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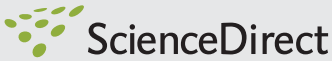

Review of bevacizumab in the treatment of metastatic breast cancer

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ABSTRACT

Vascular endothelial growth factor (VEGF) inhibition is a rational therapeutic approach in breast cancer because VEGF plays an important role in tumour blood vessel growth, tumour progression and metastasis. Bevacizumab is a recombinant humanised antibody targeted at VEGF. As VEGF is overexpressed in early tumour development, there is a strong rationale for studies using bevacizumab in a first-line setting. The E2100 trial demonstrated significantly greater progression-free survival and overall response rates with a bevacizumab plus paclitaxel combination compared with paclitaxel alone as first-line therapy in previously untreated metastatic breast cancer patients. Other studies in heavily pretreated patients have shown that bevacizumab in combination with capecitabine confers varying survival benefits, which might be due to the decreased significance of VEGF in advanced stages of tumour development.

1. Introduction

Vascular endothelial growth factor (VEGF) expression is increased in many tumour types including breast cancer.[1] In breast cancer, this increase is associated with poor clinical outcome, including decreased disease-free and overall survival.[2–4] These observations suggest that inhibition of VEGF could be a rational therapeutic approach for the treatment of breast cancer. This view was further supported by animal studies, in which anti-VEGF treatment using A4.6.1, an anti-VEGF monoclonal antibody, caused significant suppression of angiogenic activity and tumour growth rates in human breast tumour xenografts in nude rodents.[5,6] Bevacizumab is a recombinant humanised version of A4.6.1 that is effective in the treatment of metastatic colorectal cancer, non-small cell lung cancer and other solid tumours, and which is now being investigated for its effects in breast cancer.

2. Angiogenic activity in human breast cancer

2.1. Vascular endothelial growth factor and tumour growth

Breast cancer progression is accompanied by the production of a wide array of pro-angiogenic growth factors that promote and support tumour growth. Once tumours exceed a size of 2–3 mm they need an adequate supply of nutrients and oxygen to progress further. Hypoxia-induced signals cause the secretion of VEGF, which acts as a paracrine factor to stimulate endothelial cell proliferation and blood vessel formation. The access of tumours to newly formed vessels is not only the basis for tumour growth, but also allows haematogenic

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metastasis. In 1971 Folkman postulated that tumours undergo a switch to an angiogenic phenotype.[7] While VEGF may be rate-limiting in the early stages of tumour growth, a multitude of additional factors are involved in stimulating further angiogenesis, including acidic and basic fibroblast growth factor, transforming growth factor β1, placental growth factor, platelet-derived endothelial cell growth factor and pleiotrophin.[8] Clearly, the inhibition of VEGF alone can only be beneficial for a period of time when other pro-angiogenic factors are either not expressed or are regulated by VEGF. These observations provide support and justification for targeting tumour metastases when they are most susceptible to anti-VEGF therapy. Therefore, it may be hypothesized that the greatest efficacy of anti-VEGF therapy can be expected during early treatment of metastatic breast cancer (MBC).

2.2. *Vascular endothelial growth factor and oestrogen*

A complex relationship between oestrogen, the oestrogen receptor and VEGF has been observed in several preclinical models. It was shown in breast cancer cell lines that oestrogen induces VEGF expression at the transcriptional level through oestrogen receptors.[9] Overexpression of VEGF not only enhances oestrogen-dependent tumour growth, but also has an oestrogen-independent effect through an autocrine mechanism of growth stimulation.[10] Combined inhibition of the oestrogen receptor and VEGF has been tested for efficacy in preclinical experiments and is presently being tested in clinical trials. The common combined use of fulvestrant (an oestrogen receptor inhibitor) and bevacizumab has demonstrated greater loss of blood vessel density in tumours compared with either single agent alone.

2.3. *Effects of bevacizumab on blood vessel architecture*

In addition to the effect bevacizumab has on blood vessel growth, there is some evidence (much of it from colorectal cancer studies) that bevacizumab also changes the abnormal chaotic and hyperpermeable structure of tumour blood vessels to a more normalised structure (reduced vessel diameter, density and permeability).[11] Specifically, the bevacizumab-induced decrease in vessel permeability might help to reduce the high interstitial fluid pressure normally found in tumours and reinstate normal flow of fluid and macromolecules in blood vessels, thereby also increasing the transport of drugs to the tumour.[12,13]

