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Breast Cancer RESEARCH

SHORT COMMUNICATION

Angiogenesis - still a worthwhile target for breast cancer therapy?

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Introduction

Tumour angiogenesis was identified as a target for cancer therapy in the 1970s. To date, one anti-angiogenesis treatment, bevacizumab, which targets the vascular endothelial growth factor (VEGF) signalling pathway, has been licensed for the treatment of advanced breast cancer. However, in clinical studies only modest improvements in progression-free survival have been seen for anti-angiogenic treatment of this disease (Table 1). Many patients have no response to these drugs at all, and often after an initial response patients soon relapse. Indeed, the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) recently voted almost unanimously to remove the treatment of advanced breast cancer as a licensed indication for bevacizumab. Results from trials in the adjuvant and neoadjuvant setting for breast cancer are still awaited. We discuss why anti-angiogenesis therapies have not lived up to their early expectations and how new strategies for their use may lead to their greater effectiveness.

Mechanisms of resistance to anti-angiogenic therapy

Several mechanisms for intrinsic and acquired tumour resistance to anti-angiogenic therapy have now been proposed. It is now clear that revascularisation can occur after the inhibition of VEGF signalling due to the upregulation of alternative angiogenic signalling pathways. This was first revealed in a mouse model of pancreatic neuroendocrine cancer treated with the anti-VEGF receptor (VEGFR) monoclonal antibody DC101; in this model an initial response was followed by tumour regrowth and revascularisation. This was associated with higher levels of mRNAs for the pro-angiogenic factors fibroblast growth factor 1 and 2, Ephrin A1 and A2 (Efna1 and Efna2) and Angiopoietin 1 (Angpt1) [1]. Further *in vivo* studies have suggested the importance of the promotion of a multitude of pro-angiogenic factors in response to anti-angiogenic therapy, including interleukin-8, VEGF, platelet derived growth factor (PDGF)A and placental growth factor [2-4].

Another angiogenic pathway, Delta-like ligand-4 (DLL4)-Notch signalling, is induced by VEGF and acts as a counterbalance to VEGF upregulation by inhibiting angiogenesis. Inhibition of DLL4-Notch signalling leads to an increase in blood vessel density, intratumoural hypoxia and the induction of pro-angiogenic factors. Preclinical studies have suggested that tumours that are resistant to anti-VEGF therapy are susceptible to blockade of DLL4-Notch signalling due to the promotion of non-productive angiogenesis [5,6].

Pericytes, the periendothelial support cells of the microvascular structure, also seem to play an important role in treatment resistance. It has been observed that even after tumour devascularisation in response to VEGF inhibition, vessels remain that are heavily covered with pericytes. Furthermore, those vessels that do not have this 'pericyte scaffold' are more susceptible to VEGF inhibition. Lastly, pericytes have the ability to release pro-angiogenic factors in response to PDGF. Hence, one strategy to overcome this 'pericyte resistance' mechanism may be to use PDGFR inhibitors to dissociate pericytes from the endothelium. However, some studies suggest that a lack of pericyte endothelial coverage may promote metastasis due to a loss of endothelial integrity [7-9].

Several single nucleotide VEGF polymorphisms have been described that may be involved in anti-angiogenic treatment resistance. It is likely that only a few of these polymorphisms have an effect on protein expression and some polymorphisms may in fact predict positively for response to anti-angiogenic therapy.

Anti-angiogenic treatment almost certainly leads to intratumoural hypoxia and subsequent induction of the hypoxia inducible factor (HIF)-1 pathway [10]. Thus, the treatment may rapidly activate a key transcription factor that induces angiogenesis. HIF activation has been correlated with poor prognosis in a variety of solid tumours. A clinical study has demonstrated that elevated carbonic anhydrase 9 (encoded by *CA9*, a HIF-1 target gene) is associated with both poor prognosis and poor

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Table 1. Phase 3 trial results, to date, of anti-angiogenic agents in the treatment of advanced breast cancer

