Clinical Oncology (2005) **17**: 277–290
doi:10.1016/j.clon.2004.11.011

Overview

Vascular Disrupting Agents: A New Class of Drug in Cancer Therapy

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ABSTRACT:
Aims: To provide a comprehensive overview of the current state of development of a novel class of anti-cancer drugs, the vascular disrupting agents (VDAs), previously known as vascular targeting agents (VTAs).
Materials and methods: A comprehensive review, analysis and commentary of the published medical literature on VDAs was performed.
Results: Tumour vascular targeting therapy exploits known differences between normal and tumour blood vessels. VDAs target the pre-existing vessels of tumours (cf anti-angiogenics), and cause vascular shutdown leading to tumour cell death and rapid haemorrhagic necrosis within hours. It is becoming clear that VDAs have overlapping activity with anti-angiogenic drugs, which prevent the formation of new blood vessels. There are two types of VDA. First, biological or ligand-directed VDAs use antibodies, peptides or growth factors to target toxins or pro-coagulants to the tumour endothelium. In contrast, small molecule VDAs work either as tubulin-binding agents or through induction of local cytokine production. VDAs can kill tumour cells resistant to conventional chemotherapy and radiotherapy, and work best on cells in the poorly perfused hypoxic core of tumours, leaving a viable rim of well-perfused tumour tissue at the periphery, which rapidly regrows. Consequently, responses of tumours to VDAs given as single agents have been poor; however, combination therapy with cytotoxic chemotherapy, external-beam radiotherapy, and radioimmunotherapy, which target the peripheral tumour cells, has produced some excellent responses in animal tumours. VDAs are generally well tolerated with different side-effect profiles to current oncological therapies. Dynamic magnetic resonance imaging is most frequently used to obtain a pharmacodynamic end point to determine whether the VDA is acting on its intended target.
Conclusions: VDAs are a promising new class of drug, which offer the attractive possibility of inducing responses in all tumour types with combination therapy. Gaya, A. M., Rustin G. J. S. (2005). *Clinical Oncology* **17,** 277–290

Key words: Angiogenesis, combretastatin, DCE-MRI, DMXAA, vascular targeting, ZD6126

Received: 2 June 2004 Revised: 27 October 2004 Accepted: 1 November 2004

Introduction

The genetic heterogeneity of advanced tumours leads to resistance against conventional anti-cancer therapies through the acquisition of drug-resistant phenotypes. New approaches using 'targeted therapies' to cancer cells and the tumour microenvironment are therefore becoming important additions to the oncologists' arsenal.

To date, targeted drug therapies broadly fall into two categories. First, some agents act against specific oncogenes, cell-surface receptors and second messenger signalling systems (e.g. imatinib [Glivec®] — c-kit, trastuzumab [Herceptin®] — c-erbB2, rituximab [Rituxan®, Mabthera®] — CD20, gefitinib [Iressa®], cetuximab [Erbitux®] or erlotinib [Tarceva®] — EGF receptor). The second category acts against tumour blood vessels (VDAs) or their formation (anti-angiogenics).

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The physiology of solid tumours is completely different to normal tissues. A hostile metabolic microenvironment exists with hypoxia, hypoglycaemia, bicarbonate depletion, hypercapnia, high lactate levels and acidosis [1]. Vascular permeability increases with extravasation of plasma into the interstitial compartment, and chaotic tumour blood flow.

Tumour angiogenesis, which is essential for tumour growth and metastatic spread, is an extremely complex process. It is under dynamic regulation by stimulatory (e.g. vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF], basic fibroblast growth factor [bFGF], IL-8, matrix metalloproteinases) and inhibitory (e.g. tumour necrosis factor [TNF], serotonin [5HT], nitric oxide, angiostatin or endostatin) factors released by tumour and host cells. Tumours can grow to about 1 mm without angiogenesis by obtaining oxygen and nutrients through diffusion from surrounding tissues [2]; however, for further growth, they must develop an angiogenic phenotype. Tumour angiogenesis involves several processes, including proliferation of endothelial cells, proteolytic degradation of the extra-cellular matrix and migration of endothelial cells, leading to the formation of a functioning vessel with

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a lumen [3]. VDAs selectively block or destroy the pre-existing blood vessels of tumours, leading to rapid shutdown of the tumour's blood supply, thereby killing tumour cells by depriving them of oxygen and nutrients. VDAs exploit the known differences between the vascular endothelium and basement membranes of tumours and normal tissues [4] (Table 1).