2.4. *Clinical side-effects of bevacizumab*

Bevacizumab has an acceptable profile of side-effects that can vary between different tumour entities.[14–16] Hypertension and proteinuria are among the most frequent side-effects. Grade 3/4 hypertension occurs at a rate of 7–16%, but is manageable by standard oral antihypertensive medication in most patients. Proteinuria is observed at a rate of 20–40% (all grades), but grade 3/4 proteinuria or nephrotic syndrome are rare events (1–3%). Arterial thromboembolic events occur at a low frequency (<5%) and require that patients with a known history of arterial thromboembolic events are excluded from treatment with bevacizumab. Grade 3/4 bleeding events occur at a rate of <5% and have specifically been reported for lung and gastrointestinal (GI) cancer when intracavitary tumours were present.[14,15] GI perforations are life-threatening events, and have predominantly been observed in GI cancers such as colorectal cancer (incidence 1.5%), and in ovarian cancer (incidence 11.4%).[14,17] Since bevacizumab may impair wound healing, it is necessary to keep strict intervals between major surgical interventions and bevacizumab exposure.

3. Bevacizumab for metastatic breast cancer

3.1. *Single-agent therapy*

A phase I/II trial of bevacizumab was conducted in patients with pretreated MBC, most of whom had previously received anthracyclines and/or taxanes.[18] Patients received one of three doses of bevacizumab: 3 mg/kg ($n = 18$), 10 mg/kg ($n = 41$) or 20 mg/kg ($n = 16$) intravenously bi-weekly until disease progression or to a maximum of 13 doses. The objectives of this study were to evaluate the efficacy and safety of bevacizumab as a single agent for the treatment of MBC. The primary efficacy endpoint was objective response rate. Tumour response was assessed on days 70 and 154 after starting treatment. Patients who had stable disease or better were eligible for continued bevacizumab therapy in a separate extension study.

Of the 75 patients receiving bevacizumab, 7 (9.3%) had an objective response; 1 patient (1.3%) had a complete response in the 10 mg/kg arm and 6 (8%) patients had a partial response.[18] Patients who responded to bevacizumab therapy had a smaller tumour burden, lower ECOG (Eastern Cooperative Oncology Group) scores and higher albumin levels than the overall study population. The median duration of a confirmed response was 5.5 months, and 17% of patients had stable disease or maintained a response after 5 months of bevacizumab therapy. The median time to progression was 2.4 months, and was similar in each of the three arms. The median survival time was 10.2 months. The most frequently reported side-effects, such as hypertension, proteinuria, thrombosis and bleeding, were not significantly different between arms, and there were few grade 3/4 side-effects.

Table 1 – Efficacy of bevacizumab in combination with chemotherapy

Endpoint	Treatment					
	Capecitabine [a]	Capecitabine + bevacizumab [a]	*p*-value	Paclitaxel [b]	Paclitaxel + bevacizumab [b]	*p*-value
ORR (%)	9.1	19.8	0.001	21.2	36.9	<0.001
PFS (months)	4.2	4.9	NS	5.9	11.8	<0.001
OS (months)	14.5	15.1	NS	25.2	26.7	0.160

Data from Miller et al. (2007) [16] and Miller et al. (2005). [23]
NS, not significant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a] A study performed in previously treated patients.
[b] Evaluated as initial treatment for metastatic breast cancer.

3.2. *Combination therapies*

Bevacizumab has been combined in several phase I/II clinical trials with either vinorelbine, docetaxel, trastuzumab or letrozole, and has shown good response rates and tolerability in MBC patients. [19–22] Most high-risk patients have received anthracycline-based chemotherapy during perioperative treatment of primary breast cancer. Since taxanes are the most active agents in the treatment of breast cancer there is a good rationale to offer taxanes as first-line therapy, specifically to patients with symptomatic or rapidly progressing disease. Capecitabine, by contrast, is an agent that has shown reproducible activity in intensively pretreated patients previously exposed to anthracyclines and taxanes. Therefore, this section will now focus on bevacizumab in combination with capecitabine and/or a taxane.

Bevacizumab plus capecitabine

Miller et al. conducted a phase III study of bevacizumab (15 mg/kg IV every 3 weeks) in combination with capecitabine (2500 mg/m^2/day orally for 2 weeks of every 3-week cycle, $n = 232$) versus capecitabine alone (2500 mg/m^2/day orally for 2 weeks of every 3-week cycle, $n = 230$) in heavily pretreated MBC patients until disease progression. [23] The primary endpoint of this trial was progression-free survival (PFS) and the secondary endpoints were safety, objective response rate and overall survival.

