Anticancer potential of tumor vascular disrupting agents: review of the latest clinical evidence

Solid tumors differ from normal tissue by having a low vascular density, leading to various forms of vascular stress. Tumor vascular disrupting agents (VDAs) act to potentiate this stress, increasing vascular permeability and decreasing blood flow. Two main classes of tumor VDAs have progressed so far to clinical trial: the 'flavonoid' class, represented by vadimezan, and the tubulin poisons, represented by fosbretabulin (combretastatin A-4 phosphate). Both classes have been tested clinically, generally in combination with cytotoxic drugs such as carboplatin and paclitaxel. An important feature of trials is the measurement of effects on tumor vascular permeability and blood flow. Dynamic contrast-enhanced MRI, using a gadolinium-based biomarker, has been commonly employed. Promising clinical results, as well as indications of efficacy as tumor VDAs, have been obtained in Phase II clinical trials. However, Phase III trials have not yet demonstrated an increase in patient survival.

Keywords: antivascular • combination chemotherapy • combretastatin • DMXAA • dynamic contrast-enhanced MRI • tubulin • tumor blood flow • vascular permeability

Solid tumors develop in a network of blood vessels that are essential for their growth and survival. In human cancer, the net growth rate of this network is relatively slow with a doubling time in the order of 3 months [1]. The tumor cells within the network therefore have a high rate of turnover, since their individual doubling times are in the order of 1 week [2]. The proliferation of tumor cells also leads to a low vascular density as compared with normal tissues, together with the generation of hypoxia and metabolic stress in some areas. These in turn activate HIF-1, leading to increased production of cytokines such VEGF (also known as vascular permeability factor) and other cellular responses. An important effect of VEGF is to act on the vascular endothelium, increasing vascular permeability and, hence, the interstitial pressure within tumor tissue; this is associated with inefficient drainage by the lymphatic system. Other inflammatory cytokines, such as TNF produced by innate immune cells, may contribute increased permeability of the tumor vasculature [3] and to a reduction in its efficiency.

It has been recognized for several decades [4,5] that the above properties of tumor vasculature provide potential targets for chemotherapy, and two distinct approaches have been developed. The first recognizes that net tumor growth is required for new blood vessel development (angiogenesis); this led to the development of a large number of so-called antiangiogenic drugs of which bevacizumab is the best known clinical example [6]. The second approach, which will be discussed in this review, is based on the principle that since tumor vasculature was already inefficient, application of further stress on the vascular endothelium would lead to selective compromise of tumor vascular function. Tumor vascular disrupting agents (VDAs) could lead to catastrophic vascular failure, cessation of
tumor blood flow and extravasation of blood cells into tissue. This would in turn lead, after several hours, to hemorrhagic tumor necrosis. The earliest clinical studies examining the potential of tumor vascular disruption may well have been the trials of Coley’s toxins [7], which undoubtedly affected endothelial cell function. However, more recent work has focused on low-molecular weight drugs as tumor VDAs.

**Control of tumor blood flow**

Capillary blood flow is a function of vessel diameter, pressure difference along the length of the capillary and blood viscosity [8]. Gaps in the junctions between adjacent endothelial cells not only increase vascular permeability but also allow the movement of lymphocytes and granulocytes between the vascular compartment and tissue, as well as leakage of plasma into the tissue. The induction of such gaps reduces the pressure difference along the length of the capillary, reduces vessel diameter and increases blood viscosity, all of which compromise blood flow. Strict control of vascular permeability is therefore essential for normal tissue function and a number of tissue responses act to maintain vascular permeability in the normal range. One mechanism for such control involves platelets; increased vascular permeability allows platelets to leave the capillary and make contact with collagen in the basement membrane. Such contact causes degranulation of platelets and the release of sphingosine-1-phosphate, which acts to decrease vascular permeability [9]. Certain features of tumor tissue, such as low vascular density and the presence of inflammatory cytokines, lead to an overall increase in vascular permeability in comparison with that of normal tissues and, consequently, a lowered tolerance to further permeability increases. This represents a potential Achilles’ heel that might be exploited therapeutically. However, it should be kept in mind that compensatory processes are still operating in tumor tissue and that any induced increase in vascular permeability is generally reversible and is followed by a tissue reaction that lowers permeability again. Studies of mice have shown that physically induced failure of tumor blood flow for more than 4 h is necessary to prevent reversal and to induce irreversible changes, leading to hemorrhagic necrosis [10]. Strategies for selective disruption of tumor vasculature must therefore recognize the necessity for the induction of a sustained effect on the tumor blood supply in the face of physiological responses that might restore it.

