody against VEGF, was explored in several randomised Phase III studies conducted in patients with metastatic breast cancer. However, despite bringing improvements in progression-free survival, the use of bevacizumab has not been associated with improvements in overall survival. Further improvements in predictive biomarkers and the development of biology-driven Phase II trials will be critical to help us understand which patients would benefit the most from anti-angiogenic therapy.

Keywords

Bevacizumab, breast cancer, anti-angiogenesis, vascular endothelial growth factor

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Breast cancer continues to be a very prevalent disease worldwide. It is estimated that more than 39,000 women died of breast cancer in the US in 2011.¹ Advances in the treatment of early-stage disease, including screening programmes for breast cancer detection and adjuvant systemic therapies, have improved outcomes for patients. Despite these improvements, however, many women ultimately develop metastatic breast cancer (MBC), which is essentially an incurable disease. The prognosis of patients with MBC has changed little over the past decade; the majority of patients succumb to their disease within two years of diagnosis.^{2–4} Novel treatments for patients with MBC are needed to improve the control of disease and prevent symptoms while minimising toxicity.

Role of Angiogenesis in Cancer Biology

In 1970, Folkman postulated that tumour progression might be dependent on angiogenesis – the formation of new blood vessels.⁵ The hypothesis was that a tumour cannot grow without blood supply and that, therefore, the inhibition of angiogenesis would be an important treatment for all cancers.

Angiogenesis is an important natural process of new blood vessel formation that occurs in the body, both in health and in disease.⁶ The generation and growth of solid tumours depend on an intact vascular supply, which is stimulated by several pro-angiogenic factors. Changes in the finely balanced equilibrium between angiogenic stimulators and inhibitors that regulate angiogenesis are linked to a broad range of angiogenesis-dependent diseases, including both cancer and non-neoplastic diseases.⁷ Angiogenesis is now

recognised as one of the key steps in the pathogenesis of cancer, regulating several events required for tumour development, invasion and metastasis.^{8,9}

One of the most important molecules to stimulate angiogenesis is the vascular endothelial growth factor (VEGF). Moreover, VEGF has autocrine pro-survival effects on tumour cells, protecting them from stresses such as hypoxia, chemotherapy and radiotherapy. This fundamental mechanism in biology describes a multi-step process of new blood vessel formation from existing vasculature, and it is tightly regulated by pro-angiogenic factors involving autocrine and paracrine signalling.¹⁰ To grow and obtain more blood, tumours exert multiple strategies to create or stimulate the formation of blood vessels, including sprouting angiogenesis, vessel co-option, intussusception of existing vessels and recruitment of bone marrow-derived endothelial progenitor cells into growing vessels.¹¹

VEGF is essential for the development of neovasculature in the early stages of tumourigenesis and is thought to play a key role in tumour metastasis. The transition of a tumour from the 'avascular' or 'prevascular' phase to the 'vascular' phase (increased growth and metastatic potential) is termed the 'angiogenic switch'.¹² This switch is considered a hallmark of the malignant process and is believed to be stimulated by an increase in the expression of pro-angiogenic factors (such as VEGF, basic fibroblast growth factor and transforming growth factor beta) and by a decrease in anti-angiogenic factors (such as interferon alpha and thrombospondin 1).^{13,14}

Can Discontinuation of Anti-angiogenic Therapy Lead to Cancer Rebound?

Recently, two preclinical studies suggested that the discontinuation of anti-VEGF pathway inhibition can cause tumour progression.^{15,16} There is also clinical evidence that certain solid tumours can regrow during 'drug holidays' or in patients treated with anti-VEGF monotherapy for renal cell carcinoma.¹⁷ This 'rebound effect' has led to speculation that the more rapid disease progression after cessation of anti-angiogenic therapy might explain instances where improved progression-free survival (PFS) does not correlate with overall survival (OS).¹⁵ However, a recent retrospective meta-analysis of five randomised, placebo-controlled Phase III trials in more than 4,200 patients with breast, colorectal, renal and pancreatic carcinoma treated with bevacizumab demonstrated that disease progression was not accelerated when therapy was stopped prematurely because of adverse events.¹⁸

Bevacizumab Therapy for Breast Cancer Patients Searching for Efficacy Biomarkers

Randomised trials in different epithelial malignancies have demonstrated improvements in PFS and OS in patients receiving anti-VEGF therapies. However, the benefits and toxicities of these agents have been strikingly inconsistent. Despite the thousands of patients who participated in clinical trials, there are no biomarkers that provide clear and convincing evidence to predict benefit from treatment with VEGF inhibitors.

