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Clinical data for anti-angiogenic agents in previously treated advanced breast cancer

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ABSTRACT

The vascular endothelial growth factor (VEGF) ligand and its receptor represent key targets for anti-angiogenic agents in the therapy of breast cancer. Such agents include bevacizumab, sunitinib, sorafenib and vandetanib; all of which are currently in clinical development for breast cancer. The most extensively studied of these agents is bevacizumab, and a phase III trial of this agent in combination with capecitabine demonstrated a significant improvement in response rate for the combination regimen compared with capecitabine alone in patients previously treated for metastatic breast cancer. However, the lack of a corresponding significant improvement in progression-free and overall survival may be attributable to the nature of breast cancer tumour progression. Preclinical studies suggest that VEGF may be the predominant pro-angiogenic factor expressed at early disease stages, whereas other angiogenic factors may be more important in advanced disease. Clinical evidence is not yet available, but this theory suggests that bevacizumab may be more effective when used earlier in the course of breast cancer therapy.

1. Introduction

Metastatic breast cancer is considered incurable, with a median survival of 2–3 years from the time of diagnosis;[1] treatment aims in these patients therefore include enhancing quality of life, delaying disease progression, and prolonging survival.[2] The choice of treatment for patients with metastatic breast cancer is not only influenced by the disease stage, prior therapies, steroid hormone receptor and human epidermal growth factor receptor type-2 (HER2) status, but also by physician and patient preference. Options for patients with metastatic breast cancer include surgery and radiotherapy in specific situations, but predominantly endocrine therapy (in patients with hormone receptor-positive disease), chemotherapy (anthracyclines and taxanes are considered the most active), targeted biological agents (e.g. trastuzumab for HER2-positive disease), and bisphosphonate therapy (in the case of bone involvement).

Advances in our understanding of the aetiology of metastatic breast cancer have resulted in several recent notable improvements in its treatment. These include the introduction of novel targeted agents, such as the aromatase inhibitors and trastuzumab, which have resulted in a significant prolongation of survival.[3–5] Trastuzumab is a monoclonal antibody that targets HER2 and is therefore effective in those 25% of breast cancer patients whose tumours express high levels of this receptor.[6] Trastuzumab is approved not only for HER2 overexpressing metastatic breast cancer but also for early breast cancer.[7]

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Table 1 – Inhibitors of the VEGF ligand or its receptor currently in clinical development for breast cancer

Agent	Type of molecule	Target	Development phase in breast cancer	Settings under investigation
Bevacizumab (Avastin®)	Monoclonal antibody	VEGF	Launched	mBC, adjuvant, neoadjuvant
Sunitinib (Sutent®)	Tyrosine kinase inhibitor	VEGF receptor-1, -2, -3; PDGFR-β; c-Kit; Flt-3	III	mBC, neoadjuvant
Sorafenib (Nexavar®)	Tyrosine kinase inhibitor	Raf-1; VEGF receptor-2, -3	II	mBC, adjuvant, neoadjuvant
Vandetanib (Zactima™)	Tyrosine kinase inhibitor	VEGF receptor-2, -3; EGFR	II	mBC, neoadjuvant
Cediranib (Recentin™)	Tyrosine kinase inhibitor	VEGF receptor-1, -2, -3	II	mBC
Axitinib	Tyrosine kinase inhibitor	VEGF receptor-1, -2, -3; PDGFR-β; c-Kit	II	mBC
Motesanib	Tyrosine kinase inhibitor	VEGF receptor-1, -2, -3; PDGFR-β; c-Kit; Ret	II	mBC
Vatalanib	Tyrosine kinase inhibitor	VEGF receptor-1, -2; c-Kit; c-Fms	II	mBC
Aflibercept/VEGF-Trap	Soluble VEGF receptor	VEGF	II	mBC
Pazopanib	Tyrosine kinase inhibitor	VEGF receptor-1, -2, -3; PDGFR-α, β; c-Kit	II	mBC, neoadjuvant
SU-14813	Tyrosine kinase inhibitor	VEGF receptor-1, -2, -3; PDGFR-β; c-Kit; Flt-3	II	mBC

VEGF = vascular endothelial growth factor; PDGFR = platelet-derived growth factor receptor; EGFR = epidermal growth factor receptor; mBC = metastatic breast cancer.