**Development of tumor VDAs**

Although many different potential tumor VDAs have been examined at the experimental level, clinical development has focused on two main classes, often referred to as flavonoids and mitotic poisons (Figure 1) and both were developed mainly with the use of transplantable mouse tumor models. The first class is named after flavone acetic acid (FAA), which was originally identified as a potential antitumor drug because of unexpectedly high activity against a murine colon carcinoma [11]. It was subsequently shown to act by induction of necrosis of such tumors [12] as a consequence of disruption of tumor blood flow [10]. FAA was initially advanced to Phase I clinical trial as the acetic acid ester, based on its activity against murine solid tumors, but it was realized subsequently that the ester was rapidly hydrolyzed by esterases in plasma to FAA, and FAA itself was tested in a large number of patients in multiple trials [13]. A combination trial of FAA with IL-2 was also undertaken [14]. These trials did not attempt to examine effects on the tumor vasculature because it was assumed at that stage that FAA had a direct effect on tumor cells; all trials produced negative results.

Development of analogues of FAA was conducted in several laboratories, but the most fruitful concerned derivatives of the tricyclic analog xanthene-4-acetic acid (XAA), which, while chemically not a flavonoid, is included in the flavonoid class of tumor VDAs. The synthetic opportunities provided by XAA, whereby new molecules could be produced by combining two phenyl derivatives, led to the elaboration of an extensive series [15]. The most active of the XAA series was a 5,6-dimethyl derivative called DMXAA, ASA404 or vadimezan [16]. The effect of vadimezan appears to involve a combination of a direct effect on the tumor vasculature including increased vascular permeability [17], endothelial cell apoptosis [18] and decreased tumor blood flow, and an indirect antivascular effect mediated by cytokines such as TNF, as well as other vasoactive compounds [19].

The second class of tumor VDAs stems from early experimental studies showing that the mitotic poison colchicine disrupted the vasculature of murine tumors [20]. Subsequent studies showed that mitotic poisons such as podophyllotoxin, vincristine and vinblastine [21] and vinca alkaloids in general [22] had a vascular disrupting effect similar to that of colchicine. Further work identified a number of further mitotic poisons, mainly natural products, which showed efficacy as tumor VDA [23] and in particular identified combretastatin A-4 [24]. Lack of solubility was a significant problem with combretastatin A-4, as with other natural products, and a key advance was the synthesis of phosphate prodrugs, which had the advantage of being water soluble and of releasing active drug into the blood through the action of serum phosphatases.
This approach led to the prodrug combretastatin A-4 phosphate (fosbretabulin), which showed excellent activity [25], as well as to several other prodrugs such as OXi4503 [26], BNC105 [27] and CKD-516 [28].

The cellular action of this class of drugs appears to involve effects on actin as well as tubulin, leading to changes in the endothelial cell cytoskeleton. Fosbretabulin also affects the small GTPase RHO, RHO kinase and stress-activated protein kinase 2 (p38 MAP kinase), and these may also contribute to an increase in vascular permeability [29]. The basis for a sustained antivascular effect is not clear and may involve a cytotoxic action on vascular endothelial cells undergoing mitosis.

- **Biomarkers for tumor VDAs**

Biomarkers for tumor VDAs are essential not only for drug-development studies but also for advancement to clinical trial. The earliest marker for both classes of tumor VDA was tumor hemorrhagic necrosis, which developed over the first 24 h after drug treatment and could be readily measured by staining tumor sections with hematoxylin/eosin and scoring necrotic areas [30]. However, this approach method is clearly not appropriate for clinical studies. Therefore, other biomarkers, based on increased tumor vascular permeability and/or decreased tumor blood flow, have been investigated. A list of current biomarkers is shown in Figure 2.