Patients with early-stage breast cancer who have an elevated expression of VEGF are associated with shorter relapse-free survival and OS times, regardless of lymph node status.^{19,20} By an interesting mechanism, the amplification of human epidermal growth factor receptor (HER)-2 in breast cancer induces overexpression of VEGF, suggesting that the induction of angiogenesis may contribute to a worse prognosis in these patients.²⁰ In a recent publication, Linderholm et al. demonstrated that triple receptor-negative breast cancer possesses higher intra-tumoural levels of VEGF and is associated with a shorter OS duration.²¹

Recently, new therapeutic agents that modulate tumour angiogenesis have been developed. Molecules that block the VEGF pathway have shown efficacy in preclinical tumour models, inhibiting tumour angiogenesis and growth. Extensive research has been conducted in the past years to adequately target VEGF by different mechanisms, many of which have been translated to the clinic.⁶ These mechanisms include:

- ligand sequestration;
- external receptor blocking;
- internal receptor blocking (tyrosine kinase inhibitors); and
- inhibition of the VEGF receptor message.⁶

Bevacizumab has been the most studied agent in the field of angiogenesis in multiple cancer types.²² An experimental study showed that bevacizumab neutralised all isoforms of human VEGF with a dissociation constant of 1.1 nmol/l.²³ Another study showed that bevacizumab inhibited VEGF-induced endothelial cell proliferation and migration. Furthermore, bevacizumab led to significantly slower tumour growth in an *in vivo* model of a range of tumour types (including breast cancer).²⁴ The Avastin in combination with herceptin/docetaxel in patients with HER2-positive metastatic

breast cancer (AVEREL) is an ongoing randomised Phase III trial that evaluates bevacizumab in combination with trastuzumab plus docetaxel as first-line therapy for HER2-positive advanced breast cancer. The preliminary results showed that, in patients with high VEGF-A levels, the addition of bevacizumab to the combination of trastuzumab plus docetaxel significantly improved PFS compared with trastuzumab plus docetaxel alone.²⁵

Randomised Phase III Trials Using Bevacizumab in Metastatic Breast Cancer Patients

Started in 1997, several Phase I and II studies of bevacizumab alone and in combination with chemotherapy were performed. They showed that bevacizumab was safe and could be combined with chemotherapy without apparent additional toxicity.^{24,26,27} Based on the results of these studies, Phase III randomised trials have been undertaken to evaluate the role of the drug as first-line therapy in women with MBC. These studies are summarised in *Table 1*.

The first was a randomised Phase III trial of capecitabine alone compared with bevacizumab plus capecitabine in a group of heavily pre-treated breast cancer patients.²⁸ Patients who received the combination therapy had a superior overall response rate (ORR). However, this did not translate into longer PFS and OS, and quality of life was comparable in both treatment groups.

The second was the Eastern cooperative oncology group E2100 study, an open label, Phase III randomised clinical trial in which bevacizumab was added to weekly paclitaxel chemotherapy as first-line therapy for MBC.²⁹ The primary endpoint was PFS, which was significantly longer in patients who received the drug combination than in those who received paclitaxel alone. There was also a significant improvement in the ORR. However, despite the improvement in PFS by more than a mean 5.5 months, there was no improvement in OS. The US Food and Drug Administration (FDA) granted accelerated approval to the combination of bevacizumab and paclitaxel as first-line chemotherapy for patients with HER2-negative MBC in February 2008.

Since then, two Phase III placebo-controlled studies designed to confirm the outcomes of the E2100 trial – the Avastin and docetaxel (AVADO) trial³⁰ and the Regimens in bevacizumab for breast oncology RIBBON-1 trial (chemotherapy [capecitabine, a taxane or an anthracycline] with and without bevacizumab)³¹ – did not demonstrate the magnitude of benefits observed in E2100 despite meeting their predefined endpoints.

The AVADO trial was a Phase III placebo-controlled, randomised study of two doses of bevacizumab (7.5 mg/kg or 15 mg/kg every three weeks) with or without docetaxel (100 mg/m² every three weeks) as first-line therapy for patients with recurrent breast cancer or MBC.³⁰ A longer PFS interval was observed with docetaxel plus bevacizumab at both doses compared with docetaxel alone. The ORR was highest with docetaxel plus bevacizumab at 15 mg/kg. However, there was no statistically significant difference in OS duration between treatment groups. The study showed that the addition of bevacizumab at a dose of 15 mg/kg to docetaxel resulted in a significant increase in PFS.

