



# Angiogenesis inhibitors in cancer – clinical applications

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## Summary

**New blood vessel formation, or angiogenesis, is crucial for sustaining tumours. Strategies are being developed to treat or prevent cancer, as a result of improved understanding of angiogenesis. Antivascular treatment may be divided into anti-angiogenic and vascular targeting therapy. It may improve survival in advanced colorectal and lung cancer. Clinical trials are using angiogenesis inhibitors in a variety of tumour types. The efficacy and safety of these drugs are still uncertain.**

Key words: bevacizumab, colorectal cancer, lung cancer.

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## Introduction

The shortcomings of 'modern' systemic therapy for cancer are well understood. Even destroying 99.9% of cancer cells is not enough to prevent relapse of a primary tumour. The most successful strategy so far has been with targeted therapy using small molecules such as tamoxifen for hormone-receptor positive breast cancer or rituximab for non-Hodgkin's lymphomas.

## Angiogenesis and neovascularisation

The growth and proliferation of new blood vessels has a physiological role in wound healing and embryogenesis. It also has a pathological role in proliferative retinopathy, age-related macular degeneration and malignancy. When tumour cells are supplied by diffusion their growth is arrested at a size of 1–2 mm<sup>3</sup>. The tumour therefore induces a proliferative vascular response from host vessels. These new vessels supply the tumour with the nutrients it needs to grow.

An increased microvessel density count has poor prognostic value in almost all tumour types. Similarly, overexpression of vascular endothelial growth factor (VEGF) suggests the patient's prognosis is poor, but more accurate surrogate markers of response, resistance and prognosis are needed.

## Antivascular therapy

Antivascular therapy for cancer can be divided into two classes of drugs:

- anti-angiogenic drugs which aim to inhibit new vessel formation

- vascular targeting compounds which aim to selectively destroy the blood vessels supplying the tumour leading to secondary tumour cell death.

In numerous preclinical studies over the last decade both anti-angiogenic drugs and vascular targeting drugs have shown evidence of antitumour activity.

Phase I clinical studies, designed to define maximum tolerated or optimal biological doses, revealed a number of relatively well-tolerated compounds. However, antivascular treatment lacked sufficient efficacy as monotherapy. Clinical trials are therefore exploring the combination of antivascular therapy in combination with other treatment modalities such as chemo- and radiotherapy.

## Monoclonal antibodies

Antibodies have a variety of actions. Genetic engineering enables the production of monoclonal antibodies with antitumour activity.

### *Bevacizumab*

Phase I clinical trials showed that bevacizumab as a single drug was relatively non-toxic and that adding it to standard chemotherapy regimens did not significantly exacerbate their toxicities. Phase II studies investigated bevacizumab in hormone-refractory metastatic prostate cancer, relapsed metastatic breast cancer and in renal cell cancer that had progressed following therapy with interleukin-2. Bevacizumab was also studied in combination with standard first-line chemotherapy in metastatic colorectal cancer and stage IIIb/IV non-small cell lung cancer. The most encouraging efficacy results were seen when bevacizumab was combined with chemotherapy in advanced colorectal cancer<sup>1</sup> and in non-small cell lung cancer, and when it was used as a single drug in renal cell cancer. Bevacizumab costs approximately \$4000 per month so its cost-effectiveness is uncertain.

### *Colorectal cancer*

In metastatic colorectal cancer the benefit of adding bevacizumab to the North American combination regimen of irinotecan, 5-fluorouracil and folinic acid was statistically significant across all patient sub-groups, including age, sex, performance status, number of metastatic sites and tumour load (Table 1). There were clinically relevant improvements in

response rate, progression-free survival, median duration of response and overall survival. This trial was important because it confirmed the feasibility of combining anti-VEGF antibodies with chemotherapy.<sup>1</sup>