Solid tumours need to stimulate angiogenesis (the production of new vasculature) in order to grow beyond a diameter of 1–2 mm, the distance across which oxygen and nutrients are able to diffuse.[8] In addition to promoting tumour growth, angiogenesis is essential for metastatic spread.[9] A multitude of studies have investigated the relationship between tumour microvessel density (MVD) and prognosis in breast cancer, some of which found evidence for a correlation between higher MVD and poorer prognosis,[10,11] while others failed to establish such a link.[12,13] Higher vascular endothelial growth factor (VEGF) levels are correlated with expression of mutant p53 in primary breast cancer; combining these two variables provides important prognostic information.[14] The inhibition of angiogenesis has therefore long been suggested as a potential strategy for anticancer therapy.[15] Agents targeting angiogenic pathways show promise in the breast cancer setting and are currently in the development process.

2. Anti-angiogenic agents in development for breast cancer

Many therapeutic agents that inhibit angiogenesis are currently in development for breast cancer and several of these agents work by inhibiting the VEGF ligand or its receptors (Table 1). VEGF is often overexpressed in breast cancer.[16] Indeed, it is an independent prognostic factor in invasive disease and several studies have found an association between high levels of VEGF and reduced relapse-free and overall survival in both node-positive and -negative disease.[17–22]

Bevacizumab is a humanised recombinant monoclonal antibody that specifically blocks the binding of VEGF to high-affinity receptors.[23] It is the only anti-angiogenic agent to date that has demonstrated substantial clinical efficacy when used with conventional chemotherapy in breast cancer.[24]

In addition to agents specifically designed to target angiogenesis, metronomic dosing schedules – the administration of relatively low, but frequent doses – of conventional chemotherapeutic agents (e.g. paclitaxel[25] and cyclophosphamide,[26] also shown to be *in-vivo* inhibitors of angiogenesis) have been proposed as having prolonged anti-angiogenic effects. The lower doses of chemotherapy enable weekly schedules to be administered without the need for treatment breaks due to adverse events. In contrast to conventional dosing regimens, which enable recovery of tumour vasculature during treatment breaks, the anti-angiogenic effects of metronomic schedules of low-dose chemotherapeutic agents are maintained. Although few clinical data support this hypothesis, one group has reported reduced levels of circulating VEGF relative to baseline measurements in patients with advanced breast cancer who received a metronomic schedule of cyclophosphamide and methotrexate for 2 months.[27] This type of treatment scheduling may be further enhanced with the addition of a VEGF inhibitor, such as bevacizumab.

2.1. *Bevacizumab in previously treated metastatic breast cancer*

A phase I/II dose escalation trial of single-agent bevacizumab examined three doses (3, 10, and 20 mg/kg

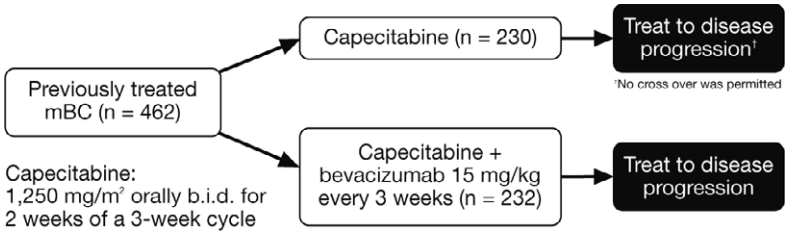

Fig. 1 – Schematic diagram illustrating the design of the AVF2119g phase III trial of capecitabine with or without bevacizumab in patients with previously treated metastatic breast cancer (mBC). [28]

every 2 weeks) in 75 patients who had received prior therapy for metastatic breast cancer.[23] Objective response rates were 5.6%, 7.3%, and 6.3% for patients receiving bevacizumab at 3, 10 and 20 mg/kg doses, respectively. The duration of median response was 3.1, 5.6, and 8.0 months, and median survival was 14.0, 12.8, and 7.6 months, respectively. When data were combined for all three treatment arms, the overall response rate was 6.7% (16% of patients had stable disease or better at day 154 of therapy), the median duration of response was 5.6 months and median overall survival was 10.2 months.[23]

Bevacizumab was generally well tolerated; adverse events were consistent with those previously observed with this agent, including hypertension, minor bleeding, and proteinuria. Four patients who received bevacizumab at 20 mg/kg reported severe headaches associated with nausea and vomiting. This was not seen at either of the lower doses and this toxicity was considered dose limiting. The sample size was too small to enable conclusions to be drawn on the efficacy of the different doses, however, the greater incidence of adverse events at the highest dose of 20 mg/kg led to the recommendation of 10 mg/kg every 2 weeks as the dose for further investigation in this indication.[23]