RIBBON-1 was a randomised, double-blind, placebo-controlled trial. Patients were randomised in a 2:1 ratio to receive either

Table 1: A Summary of Phase III Studies of Bevacizumab in Metastatic Breast Cancer

Trial and Reference	Regimen and Setting	Patient number	Endpoints	Overall Response Rate (%)	Median Progression-free Survival (Months)	Median Overall Survival (Months)
AVF ²⁸	Cap 1,250 mg/m ² twice a day for 14 days followed by a 7-day rest period, with or without Bev 15 mg/kg every three weeks; second- or third-line treatment	462	mPFS, mOS	Bev: 19.8 % versus Cap: 9.1% (p=0.001); investigator assessed, Bev: 30.2 % versus Cap: 19.1 % (p=0.006)	Not increased (Bev: 4.86 versus Cap: 4.17 [HR 0.98, 95 % CI 0.77–1.25, p=0.857])	Not increased (Bev: 15.1 versus Cap: 14.5)
E2100 ²⁹	Pac 90 mg/m ² on Days 1, 8 and 15 every four weeks, with or without Bev 10 mg/kg every two weeks; first-line treatment	722	mPFS, mOS	Bev: 36.9 % versus Pac: 21.2 % (p<0.001)	Bev: 11.8 versus Pac: 5.9 (HR 0.60, p<0.001)	Not increased (Bev: 26.7 versus Pac: 25.2 [HR 0.88, p=0.16])
AVADO ³⁰	Doc 100 mg/m ² combined with Bev 15 mg/kg or 7.5 mg/kg every three weeks or placebo; first-line treatment of HER2-negative tumours	736	mPFS, mOS	Doc plus placebo: 46 % versus Doc plus Bev 7.5 mg/kg: 55 % (p=0.07) and Doc plus Bev 15 mg/kg: 64 % (p<0.001)	Doc plus placebo: 8.2; Doc plus Bev 7.5 mg/kg: 9.0 (HR 0.86, 95 % CI 0.72–1.04, p=0.12); Doc plus Bev 15 mg/kg: 10 (HR 0.67, 95 % CI 0.64–0.93, p<0.001)	Not increased (31 [HR 1.05 for Bev 7.5 mg/kg and 1.03 for Bev 15 mg/kg])
RiBBON-1 ³¹	Cap 2,000 mg/m ² for 14 days, or Tax (Doc 75 mg/m ² or 100 mg/m ² or Nab-pac 260 mg/m ²), or Anthra-based chemotherapy every three weeks, with or without Bev 15 mg/kg every three weeks; first-line treatment of HER2-negative tumours	1,237	mPFS, mOS	Cap plus Bev: 35.4 % versus Cap alone 23.6 % (p=0.0097); Tax or Anthra plus Bev: 51.3 % versus Tax or Anthra alone 37.9 % (p=0.0054)	Cap: increased from 5.7 to 8.6 (HR 0.69, 95 % CI 0.56–0.84, p<0.001); Tax/Anthra: increased from 8.0 to 9.2 (HR 0.64, 95 % CI 0.52–0.80, p<0.001)	Not increased (Cap: HR 0.85, 95 % CI 0.63–1.14, p=0.27; Tax/Anthra: HR 1.03, 95 % CI 0.77–1.38, p=0.83)
RiBBON-2 ⁴²	Bev 10 mg/kg every two weeks or 15 mg/kg every three weeks (depending on chemotherapy regimen) or placebo with one of the following: • Tax (Pac 90 mg/m ² /week for three weeks of a four-week cycle, or Pac 175 mg/m ² , or Nab-pac 260 mg/m ² , or Doc 75–100 mg/m ² [the last three given every three weeks]) • Gem 1,250 mg/m ² on Days 1 and 8 of a three-week cycle • Cap 2,000 mg/m ² on Days 1–14 of a three-week cycle • Vin 30 mg/m ² /week Second-line treatment of HER2-negative tumours	684	mPFS, mOS	Placebo: 29.6 % and Bev: 39.5 % (p=0.0193)	Placebo: 5.1 and Bev: 7.2 (HR 0.78, 95 % CI 0.64–0.93, p=0.0072)	Not increased (HR 0.90, 95 % CI 0.71–1.14, p=0.37)
AVEREL ²⁵	Tras 6 mg/kg, Doc 100 mg/m ² , with or without Bev 15 mg/kg every three weeks; first-line treatment of HER2-positive tumours	424	mPFS, mOS	Investigator assessed, Bev: 74.3 % versus Tras/Doc: 69.9 % (p=0.3492); independently reviewed, Bev: 76.5% versus Tras/Doc: 65.9% (p=0.0265)	Investigator assessed, Bev: 16.5 versus Tras/Doc: 13.7 (HR 0.82, 95 % CI 0.65–1.02, p=0.08); independently reviewed, Bev: 16.8 versus Tras/Doc: 13.9 (HR 0.72, 95 % CI 0.54–0.94, p=0.02)	Not increased (unstratified analysis, HR 1.01, 95 % CI 0.74–1.38, p=0.95; stratified analysis, HR 0.94, 95 % CI 0.68–1.30, p=0.71)