Changes in tumor blood flow have been measured experimentally by double labeling of tumor vasculature (before and after administration of the tumor VDA) [10]. A simple method to measure changes in tumor vascular permeability involves administration of the dye Evans Blue, which binds strongly to albumin and, thus, monitors the rate of extravasation of albumin from the vasculature into surrounding tissue. Tumor blood flow and tumor vascular permeability have been found to be inversely related in tumors from mice treated with vadimezan [17]. A major advance in the development of a biomarker for clinical studies was the development of dynamic contrast-enhanced (DCE) MRI, in which gadolinium diethylenetriamine pentaacetic acid is administered intravenously. This gadolinium derivative, like Evans Blue, is tightly bound to serum albumin, so that increased vascular permeability associated with extravasation and decreased tumor clearance can be followed by the paramagnetic signal of gadolinium. On the other hand, decreased tumor blood flow could be detectable by decreased distribution into tissue following administration of the gadolinium derivative at different times after administration of a tumor VDA. These two opposing effects can be distinguished by appropriate instrumentation and timing [31].

A second potential biomarker exploits platelets, which respond to increased vascular permeability or vascular injury, by extravasation from the vasculature. Platelets respond to collagen in the underlying vascular sheath by degranulation [16] and release of multiple factors including serotonin (5-hydroxytryptamine) and vWF. Serotonin is unsuitable as a biomarker as it is easily oxidized in air, but its hepatic metabolite, 5-hydroxyindoleacetic acid (5-HIAA), which has greater stability, provides a practical biomarker in plasma [32].

vWF has been used as a biomarker experimentally for fosbretabulin [33] and vadimezan [34] and also clinically as a biomarker for the tubulin binder CYT997.
Phase III clinical trials of vadimezan

Phase I/II clinical trials of vadimezan
Phase I clinical trials of vadimezan used escalating doses at three-weekly [39] and weekly [39,40] schedules, as well as a crossover three-weekly design [41]. DCE-MRI demonstrated a reduction in tumor blood flow, as well as an increase in tumor vascular permeability; these changes occurred within 4 h of treatment with recovery at later times [41,42]. The trials also utilized plasma 5-HIAA as a biomarker and showed dose- and time-dependent increases [41,43]. A plethora of side effects included changes in visual perception, urinary incontinence and anxiety, but side effects rapidly reversed following cessation of the drug infusion. Transient reversible increases in corrected-QT (QTc) interval were also noted at the highest doses. Drug-induced changes in visual perception may have been caused by inhibition of phosphodiesterases [44]. Two unconfirmed partial responses were recorded, the first in metastatic melanoma and the second with cervical carcinoma.

The design of Phase II trials of vadimezan took into account a number of preclinical studies showing that co-administration of vadimezan enhanced the antitumor activity of ionizing radiation, hyperthermia and a variety of cytotoxic drugs [45]. Of particular note was the observation that combination of vadimezan with carboplatin and paclitaxel induced lasting complete remissions in mice [46]. Vadimezan was administered clinically at doses that were generally lower than those causing side effects in the Phase I trial, although visual disturbances were noted during drug infusion for many patients. DCE-MRI studies confirmed effects on tumor vasculature and the reported side effects were similar in both the standard therapy and the combination therapy arms, suggesting that vadimezan was well tolerated in these trials. Phase II trials were carried out in patients with non-small-cell lung cancer (NSCLC), ovarian cancer and prostate cancer. The open-label randomized trial against stage IIIB or IV NSCLC utilized carboplatin (AUC = 6 mg/ml/min) and paclitaxel (175 mg/m²) every 21 days for up to six cycles, with or without vadimezan (1200 mg/m²). Toxicity was generally similar in both arms. The RECIST response rate was 31.3% in the vadimezan arm versus 22.2% in the control arm, and the median overall survival was 14 months in the vadimezan arm versus 8.8 months in the control arm. In an extension to the trial, the dose of vadimezan was increased to 1800 mg/m², giving a partial response rate of 37.9% and a median survival of 14.9 months [47].