### Non-small cell lung cancer

In 2005 the data monitoring committee overseeing a trial in 878 patients with advanced non-squamous non-small cell lung cancer recommended that the results of a recent interim analysis be made public, because the study had met its primary end point of improving overall survival. The researchers found that patients who received bevacizumab in combination with standard chemotherapy (paclitaxel and carboplatin) had a median overall survival of 12.5 months compared to 10.2 months in patients treated with the standard combination chemotherapy alone. This difference is statistically significant.<sup>2</sup>

Patients with squamous cell carcinoma of the lung were not included in the study because previous clinical experience suggested that patients with this particular type of cancer had a higher risk of serious bleeding from the lung after bevacizumab therapy. Those with a history of frank haemoptysis were also not enrolled.

The most significant adverse event observed in this trial was life-threatening or fatal bleeding, primarily from the lungs. This occurred infrequently, but was more common in the patient group that received bevacizumab in combination with chemotherapy than in the patient group that received only chemotherapy. Five patients died of haemoptysis among the 434 who received bevacizumab.

### Renal cancer

In patients with advanced clear cell renal cell carcinoma, the combination of bevacizumab and interferon-alfa is currently being compared to interferon-alfa alone.

### Adverse effects

Bevacizumab seems more effective when combined with chemotherapy than when given as a single drug. However, the combined effects of chemotherapy and the vascular effects of an angiogenesis inhibitor could promote thromboembolic disease and myocardial infarction. Adverse reactions include a low incidence of severe hypertension, arterial and venous

thromboses, proteinuria and bleeding. Another uncommon toxicity has been bowel perforation, but the aetiology has yet to be determined.

### VEGF-Trap

VEGF-Trap is a potent angiogenesis inhibitor. In a phase I trial a total of 30 patients with a broad range of tumours have been treated across six dose levels. Hypertension and proteinuria are the major toxicities.

### Small molecule tyrosine kinase inhibitors

Inhibiting tyrosine kinase disrupts the angiogenic signalling pathways in the cells.

### Sunitinib (SU11248)

In a phase I trial there were responses to sunitinib in renal cell and neuroendocrine tumours. At higher doses, tumour responses were often associated with reduced vascularisation inside the tumour and central tumour necrosis.

Sunitinib therapy induced an objective response or stable disease for more than six months in 26/48 (54%) of patients with previously progressing gastrointestinal stromal cell tumours. Six patients (13%) had confirmed partial responses.

There is an extensive clinical trials program investigating the addition of sunitinib to standard chemotherapy in most advanced solid tumours. In Australia, a phase III trial is underway comparing oral sunitinib with interferon-alfa in advanced clear cell renal cell cancer.

The toxicities associated with sunitinib include fatigue, neutropenia and thrombocytopenia.

### PTK787

PTK787 inhibits the tyrosine kinases found in vascular endothelial growth factor receptors (VEGFR) 1 and 2. Early clinical trials have investigated the addition of this drug to combination chemotherapy in advanced colorectal cancer. Response rates were 10% higher than previously reported with chemotherapy alone and progression-free survival was 30% longer than previously reported. In metastatic colorectal cancer progression-free survival was slightly longer (7.7 vs 7.6 months) with PTK787 than with combination chemotherapy. It may also have some activity in advanced renal cell carcinoma.

Table 1

#### Response to bevacizumab in advanced colorectal cancer<sup>1</sup>

Regimen	Number of patients	Response rate (%)	Progression-free survival (months)	Overall survival (months)
Irinotecan/5-fluorouracil/folinic acid	411	34.8	6.2	15.6
Bevacizumab + irinotecan/5-fluorouracil/folinic acid	402	44.8 *	10.6 *	20.3 *

\* statistically and clinically significant

## **ZD6474**

This oral tyrosine kinase inhibitor has activity at the VEGFR-2 and the epidermal growth factor receptor (EGFR). It has been tried in 15 patients with a good performance status, who had metastatic non-small cell lung cancer which had not responded to platinum-based chemotherapy. The patients received ZD6474 in combination with docetaxel. There was no significant adverse toxicity except an acneiform rash, sometimes with desquamation or photosensitivity.