A dose and schedule of bevacizumab with similar intensity was used in a phase III trial (AVF2119g) to investigate the efficacy and safety of capecitabine with or without bevacizumab in 462 patients who had received previous therapy for metastatic breast cancer (Figure 1).[28] Patients eligible for entry into the trial had received treatment with both an anthracycline and a taxane, and no more than two chemotherapy regimens for metastatic disease. Alternatively, patients who had relapsed within 12 months of adjuvant anthracycline and taxane therapy were eligible, even without receiving prior chemotherapy in the metastatic setting. This poor prognosis subset comprised approximately 15% of the study population. The design of the study did not permit patients who were randomised to receive single-agent therapy with capecitabine to cross over and receive bevacizumab at any time.[28]

A significant increase in response rate was observed in patients who received capecitabine plus bevacizumab compared with capecitabine alone as determined by the investigators (30.2% vs. 19.1% [$p = 0.006$]), as well as by an independent review facility (19.8% vs. 9.1% [$p = 0.001$]), while no significant differences between the treatment arms were reported for progression-free survival (4.9 vs. 4.2 months; hazard ratio = 0.98), the primary trial endpoint, or for overall survival (15.1 vs. 14.5 months) (Table 2). Adverse events attributed to bevacizumab were consistent with those reported in the phase I/II trial and rarely limited the administration of therapy; 12.6% of patients in the capecitabine arm and 12.2% of those in the combination arm discontinued treatment as a result of toxicity.[28] A more detailed review of adverse events reported in this and other trials of bevacizumab can be found later in this supplement.

The significant improvement in objective response rate reported in this trial with very heavily pretreated patients provides evidence that bevacizumab is clinically active in patients who have previously received treatment for metastatic breast cancer. Nevertheless, the observed response together with the failure to meet

Table 2 – Summary of efficacy data from phase III trial AVF2119g of capecitabine with or without bevacizumab in previously treated metastatic breast cancer [28]

	Capecitabine alone (n = 230)	Capecitabine plus bevacizumab (n = 232)	*p*-value
Overall response rate			
INV	19.1	30.2	0.006
IRF	9.1	19.8	0.001
Progression-free survival (months)	4.17	4.86	0.857
Overall survival (months)	14.5	15.1	–

INV = as determined by investigators; IRF = as determined by an independent review facility.

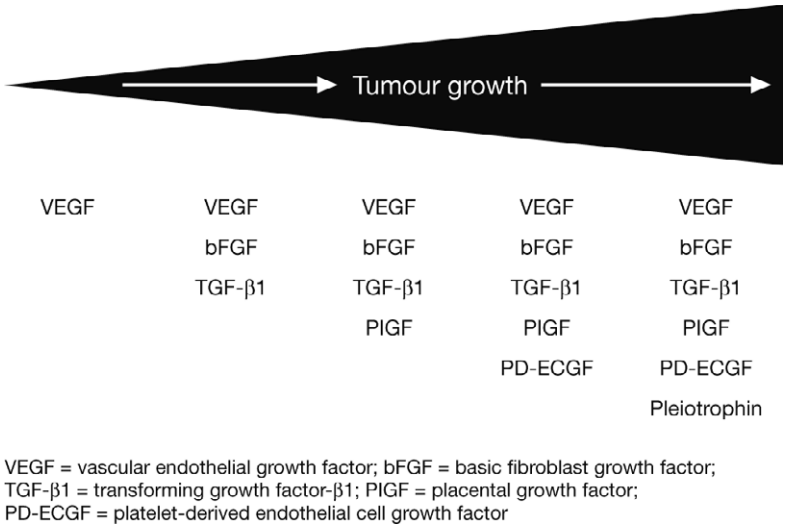

Fig. 2 – Progression of angiogenic activity in breast cancer: VEGF is not the only angiogenic factor involved in tumour growth. [33] **Reprinted with permission from Folkman J, Antiangiogenesis agents. In:** ***Cancer: principles and practice of oncology*****; 2006.**

the primary endpoint in this advanced patient population stimulated the earlier use of bevacizumab in disease progression. [29,30]

2.2. The expression of pro-angiogenic factors in breast cancer

Despite more than doubling the response rate for combination therapy compared with capecitabine alone, the AVF2119g trial failed to show an improvement in the primary endpoint – progression-free survival – for the combination. A number of potential explanations have been proposed for this observation. The first is that patients included in the study were heavily pretreated, having all received prior anthracycline and taxane therapy, with a substantial proportion of patients having progressed within 12 months of receiving these agents in the adjuvant setting; the latter being an indication of a particularly aggressive disease. Furthermore, some patients had received up to five prior regimens for the treatment of metastatic disease and 9.5% had received high-dose therapy with stem cell rescue, making this a highly treatment-refractory patient population. These patients may have been unlikely to gain a substantial survival benefit from any therapeutic regimen.