Although the addition of bevacizumab to capecitabine did not improve PFS (hazard ratio 0.98, $p = 0.857$), there was an absolute increase of approximately 11% in overall response rate compared with capecitabine alone (19.8% vs. 9.1%, $p = 0.001$). Similar to PFS, the overall survival for both arms was comparable (see Table 1). Bevacizumab did not have a major impact on chemotherapy-associated toxicity. As a consequence, diarrhoea, stomatitis, or hand-foot syndrome, side-effects notably associated with capecitabine, were not affected by the addition of bevacizumab. Side-effects, such as hypertension, proteinuria and thrombotic events, were, however, more frequent in patients receiving bevacizumab (see Table 2). It remains unclear why the addition of bevacizumab to capecitabine failed to improve PFS despite its positive effect on tumour response. However, it could be hypothesized that VEGF alone decreases in importance when more numerous and redundant pathways of angiogenesis become effective in the later stages of tumour progression. [8] As a consequence bevacizumab might be more effective if it is used in the treatment of less advanced disease.

At the 2007 ASCO (American Society of Clinical Oncology) Annual Meeting, Sledge et al. presented the results of the XCaliBr (Xeloda in Combination with Avastin as First-Line Treatment for HER2-Negative Metastatic Breast Cancer) trial investigating bevacizumab (15 mg/kg IV every 3 weeks) plus a lower dose of capecitabine (1000 mg/m^2 twice daily for 2 weeks of every 3-week cycle) as first-line treatment for human epidermal growth factor receptor (HER)2-negative MBC patients ($n = 106$). [24] Time to tumour progression (TTP) was evaluated as the primary endpoint. The median TTP was 5.7 months and thereby the trial met its predefined endpoint (TTP >4 months). A subgroup analysis revealed

Table 2 – Bevacizumab-associated side-effects (addition of bevacizumab to capecitabine)

Side-effect	Incidence			
	Capecitabine + bevacizumab ($n = 229$)		Capecitabine ($n = 215$)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Hypertension	17.9	0.0	0.5	0.0
Proteinuria	0.9	0.0	0.0	0.0
Bleeding	0.4	0.0	0.5	0.0
Thrombotic event	3.9	1.7	2.3	1.4
Pulmonary embolism	0.0	1.3	0.0	1.4

Data from Miller et al. (2005). [23]

Table 3 – Bevacizumab-associated side-effects (addition of bevacizumab to paclitaxel)

Side-effect	Incidence				
	Paclitaxel + bevacizumab ($n=365$)		Paclitaxel ($n=346$)		p-value
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	
Hypertension	14.5	0.3	0.0	0.0	<0.001
Proteinuria	2.7	0.8	0.0	0.0	<0.001
Haemorrhage	0.5	0.0	0.0	0.0	–
Thrombosis or embolism	1.6	0.5	0.6	0.9	–
Cerebrovascular ischaemia	0.8	1.1	0.0	0.0	0.020
Headache	2.2	0.0	0.0	0.0	0.008
Gastrointestinal perforation	0.5	0.0	0.0	0.0	–

Data from Miller et al. (2007).[16]

that oestrogen receptor-positive patients had a much longer TTP (8.9 months) compared with oestrogen receptor-negative patients (4.0 months). Although this result needs to be treated with caution it might be significant with regard to the known effect of oestrogen on VEGF expression.

Bevacizumab plus paclitaxel

The E2100 trial randomised patients with previously untreated locally recurrent or metastatic disease to either bevacizumab (10 mg/kg bi-weekly) plus paclitaxel (90 mg/m^2/week for 3 weeks of a 4-week cycle, $n=368$) or paclitaxel alone (90 mg/m^2/week for 3 weeks of a 4-week cycle, $n=354$).[16] The primary endpoint was PFS, and the secondary endpoint was overall survival. The percentage of oestrogen-receptor-positive patients was approximately 60% in both arms, and HER2-positive patients constituted <2% of patients in each arm. Prior exposure to taxanes and anthracyclines was equally distributed between arms.

There was a significantly higher median PFS in the combination arm than in the paclitaxel-alone arm (11.8 months vs. 5.9 months; hazard ratio for progression 0.60; $p<0.001$) (see Table 1). An effect of this magnitude had previously only been observed with trastuzumab treatment.[25,26] A subgroup analysis indicated that a benefit from bevacizumab was evident in all patient groups. Patients who had received previous adjuvant chemotherapy appeared to receive the greatest benefit from the combination of bevacizumab plus paclitaxel compared with the paclitaxel-alone arm. In patients pretreated with adjuvant taxanes, the addition of bevacizumab to paclitaxel prolonged PFS from 3.0 to 12.0 months (HR = 0.46, $p<0.001$). Further subgroup analyses indicated that the beneficial effect of the bevacizumab plus paclitaxel combination declined with increasing age.