Anthra = anthracycline; AVF = A study of rhumab vascular endothelial growth factor (bevacizumab) in combination with chemotherapy in patients with previously treated breast cancer; AVADO = Avastin and docetaxel trial; AVEREL = Avastin in combination with herceptin/docetaxel in patients with HER2-positive metastatic breast cancer; Bev = bevacizumab; Cap = capecitabine; CI = confidence interval; Doc = docetaxel; E2100 = Eastern cooperative oncology group study; Gem = gemcitabine; HER = human epidermal growth factor receptor; HR = hazard ratio; mPFS = median progression-free survival; mOS = median overall survival; Nab-pac = nanoparticle albumin-bound paclitaxel; ORR = overall response rate; Pac = paclitaxel; RiBBON = Regimens in bevacizumab for breast oncology; Tax = taxane; Tras = trastuzumab; Vin = vinorelbine.

bevacizumab (15 mg/kg every three weeks) in addition to standard first-line chemotherapy by physician choice, or placebo plus chemotherapy, as first-line treatment for MBC.³¹ The PFS and ORR were superior for the group treated with bevacizumab, regardless of the standard chemotherapy regimen used. There were no statistically significant differences in OS and one-year survival rates. The toxicity profiles were similar to those seen in other trials using bevacizumab.

Is Overall Survival the Most Important Endpoint in Metastatic Breast Cancer Patients?

This lack of OS benefit and the relatively inferior results of the confirmatory trials^{30,31} created uncertainty regarding the utility of bevacizumab in MBC. When observing different outcomes in clinical trials with similar designs, it is essential to examine the potential causes of such differences. In this case, one of the points to consider is the type and schedule of chemotherapy that were used in the

E2100 trial. Weekly paclitaxel is superior to three-weekly paclitaxel; it led to a doubling of time to progression and pathological complete response in patients with metastatic and early-stage breast cancer, respectively.³² Furthermore, the good tolerance of this regimen allows patients to receive multiple cycles, which is not the case with the maximum doses of docetaxel or anthracycline-based regimens. Thus, the success of combining VEGF-targeted therapies and chemotherapy may not be random, but is likely to depend on the type of chemotherapy used.³³

Another important point to consider is the trial design and how it can impact the interpretation of OS outcomes. Studies that give patients the possibility to cross over upon progression cannot accurately report OS, given that a significant proportion of patients will receive bevacizumab at some point in their treatment, either as first- or as second-line therapy. Indeed, the AVADO and RiBBON-1 trials had a high percentage of post-progression cross-over rates.³⁴

In July 2010, based on the results of AVADO and RiBBON-1, the Oncologic Drugs Advisory Committee of the FDA's Center for Drug Evaluation and Research voted 12 to one to recommend withdrawing the conditional approval of bevacizumab in combination with paclitaxel as first-line therapy for HER2-negative MBC. It is important to mention that, as of June 2012, the National Comprehensive Cancer Network and the Centers for Medicare & Medicaid Services continue to support the indication of MBC for first-line bevacizumab plus paclitaxel.³⁵ Moreover, based on the results of the RiBBON-1 trial, the European Medicines Agency has chosen to maintain the indication of MBC for bevacizumab plus capecitabine.³⁵