A further explanation – suggested by findings in animal models – is that tumours in the early stage of disease are reliant upon single angiogenic factors, predominantly VEGF, whereas those at more advanced disease stages express a greater number of such factors. [31] This is supported by data from a preclinical study using a human breast cancer xenograft model in nude mice. [32] The effects of VEGF suppression on tumour growth were dependent on the stage at which suppression was initiated, with removal of VEGF at the time of cell inoculation leading to an almost complete prevention of xenograft growth. Tumours of 175 mm^3 underwent a 6-fold reduction in size upon suppression of VEGF, whereas those that had reached a size of 820 mm^3 were not affected by VEGF removal. After VEGF suppression, expression of additional pro-angiogenic factors such as basic fibroblast growth factor (bFGF) and transforming growth factor alpha (TGF-α) was seen only in the largest tumours. It is suggested, therefore, that increased numbers of various pro-angiogenic factors come into play as tumours progress, thus making VEGF inhibition alone a less effective anti-angiogenic strategy in advanced disease (Figure 2). [33,34] In order to maximise its effects, bevacizumab should therefore be used earlier in the course of disease, when tumours are primarily dependent upon VEGF for generating an enriched environment for tumour growth. The characterisation of clinical findings in breast cancer patients to support this hypothesis represents an important area of research.

This is substantiated by the results of a phase II trial, XCALIBr, and a phase III trial, E2100, in previously untreated advanced breast cancer. E2100, which is discussed in greater detail elsewhere in this supplement, reported a doubling in progression-free survival resulting from the addition of bevacizumab to chemotherapy. [29] XCALIBr is investigating the capecitabine plus bevacizumab combination in patients with previously untreated metastatic breast cancer. [30] This single-arm phase II trial was designed to give 90% power to test the null hypothesis of 4 months median time to progression (based on historical data with first-line capecitabine) versus the alternative hypothesis of 5.6 months. This primary endpoint was met, with a median time to progression of 5.7 months in the 106 patients recruited. As reported in the phase III trial, the combination of capecitabine and bevacizumab

was well tolerated. Patients in the XCALIBr trial who progress on capecitabine plus bevacizumab receive a protocol-defined second-line regimen of vinorelbine plus bevacizumab.[30] This stage of the trial will address the question of whether it is beneficial to continue to treat patients with bevacizumab beyond disease progression. XCALIBr has provided clinical evidence to support the hypothesis that trial AVF2119g failed to meet its primary endpoint due to the late-stage, heavily pretreated disease involved, rather than the therapy regimen used.

2.3. Other anti-angiogenic therapies in previously treated breast cancer

Sunitinib (SU11248) is a small molecule tyrosine kinase inhibitor of VEGF receptor-1, -2 and -3, in addition to being an inhibitor of platelet-derived growth factor receptor beta (PDGFR-β), the class III receptor tyrosine kinase stem cell factor receptor (c-Kit) and fms-like tyrosine kinase 3 (Flt-3). Sunitinib is currently approved for use in both renal cell carcinoma and in gastrointestinal stromal tumours after failure of first-line standard therapy. A phase II trial of sunitinib monotherapy in 64 patients with metastatic breast cancer reported an unconfirmed response rate of 17% (9% confirmed), all partial responses, and an overall clinical benefit rate of 39%.[35] The most frequently reported therapy-related grade 1–3 adverse events were neutropenia (74%), thrombocytopenia (61%), diarrhoea (56%), anaemia (55%), fatigue (47%) and nausea (40%). The most common grade 3 events were neutropenia (39%), thrombocytopenia (15%), hand-foot syndrome and diarrhoea (both 7%).

Like sunitinib, sorafenib (BAY 43-9006) is also a small molecule tyrosine kinase inhibitor and has received approval for use in renal cancer. Its primary target is Raf-1, but it has additional activity against VEGF receptor-2 and -3, PDGFR, c-Kit, and glial cell-line derived neurotrophic factor receptor (RET). A phase II trial of sorafenib in 54 patients who had received previous treatment for metastatic breast cancer reported a partial response in one patient (2%) and stable disease in 19 patients (35%).[36] Median time to progression was 55.5 days (range 0–280). Common adverse events of all grades included skin rash/desquamation (32%; 5.6% grade 3), anorexia (28%), hand–foot syndrome (22%; 3.7% grade 3), pruritus (22%) and diarrhoea (19%). A similar phase II trial was halted before the second phase of recruitment owing to insufficient response rates.[37] No grade 4 adverse events were reported, but the most frequently observed grade 3 events included acne (8.7%), hand-foot syndrome (4.3%), neutropenia (4.3%) and cough (4.3%).