Two open-label randomized trials were carried out in ovarian cancer and prostate cancer. Patients with previously treated but platinum-sensitive ovarian cancer were treated with carboplatin (AUC = 6 mg/ml/min) and paclitaxel (175 mg/m²) every 21 days for up to six cycles, with or without vadimezan (1200 mg/m²). The RECIST response rate was 63.9% in the vadimezan arm versus 48.6% in the control arm, but the median overall survival was similar in the two arms (8.6 months in the vadimezan arm versus 9 months in the control arm) [48]. Patients with metastatic androgen-independent prostate cancer were treated with docetaxel (75 mg/m²) every 21 days for up to six cycles, with or without vadimezan (1200 mg/m²). The RECIST response rate was 23.1% in the vadimezan arm versus 9.1% in the control arm, but the time to tumor progression was similar in the two arms (8.7 months in the vadimezan arm versus 8.4 months in the control arm) [49].

Phase III clinical trials of vadimezan

The promising results of the Phase II trials led to the design and execution of two Phase III trials in NSCLC; both were randomized double-blind placebo-controlled multicenter studies. The first (ATTRACT-1) utilized carboplatin (AUC = 6 mg/ml/min) and paclitaxel (200 mg/m²) every 21 days with or without vadimezan (1800 mg/m², calculated as the free base rather than the sodium salt) and administered to patients with previously untreated NSCLC. Toxicity was generally similar in both arms but the trial was ceased following interim analysis that demonstrated no survival benefit. The second (ATTRACT-2) utilized docetaxel; 75 mg/kg every 21 days with or without vadimezan (1800 mg/m² free base) in patients as second-line treatment of advanced NSCLC. Again, toxicity was similar in both arms but the trial was ceased following interim analysis that demonstrated no median survival benefit [50].
Phase I/II clinical trials of fosbretabulin (combretastatin A-4 phosphate)
The novelty of the preclinical effects observed for fosbretabulin [25,51] led to the initiation of Phase I clinical trials. Single [52], daily [53] and weekly dose [54] schedules were investigated using fosbretabulin as a single agent. DCE-MRI analysis was used to demonstrate drug effects on tumor blood flow and vascular permeability, and to compare them with studies in rats [55]. The toxicity profile showed a variable and complex series of side effects including flushing, hot flashes, pruritus, headache, diarrhea, cramping abdominal pain, nausea and vomiting. Some episodes of QTc interval prolongation were also seen. However, little evidence of effects expected for a mitotic poison was obtained, suggesting that the drug was acting mainly as a tumor VDA.

A Phase Ib combination study was carried out using fosbretabulin at doses of 36–54 mg/m², with carboplatin AUC 4–5 mg/ml/min and paclitaxel 135–175 mg/m². Dose-limiting toxicity of grade 3 hypertension or grade 3 ataxia was seen in two patients at 72 mg/m². Responses were seen in ten of 46 patients with ovarian, esophageal, small-cell lung cancer and melanoma [56]. A further small Phase Ib study evaluated fosbretabulin combined with radiotherapy in NSCLC. Radiotherapy (27 Gy) was delivered in six fractions, administered twice weekly, and fosbretabulin (50 mg/m²) was administered after the second fraction of radiotherapy. Vascular effects were again monitored by DCE-MRI. The drug was administered as a 10-min intravenous infusion on days 1, 8 and 15 of a 28-day cycle. Treatment was continued until disease progression. QTc prolongation delayed treatment in four patients, causing one to stop treatment. Median survival was 4.7 months with 34 and 23% alive at 6 and 12 months, respectively. Median duration of stable disease in seven patients was 12.3 months (range: 4.4–37.9 months). A further Phase II trial of fosbretabulin (63 mg/m²) combined with carboplatin and paclitaxel was carried out in 44 patients with platinum-resistant ovarian cancer [59]. The drug was administered at a minimum of 18 h before treatment with paclitaxel (175 mg/m²) and carboplatin (AUC; 5 mg/ml/min), repeated every 3 weeks. The combination was well tolerated, with hypertension as the main side effect attributable to C4AP. The response rate was 13.5% by RECIST criteria and the authors concluded that the results warranted a Phase III trial. The FALCON trial of fosbretabulin combined carboplatin, paclitaxel and bevacizumab in an open-label, randomized controlled study for patients with untreated stage IIIb/IV NSCLC [60]. The primary endpoint was progression-free survival with secondary endpoints of response rate and overall survival. There were three reversible cardiac ischemia events in the fosbretabulin arm, none of which required hospitalization, and it was concluded that the addition of fosfretabulin to standard therapy did not add significant additional toxicity and may have provided a survival benefit.