Trial name and design	Treatment type	Progression free survival (months)[a]	Overall survival (months)[a]	Response rate[a]
Capecitabine ± bevacizumab	Refractory	4.86 versus 4.17 (HR 0.98; $P = 0.857$)	15.1 versus 14.5	19.8% versus 9.1% ($P = 0.001$)
RIBBON-2: second line chemotherapy ± bevacizumab	Second line	7.2 versus 5.1 (HR 0.775; $P = 0.0072$)	18.0 versus 16.4 ($P = 0.372$)	39.5% versus 29.6% ($P = 0.0193$)
E2100: paclitaxel ± bevacizumab	First line	11.8 versus 5.9 (HR 0.60; $P = <0.001$)	26.7 versus 25.2 (HR 0.88; $P = 0.16$)	36.9% versus 21.2% ($P < 0.001$)
AVADO: docetaxel ± bevacizumab	First line	8.8 versus 8.0 (HR 0.61; $P = 0.0001$)	Not published	44.4% versus 63.1% ($P = 0.0001$)
RIBBON-1: capecitabine (C) or taxane (T) or anthracycline (A) ± bevacizumab or placebo	First line	C: 8.6 versus 5.7 (HR 0.688; $P = 0.0002$) A + T[b]: 9.2 versus 8.0 (HR 0.644; $P \leq 0.0001$)	C: 29.0 versus 21.2 (HR 0.847; $P = 0.2706$) A + T[b]: 25.2 versus 23.8 (HR 1.032; $P = 0.8298$)	C: 35.4% versus 23.6% ($P = 0.0097$) A + T[b]: 51.3% versus 37.9% ($P = 0.0054$)
Capecitabine ± sunitinib	Refractory	5.5 versus 5.9 (HR 1.224)	16.4 versus 16.5 (HR 0.995)	18.6% versus 16.3%
Capecitabine versus sunitinib	Refractory	2.8 versus 4.2 (HR 1.473; $P < 0.001$)	Not published	9.1% versus 12.9%
Docetaxel ± sunitinib	First line	8.6 versus 8.3 (HR 0.922)	24.8 versus 25.5 (HR 1.207)	51% versus 39% ($P = 0.0018$)

[a]Anti-angiogenic treatment group first. [b]Anthracycline and taxane cohorts analysed as a pooled group. HR, hazard ratio.

response to irinotecan and bevacizumab for malignant astrocytoma [11-13]. Hypoxia leads to the recruitment of bone marrow derived cells, such as tumour-associated macrophages and pro-angiogenic monocytic cells, including CD11b+ myeloid cells, VEGFR1+ haemangiocytes and TIE2+ monocytes. In a mouse glioblastoma model, their recruitment to the tumour microenvironment has been associated with HIF-1 activation and subsequent tumour progression and angiogenesis [14]. These inflammatory cells are associated with tumour progression and refractoriness to anti-VEGF therapy in mouse models [15]. It has also been shown that HIF-1 in a pancreatic cancer model increases expression of c-MET and secretion of hepatocyte growth factor, both of which are associated with poor prognosis, metastasis and angiogenesis in solid tumours [16-18].

Metabolic reprogramming of the cancer cell by HIF-1, to aid the switch from aerobic to anaerobic metabolism, involves the activation of key metabolic enzymes, including lactate dehydrogenase A and pyruvate dehydrogense 1 [19,20]. HIF-1 has also been associated with the upregulation of the glucose transporter GLUT1 and reduced mitochondrial mass due to upregulation of the *BNIP3* gene [21,22]. Evidence is growing that lipid metabolism is significantly altered under hypoxic conditions and that this is, at least in part, regulated by the HIF axis [23]. These profound changes in cancer metabolism are likely to play a significant role in resistance to anti-angiogenic therapy, and the development of drugs that exploit these changes in cancer metabolism may well give rise to synergistic combination with anti-angiogenic treatments.

Are we treating the wrong patients?

Early studies of anti-angiogenic agents predominantly assessed their use as a single agent therapy and in heavily pretreated patients. However, phase 3 trial data have predominantly demonstrated benefit in terms of progression-free survival for anti-angiogenic treatment in advanced breast cancer for patients that have received only minimal prior treatment and when therapy is given in combination with chemotherapy (Table 1). Late stage breast cancers express many different angiogenic factors, such as fibroblast growth factor 2, in contrast to early stage breast cancers, which predominantly express VEGF [24]. Hence, it may be that heavily pretreated tumours have angiogenesis resistance pathways that have already become activated. It is also hypothesised that the associated normalisation of tumour vasculature with anti-angiogenic therapy results in improved delivery of chemotherapy and hence efficacy.