## **GW786034**

The pharmacokinetic and pharmacodynamic properties of GW786034, another VEGFR tyrosine kinase inhibitor, have been reported in abstract form. Tumour shrinkage was observed in three patients with renal cell cancer and in one patient with Hurthel cell tumour. GW786034 is therefore being studied in Australia for renal cell carcinoma.

## **BAY 43-9006**

BAY 43-9006 inhibits tumour cell proliferation by targeting a signalling pathway. It also exerts an anti-angiogenic effect. In a large randomised study of over 800 patients with advanced kidney cancer, median progression-free survival was 24 weeks for BAY 43-9006 versus 12 weeks for placebo (hazard ratio 0.44;  $p < 0.00001$ ). The 12-week progression-free rate was 79% versus 50% for placebo. Final study details are yet to be published.

## **Thalidomide**

Thalidomide has some anti-angiogenic actions. It is available in Australia for the treatment of patients with multiple myeloma which has not responded to previous chemotherapy. There have been mixed results in a range of solid tumours. Thalidomide can be combined with chemotherapy, but has an unexpectedly high rate of thromboembolic events. The other predominant adverse effects are fatigue, rash, nausea and vomiting, peripheral neuropathy and somnolence.

## **Vascular targeting drugs**

Selective induction of tumour vascular collapse can be achieved by synthetic low molecular weight inducers of tumour necrosis factor (TNF). Strategically these drugs have the potential benefits of non-overlapping dose-limiting toxicities and selective effects in poorly-perfused hypoxic regions. They may also potentially sensitise tumours to the cytotoxic effects of chemotherapy and radiotherapy.

Unexpectedly, flavone acetic acid, which was originally synthesised as a non-steroidal anti-inflammatory drug, was found to have excellent antitumour activity in preclinical studies because of its antivasular activity resulting from TNF induction. Flavone acetic acid was chemically modified to the flavonoid 5,6-dimethylxanthenone-4-acetic acid (DMXAA), representing a promising synthetic small molecular inducer of

TNF with demonstrable preclinical antitumour effects. Australian investigators are participating in trials of DMXAA in a variety of solid tumours. The dose-limiting toxicities seem to occur at significantly higher doses than those used in current studies.

The second class of leading vascular targeting drugs are small-molecule, tubulin-binding drugs. These include combretastatin A-4 and the combretastatin analogues AVE8062A and Oxi4503 as well as the phosphate prodrug of N-acetylcolchicolin ZD6126. After binding and destabilisation of the tubulin cytoskeleton, these drugs induce rapid changes in endothelial cell shape. This rapid change of endothelial cell morphology leads to disruption of the endothelial cell layer and exposure of the procoagulant underlying basement membranes.

In a phase I trial, 37 patients were given combretastatin A-4. There was dose-limiting cardiopulmonary toxicity (syncope and dyspnoea or hypoxia) as well as hypotension, ataxia, dyspnoea, nausea or vomiting, headache and transient sensory neuropathy. A partial response was observed in a patient with metastatic soft tissue sarcoma. In another trial, 16 patients with solid tumours were given the drug with carboplatin. The dose-limiting toxicity of thrombocytopenia halted the dose escalation phase of the study.

## **Radiotherapy**

Radiotherapy increases the expression of VEGF. This could be the response of the tumour to radiation stress and may contribute to tumour resistance. Blocking the radiation-mediated increase in VEGF with anti-VEGF therapy could therefore increase the destruction of tumour cells and produce additive antitumour effects. Clinical trials designed to address this issue are just beginning.

## **Conclusion**

Antivasular therapy for cancer represents a new spectrum of molecules with a broad range of putative mechanisms of action. The activity of angiogenesis inhibitors has been demonstrated, but the indications for these drugs are unclear. The role of each drug in combination with standard therapy will take many years of clinical research.

## **References**

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