Other clinical trials of tumor VDAs
A number of clinical trials of other tubulin-binding tumor VDAs have been carried out and can be viewed at the clinicaltrials.gov website. However, it is not yet possible to determine, from the available data, whether these drugs show clinical efficacy.

Oxi4503 is a phosphate ester prodrug of combretastatin-A1, which, like fosbretabulin, is hydrolyzed by plasma esterases [26]. A Phase I clinical trial showed, using DCE-MRI, a significant antivascular effect at doses of 11 mg/m² or higher. Adverse drug reactions included hypertension, tumor pain and atrial fibrillation. One partial response was seen in a heavily pretreated patient with ovarian cancer and the recommended dose for the Phase II trial was 11–14 mg/m².

BNC105P is the disodium phosphate ester prodrug of BNC105, an analog of combretastatin A-4. In a Phase I clinical trial [61], BNC155P administration induced a significant decline in tumor perfusion in some patients, as determined using DCE-MRI. Increases in blood pressure were closely monitored but were not prominent within the study. Four patients achieved stable disease but there were no objective responses; the recommended dose for Phase II trial was 16 mg/m².

Plinabilin (NPI-2358) is a diketopiperazine derivative with colchicine-like tubulin binding activity. Phase I trial demonstrated a drug-induced decrease in tumor blood flow, as measured by DCE-MRI. Hypertension was observed in several patients and side effects such as nausea, vomiting, tumor pain and fever were similar to those observed in other trials of tumor VDA. The recommended dose for Phase II trial was 16 mg/m² [62].

CYT997 is a methylbenzylaminopyrazine derivative that binds to the colchicine site of tubulin. Oral bioavailability was observed in a Phase I trial with approximate linear pharmacokinetics over an 11-fold dose range. The trial utilized plasma VWI.
concentrations as well as DCE-MRI as biomarkers for tumor VDA activity. Fatigue and hypoxia were dose limiting and the recommended oral dose Phase II trial was 118 mg/m² [35].

Two further trials are in progress. First crilobulin (crinobulin; EPC2407) is a small-molecule inhibitor that binds to the colchicine binding site or tubulin. Phase I trials are in progress and have shown signs of antivascular activity [63]. Second, CKD-516 is a valine-ester prodrug of SS16, which is an analog of combretastatin A-4 and BNC105 [28].

Future perspective
Clinical trials of tumor VDAs have now been in progress for some years and while evidence for anti-tumor activity in Phase II studies has been encouraging, Phase III trials have so far failed to provide significant increases in median survival. These disappointing results can be compared with those of bevacizumab, the most commonly used antiangiogenic agent [64], and raise broader questions on the general efficacy of vascular directed therapy in humans. They also raise the question of why the high activity of both tumor VDAs and antiangiogenic agents in preclinical rodent models have not translated to clinical trials. However, results to date should not be taken as an indication that vascular-directed anticancer treatment is ineffective, but rather that we need to obtain a better understanding of how these approaches can best be applied to cancer patients.

One of the main roadblocks to clinical progress with tumor VDAs has been a lack of detailed knowledge of molecular targets and signaling pathways. The molecular target of vadimezan is still unknown, although a number of signaling pathways, including those involving cytokines and ceramide, as well as changes in the actin cytoskeleton, have been identified [16,38]. Tubulin has been identified as a molecular target for fosbretabulin and related compounds but not for vadimezan, and complex changes in cellular signaling occur in response to fosbretabulin [29] but the relationship between these changes and on the in vivo effects on endothelial cells needs further study. In addition, unanswered questions on molecular targets and several issues relating to the administration of tumor VDAs need to be addressed, as outlined below.