The selection of patients on the basis of biomarkers associated with intrinsic tumour resistance is a key strategy to improve the likelihood of clinical benefit. So far every phase 3 trial of anti-angiogenic treatments has been undertaken in essentially unselected patients with little effort made to assess for biomarkers of response or resistance. This is in contrast to other highly targeted agents, in particular trastuzumab or anti-epidermal growth factor receptor (EGFR) therapy.

Several surrogate markers for anti-angiogenesis are under investigation to predict response. Microvessel density is one such marker, which can be assessed after staining specific to an endothelial cell-specific marker, such as CD31, CD34 or CD105. However, this has not as

yet yielded useful data, probably because it does not assess functional vessels. It is thought that highly vascularised tumours are more susceptible to anti-angiogenesis therapy, although some preclinical studies have suggested that less well vascularised tumours may also respond well [25]. Tumour vascular function in terms of patency and 'blood vessel leakiness' can also be assessed using the fluorescent dye Hoescht 33342 and high molecular weight tracers (for example, fluorescence-labelled dextran), respectively [8,26]. Thus far, most of these markers have predominantly been assessed in preclinical studies alone.

The phase 3 E2100 study that examined combination treatment with paclitaxel and bevacizumab versus paclitaxel alone in advanced breast cancer demonstrated that the VEGF-2578 AA genotype was associated with a superior median overall survival. However, to be of value this needs confirmation in other studies and other tumour types, with much more extensive validation. Plasma levels of VEGF and vascular cell adhesion molecule 1 did not correlate with clinical outcome and so far neither are of value [27].

Several studies have investigated the predictive potential of circulating endothelial cells and circulating tumour cells in patients with advanced breast cancer receiving combination treatment with bevacizumab. Higher levels of circulating endothelial cells at baseline have consistently correlated with prolonged clinical benefit [28-31]. At least one study has also shown that an increase in circulating endothelial cells during treatment is associated with improved time to progression [28]. Baseline circulating tumour cell positivity has been shown to negatively predict clinical outcome, although changes during treatment have not been shown to be significant [28]. Development of viable assays for these markers may allow for their routine use in the clinical setting in the near future.

Real-time monitoring of tumour response and alterations in vascularity using non-invasive imaging techniques are the most likely approach to succeed in the targeting of treatment. Positron emission tomography-computed tomography (PET-CT) and single photon emission computed tomography (SPECT) tracers linked to VEGF or VEGFR antibodies are being developed. Contrast enhanced ultrasound is also being assessed as a tool to characterise tumour angiogenesis [32]. Dynamic contrast enhanced MRI is a promising imaging modality that has been used as a biomarker of efficacy in clinical trials of anti-angiogenesis inhibitors. The main biomarker used in these studies has been the measurement of the volume transfer coefficient of a contrast agent across the capillary wall (K^{trans}) and changes in K^{trans} have been shown to independently predict prognosis for patients with high grade gliomas [33]. In a small study, patients with advanced breast cancer treated with bevacizumab had significant reductions in K^{trans} from baseline, although this did not predict response [34]. However, the variables obtained from dynamic contrast enhanced MRI (DCE-MRI) are highly dependent on the data acquisition and image analysis methods used. Hence, reproducibility has been problematic and clinical adoption outside of the research setting has been slow [35].

Conclusion

Anti-VEGF therapy clearly affects the growth of breast cancer, and new targets for anti-angiogensis therapy continue to be discovered. Combination treatment may deliver greater benefit by circumventing resistance mechanisms. This particularly relates to the use of drugs that target the hypoxia-induced pathways - for example, met and carbonic anhydrase 9. Clinical research, especially in phase 3, needs to place a greater emphasis on the discovery of biomarkers that allow clinicians to select patients that are likely to gain significant benefit from treatment. This can be achieved through 'window of opportunity' studies in which anti-angiogenesis agents are given in a neoadjuvant setting, allowing their study in isolation. The development of standardization for imaging techniques is also likely to improve the targeting of these treatments. Thus, the development of highly specific drugs needs to be matched by the development of biomarkers for response. In general, current trials have omitted the many opportunities to develop these, ultimately depriving patients who may respond of therapy because the cost-effectiveness of treating all-comers is too low.

Abbreviations

DLL, Delta-like ligand; EGFR, epidermal growth factor receptor; HIF, hypoxia inducible factor; MRI, magnetic resonance imaging; PDGF, platelet derived growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Competing interests

The authors declare that they have no competing interests.

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