There was a significantly higher overall response rate in the combination arm compared with the paclitaxel-alone arm (36.9% vs. 21.2%, $p<0.001$). However, median overall survival was not significantly different between the combination and paclitaxel-alone arms (26.7 vs. 25.2 months, respectively, $p=0.16$), although there was a significantly higher 12-month survival rate in the combination arm (81.2% vs. 73.4%, $p=0.01$), the clinical relevance of which is questionable (see Table 1). In terms of safety and tolerability, the combination arm was associated with higher levels of hypertension, proteinuria, headache, and cerebrovascular ischaemia than the paclitaxel-alone arm (see Table 3). The greater incidence of sensory neuropathy may be related to the longer duration of treatment observed in the combination arm.

Link et al. investigated bevacizumab in combination with albumin-bound paclitaxel in 27 heavily pre-treated MBC patients who had previously received $\geqslant 3$ chemotherapy regimens.[27] Patients were treated with one of two schedules: bevacizumab 10 mg/kg bi-weekly plus either albumin-bound paclitaxel 80–125 mg/m^2 on days 1, 8 and 15 or albumin-bound paclitaxel 170–200 mg/m^2 bi-weekly. A complete response was seen in 3 patients (11%) and a partial response in 13 patients (48%), with an overall response rate of 59%. Toxicity was acceptable and there was only 1 patient who discontinued therapy, and this was due to haemorrhage into a metastatic brain lesion.

Triplet combination therapy

The North Central Cancer Treatment Group combined a docetaxel (75 mg/m^2 on day 1) plus capecitabine (825 mg/m^2 on days 1 and 14) regimen with bevacizumab (15 mg/kg every 3 weeks) in first-line MBC patients ($n=46$).[28] The median time to disease progression was 8.4 months and the overall response rate was 53%. Toxicity, as expected from this combination, was high: the grade 3/4 neutropenia rate was 77% and grade 3/4 diarrhoea rate 18%.

3.3. Current trials

Following the positive results of the E2100 study, bevacizumab plus either taxane or anthracycline regimens are being investigated in a number of trials.

The AVADO trial is a randomised, double-blind, placebo-controlled phase III trial designed to investigate

docetaxel in combination with bevacizumab as first-line therapy in MBC patients ($n = 705$). The trial has three arms comparing docetaxel (100 mg/m^2 every 3 weeks) plus two different doses of bevacizumab (7.5 and 15 mg/kg every 3 weeks) versus docetaxel plus placebo. The primary endpoint is PFS and secondary endpoints include overall response rate, duration of response, time to treatment failure, overall survival, safety and quality of life. This trial is ongoing, but has already completed recruitment. [29] The results of the AVADO trial are eagerly awaited since they are needed to verify the data obtained in the E2100 study.

The RIBBON-1 trial is a phase III trial in previously untreated MBC patients ($n = 1200$), designed to investigate the efficacy and safety of bevacizumab 15 mg/kg every 3 weeks in combination with either a taxane- or anthracycline- or capecitabine-based regimen compared with chemotherapy alone. The primary endpoint is PFS and secondary endpoints include objective response, 1-year survival rate and overall survival. As a companion to the RIBBON-1 trial, the RIBBON-2 trial is treating pretreated MBC patients with either bevacizumab or placebo in combination with chemotherapy (taxane, gemcitabine, vinorelbine or capecitabine) until disease progression. This trial has an estimated enrolment of 700 patients and will evaluate PFS as a primary endpoint. [29]

The AVEREL study is a phase III trial performed in HER2-positive MBC patients ($n = 320$) comparing docetaxel plus trastuzumab with the experimental combination of docetaxel plus trastuzumab plus bevacizumab. At disease progression, patients in the control arm will not be permitted to cross over to the bevacizumab arm. PFS will be investigated as a primary endpoint.

4. Conclusion

We now have sufficient evidence to demonstrate the efficacy of first-line treatment of MBC with bevacizumab, specifically in combination with paclitaxel. There is some benefit shown in all analysed subgroups, with the greatest benefit seen in patients who have received a prior treatment regimen, specifically taxane chemotherapy. Patients should receive bevacizumab-based treatment with the use of a taxane as required for first-line treatment of MBC. As with other treatments, patient selection is an important factor, and patients who are symptomatic, have rapidly progressive disease and are HER2 negative will benefit most from the combination of a taxane with bevacizumab.

Conflict of interest statement

Dr Heinemann received honoraria for talks at meeting symposia from Roche and Eli Lilly and Company and received honoraria for participation at advisory boards from Roche and Eli Lilly and Company. Dr Heinemann received research funding for clinical trials from Roche and Eli Lilly and Company. Neither Dr Heinemann nor any of his family members own shares in these companies.

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