Duration of vascular disruption
Early preclinical studies using physical disruption of tumor blood flow demonstrated that tumor tissue damage was reversible for the first 2–4 h and that it was only after longer disruption times that irreversible tumor necrosis ensued [10]. It has been argued that in mice, the induction of the cytokine TNF, which occurs 3–6 h after administration of vadimezan [37], adds to the tumor vascular disrupting effect by increasing the overall duration of vascular disruption [19]. A preclinical study on the effect of vadimezan on a subcutaneous melanoma xenograft showed that maintenance of a high plasma drug concentration over more than 6 h by multiple dosing improved activity, leading to complete tumor regressions [65]. Clinical studies incorporating administration schedules of tumor VDAs that extend the period of vascular disruption have not yet been tested.

Physiological responses to tumor vascular disruption
It is clear from several studies that administration of tumor VDAs leads to increased hypoxia [66]. Tissue responses to hypoxia, particularly the induction of HIF-1α transcription factor, are also well characterized and include the induction of proangiogenic factors such as VEGF [67]. It might therefore be expected that the observed changes in tumor blood flow in clinical trials would be followed by increased angiogenesis and that a period of vascular disrupting therapy should be followed by, or alternated with, antiangiogenic therapy. No clinical trials of such timed therapy have been undertaken.

Selection of tumor types according to vascular status
The premise for tumor VDA efficacy is based on the concept that the tumor vasculature is more permeable than normal tissue vasculature and is therefore more susceptible to disruption. Preclinical studies show that some areas of tumor tissue are less affected by a tumor VDA, giving rise to a ‘viable ring’ on the tumor periphery [68], suggesting that tumor vasculature is not universally sensitive to such therapy. Ideally perhaps, individual clinical tumors might be assessed for sensitivity to tumor VDA therapy, for instance by dynamic MRI. Alternatively, tumors might be identified genetically as likely to exhibit sensitivity as a prerequisite for trial. For example, clear cell renal carcinomas lacking a VHL gene are known to activate the HIF-1α pathway and to over express VEGF, making them good candidates for VDA therapy [69]. Clinical trials specifically targeting such tumors have not been tested.

Stabilization of tumor vasculature by concomitant medication
An important distinction between tumor VDAs and antiangiogenic agents is that they act in opposite directions with the latter acting to stabilize and normalize tumor vasculature. It follows that antiangiogenic agents are likely to antagonize the action
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Executive summary

- Tumor vascular disrupting agents (VDAs) act selectively to increase vascular permeability and decrease blood flow in tumor tissue, leading to vascular failure.
- Two main classes of tumor VDAs have progressed so far to clinical trial: the ‘flavonoid’ class and the tubulin poisons class.
- Vadimezan (DMXAA) is a member of the flavonoid class and has progressed to Phase III clinical trial.
- Fosbretabulin (combretastatin A-4 phosphate) is a member of the tubulin poison class and has progressed to Phase II clinical trial.
- A number of other members of the tubulin poison class are currently undergoing Phase I/II clinical trial.
- Both classes of tumor VDAs have generally been tested clinically in combination with cytotoxic drugs such as carboplatin and paclitaxel. The tubulin poison class may also have additional intrinsic cytotoxic activity.
- An important clinical component is the measurement of effects on tumor vascular permeability and blood flow, which has generally employed dynamic contrast-enhanced MRI and a gadolinium-based biomarker.
- Promising clinical results, as well as indications of efficacy as tumor VDAs, have been obtained in Phase II clinical trials but Phase III trials have not yet demonstrated an increase in patient survival.
- Many questions as to the optimal method of designing and administering tumor VDAs have not yet been answered.

Important paper that suggests the strategy of considerable interest

A number of other members of the tubulin poison class are currently undergoing Phase I/II clinical trial.


Important paper that suggests the strategy of considerable interest

- The lack of strong evidence of clinical antitumor activity should not be taken as an indication that such drugs are intrinsically inactive, but rather that we still have much more to learn about optimal scheduling and drug combination in this type of therapy.

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No writing assistance was utilized in the production of this manuscript.

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- of interest
- of considerable interest


Important paper that suggests the strategy of considerable interest

- of interest


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