A third small molecule tyrosine kinase inhibitor currently in development is vandetanib (ZD6474). It specifically targets VEGF receptor-2, epidermal growth factor receptor, fibroblast growth factor receptor-1 and RET. A phase II trial of vandetanib found no objective responses to either a 100 or 300 mg daily dose in 46 previously treated patients with metastatic breast cancer.[38] The authors concluded that the agent had little activity as a single agent in this setting. The most commonly reported toxicity was diarrhoea, which may have been related to the dose; incidences of grade 2 or greater diarrhoea were 4.5% and 37.5% in the 100 and the 300 mg arms, respectively. Grade 1 QTc prolongation was reported in 29% of patients in the 300 mg treatment arm, while rash was observed in 26% of all patients, regardless of the dose of the study drug.[38] Two grade 4 adverse events were reported, a thromboembolic event in the 100 mg arm and one case of infection in the 300 mg arm.

3. Discussion

Numerous studies have demonstrated that angiogenesis plays a crucial role in the growth and metastasis of breast cancer. VEGF is the key angiogenic agent within this process and thus represents a fundamental target for anti-angiogenic therapy.[39] As a VEGF-targeting agent, bevacizumab prevents VEGF from binding to and activating receptors on the surface of vascular endothelial cells, thereby inhibiting angiogenesis and tumour growth.[23] In addition, bevacizumab normalises the disorganised architecture of vessels within tumours, reducing vascular permeability and interstitial fluid pressure, and potentially improving cytotoxic drug delivery.[40] Preclinical and clinical data also suggest that anti-VEGF therapy leads to the regression of recently formed tumour microvasculature that is still dependent on VEGF for survival.[41,42] Although the drug target of bevacizumab is well known, no biomarkers have been identified to predict clinical benefit from targeting circulating VEGF with bevacizumab in breast cancer.

Promising results have been obtained with bevacizumab in clinical trials in a range of solid tumours, including colorectal cancer,[43,44] non-small cell lung cancer,[45] and renal cell cancer.[46,47] Response to bevacizumab has not been correlated with VEGF levels, however, data from the phase II and III trials discussed in this review confirm the usefulness of an anti-angiogenic, biologically targeted approach to cancer therapy.

Also, an important area of research is to identify bevacizumab drug targets in the primary tumour or in metastases in order to look for better predictive markers. Ongoing studies, predominantly in the neoadjuvant setting, may aid in the collection of tumour biopsy samples and will also evaluate the potential use of molecular imaging techniques.

4. Conclusions

Several anti-angiogenic agents are currently in development for breast cancer and, of these, bevacizumab has been the most extensively investigated, displaying the greatest promise in terms of efficacy in combination

with conventional chemotherapy, including metronomic regimens. Other agents such as sunitinib, sorafenib, and vandetanib have demonstrated limited clinical benefit in small phase II trials in pretreated patients with metastatic breast cancer. [35,36,38] At present, larger phase III trials are in progress for sunitinib only. A review of currently ongoing trials with anti-VEGF agents in breast cancer can be found elsewhere in this supplement.

A phase III trial of bevacizumab in combination with capecitabine demonstrated a significant increase in response rates for the combination regimen compared with capecitabine alone. [28] However, despite this, the trial failed to meet its primary endpoint of progression-free survival. Clinical evidence support the hypothesis that the trial failed to meet its primary endpoint due to the late-stage, heavily pretreated disease involved, rather than the therapy regimen used. [30] Indeed, preclinical studies show that the number of pro-angiogenic factors expressed by a tumour increases as the disease becomes more advanced. The primary angiogenic factor is VEGF, but based on preclinical data, other factors become increasingly important as the tumour grows. This suggests that an agent such as bevacizumab, which specifically inhibits VEGF, may have greater activity the earlier it is used in the course of therapy. A heavily pretreated population may therefore not be the optimal setting for this agent. This hypothesis is supported by data from the E2100 phase III trial of bevacizumab in previously untreated advanced breast cancer, which reported a doubling in progression-free survival. Future research efforts will continue to explore the clinical utility of bevacizumab and its evolving role in the treatment of metastatic breast cancer.

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Conflict of interest statement

Professor Harbeck has received honoraria for lectures and consulting from Pfizer, AstraZeneca, and F. Hoffmann-La Roche Ltd.

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