Much of the anti-vascular research to date has focused on anti-angiogenic compounds, which prevent the formation of new blood vessels in tumours, but were thought to have no effect on pre-existing vasculature. Anti-angiogenic compounds, in contrast to VDAs, are cytostatic rather than cytotoxic. VEGF inhibitors (e.g. bevacizumab [Avastin®]) have been shown to cause vascular remodelling. Recently, there has been increasing realisation that anti-angiogenic compounds can also have a direct effect on existing blood vessels, overlapping and possibly synergistic with the actions of VDAs. VDAs, which preferentially target immature vessels, might also be perceived as having an anti-angiogenic effect. Compounds produced by tumour cells and the hypoxic microenvironment, and imbalances in growth factors (e.g. VEGF, angiopoietins, platelet-derived growth factor), can trigger the formation of highly abnormal blood vessels in experimental models [5].

Vascular basement membrane comprises 50% type-IV collagen and 30% laminin, with smaller quantities of substances such as nidogen (entactin), fibronectin and integrins [6]. Some structural proteins of basement membrane can be digested by endogenous enzymes to yield smaller fragments with potent anti-angiogenic activity. One example is endostatin, which is a COOH-terminal fragment of collagen XVIII and, another, tumstatin, is the noncollagenous-1 domain of the α3 chain of type-IV collagen [7].

The anti-vascular activity of cytokines was first proposed after observations of people with cancer experiencing remission after recovering from a severe infection [8]. Coley's toxins, a potent mixture of bacterial endotoxins and exotoxins, were active against sarcomas and lymphomas [9]. Of course, we now know that the actions of bacterial endotoxins are mediated through TNF. Recombinant TNF and recombinant interleukin-1 have both shown anti-vascular activity [10,11].

Smaller, naturally occurring vasoactive molecules, such as serotonin (5HT), histamine and nitric oxide are also thought to be important in mediating anti-vascular effects [12]. The permeability of different vascular beds ranges from lowest in the brain to highest in the intestine and renal glomeruli.

Denekamp [13], in the early 1980s, showed that tumour endothelial cells proliferate more rapidly than their counterparts in normal tissues. She proposed that the properties of tumour endothelium may be different from normal tissue, and that these differences could be exploited by selective VDAs [13] . Later studies showed that immunotherapy with antibodies to tumour vascular endothelium led to excellent responses in mice [14], and that tubulin-binding drugs have vascular targeting properties [15].

Two classes of VDA are being developed. The biological or ligand-directed VDAs, which use antibodies or peptides to target toxins or pro-coagulants to the tumour endothelium, and the small molecule VDAs (Fig. 1 and Table 2), which exploit the differences between normal and tumour endothelium to induce vascular shutdown of tumour blood vessels. Both types of VDA produce a characteristic pattern of central necrosis, leaving a peripheral rim of viable tumour cells [16–20]. This review will concentrate on the small molecule VDAs, which are at a more advanced state of clinical development.

Table 1 – Differences between tumour and normal vasculature [133]

Increased vessel tortuosity
Vessels thin walled and fragile
Increased interstitial pressure within tumour
Vessel marker immaturity
Increased vessel permeability
Variable flow rates
Huge variability in vascular density
Lack of vascular smooth muscle
Lack of lymphatic drainage
Constant remodelling
Abnormalities of endothelial cell and pericyte shape and function

Potential Advantages of Vascular Disrupting Agents

There are a number of potential advantages of VDAs over other classes of anti-cancer drug. A significant bystander effect may take place, as one single blood vessel may provide oxygen and nutrients for thousands of tumour cells. Blockage or destruction of this solitary vessel may then result in thousands of downstream cell deaths. The endothelial cell itself does not need to be killed by the VDA — a change of structure or local initiation of the coagulation cascade may be all that is needed. As the

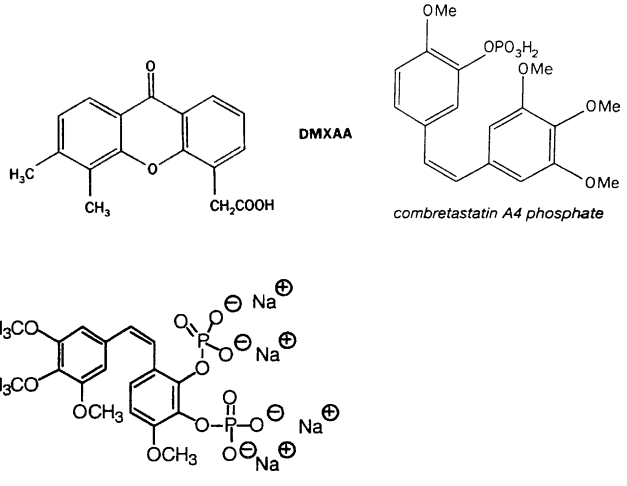

Fig. 1 – Chemical structure of selected small molecule vascular disruptive agents.