More recently, the Avastin Therapy for Advanced Breast Cancer (ATHENA) study group reported the results of a study that included 2,251 patients with HER2-negative locally recurrent or metastatic breast cancer who received bevacizumab (10 mg/kg every two weeks or 15 mg/kg every three weeks) plus taxane-based or other non-anthracycline chemotherapy as first-line therapy.³⁶ This was an open-label study whose primary endpoint was safety and secondary endpoint was PFS. The median PFS was 9.5 months (95 % confidence interval [CI] 9.1–9.9) and the ORR was (52 %), similar to those seen in the Phase III trials evaluating the approved bevacizumab dose combined with a taxane.^{30,31,37} These findings therefore support the clinical benefit seen in the randomised trials of bevacizumab combined with taxane-based chemotherapy. An important finding reported by the ATHENA study group is the feasibility of administering bevacizumab with taxane-based combination therapy, normally associated with greater toxicity than single-agent taxane.^{38,39}

In the second-line treatment of MBC, many agents – including antitubulin drugs and antimetabolites – have demonstrated activity but none is clearly superior to the others.^{38,40,41} The RiBBON-2 trial was designed to evaluate the efficacy and safety of combining bevacizumab with chemotherapies commonly used for the second-line treatment of patients with HER2-negative MBC who have received one previous cytotoxic regimen in the metastatic setting.⁴² It was a randomised, double-blind, placebo-controlled Phase III trial. The primary endpoint was PFS per investigator assessment. Secondary endpoints included ORR, OS and PFS within individual chemotherapy regimen, one-year survival rate, duration of objective response and safety. RiBBON-2 enrolled 684 patients (225 to the placebo arm and 459 to the bevacizumab arm) and

demonstrated that the combination of bevacizumab with chemotherapy improved PFS. The safety profile for bevacizumab when combined with all the chemotherapies was consistent with that observed in prior Phase III trials. Taken together, these data provide a rationale for adding bevacizumab to second-line cytotoxic therapy for patients with HER2-negative MBC.

Adding to the controversy, further results of the AVEREL study were recently reported and showed that adding bevacizumab to standard therapy prolongs PFS by about three months in women with HER2-positive locally recurrent or metastatic breast cancer.²⁵ This benefit of added bevacizumab was similar across most subgroups, except among patients aged 65 years or older and those with measurable disease, in which the benefit was greater. The ORR was significantly higher in the bevacizumab group.

Conclusions and Future Directions

Anti-angiogenic therapy that targets VEGF or its receptors has become a mainstay of therapy in patients with glioblastoma or colorectal, lung, kidney or ovarian cancer. In the last 10 years, more than 2,000 trials have been conducted with agents that target the VEGF pathway.⁴³ In contrast with the enthusiasm for VEGF-targeted therapies in 2004 and 2005, we found that these studies showed modest benefits for patients treated with anti-VEGF agents and that, with a few exceptions (renal cell carcinoma and hepatocellular carcinoma), combination with standard chemotherapy is necessary to improve efficacy.

In the case of breast cancer, studies show that bevacizumab fails to improve OS compared with standard chemotherapy. Moreover, the magnitude of benefit observed in the E2100 trial was not replicated in the two post-approval studies designated to confirm its outcomes (AVADO and RiBBON-1). One explanation is that the role of angiogenesis in breast cancer has been overestimated. In 1997, on the basis of immunohistochemistry results, Relf and colleagues showed the overexpression of six different angiogenic factors – one of which was VEGF – in multiple tumour tissues samples obtained from patients with early breast cancer.¹⁹ Conversely, in 2009, Boneberg and collaborators demonstrated that the levels of messenger RNA expression of a dozen different pro-angiogenic growth factor genes – including VEGF – were greater in adjacent normal tissues than in the primary tumour tissue.⁴⁴ The authors concluded that primary breast tumours are not a site of active angiogenesis. The role of pro- and anti-angiogenic factors in metastatic tissues needs to be elucidated.

One remarkable difference with other targeted therapies is that angiogenesis is an ubiquitous target. Furthermore, preclinical data suggest that the tumour vasculature is not the same in all cases and that there are molecular differences in tumour endothelial cells from a variety of tumours.^{45,46} Because of the lack of reproduction of the E2100 trial results, the 5.5 month improvement in PFS demonstrated by that trial has been interpreted by some authors as an outlier.⁴⁷

The limited success of anti-angiogenic therapy in breast cancer highlights the need for continued basic science investigation and clinical trials. The type of study design and how we measure success will be critical for the next generation of clinical trials using anti-VEGF therapy. ■

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