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## Literature Review

# A review of vascular disrupting agents as a concomitant anti-tumour modality with radiation

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## Abstract

*Background:* Tumour vasculature plays an important role in the development, maintenance and sustainability of a tumour. Endothelial cells which are recruited into the tumour stroma facilitate the formation of essential blood vessels that deliver nutrients and oxygen to tumour cells. A growing body of research is showing that there are synergistic anti-tumour effects when anti-vascular agents are combined with radiation. More recent reports have described favourable radiation response as a function of vascular targeting and blood vessel breakdown, primarily through interactions of radiation with vascular endothelial cells. Vascular disrupting agents are being utilised in several forms that include molecular targeting, biophysical assault and biological interference.

*Purpose:* In the present review, we examine current advances in anti-vascular agents to enhance tumour response when combined with radiation therapy.

*Methods:* A comprehensive literature search was conducted on the US National Library of Medicine, National Institutes of Health (PubMed) using the following search keywords: vascular disrupting agents, radiation sensitisation, anti-angiogenic therapy, anti-vascular therapy, radiation therapy.

*Conclusion:* Current research suggests the applicability of vascular disrupting agents as an effective radiation sensitisation agent. Pre-clinical and clinical trials have been well developed to form the theoretical framework to apply this powerful modality to the treatment of cancer.

*Keywords*: anti-angiogenesis; anti-vascular therapy; cancer therapies; radiation therapy; vascular disrupting agents

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## INTRODUCTION

Tumourigenesis from malignant neoplasms to metastatic disease involves a multi-step process

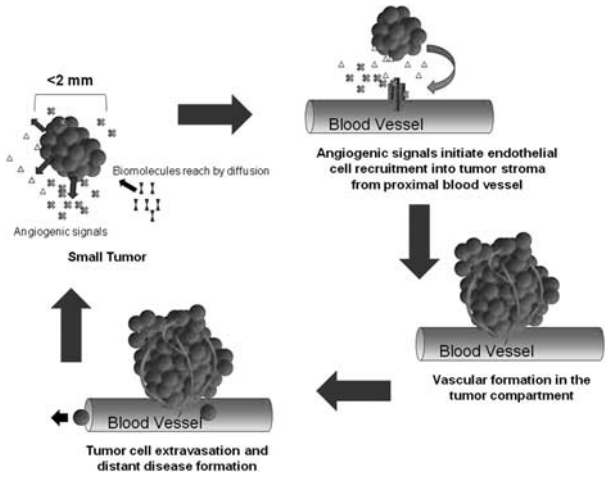


*Figure 1. Beyond ~2 mm, tumours turn on their 'angiogenic switch' by which signals recruit endothelial cells into the tumour stroma and bridge blood vessels to supply nutrients and biomolecules for tumour survival.*

that includes transformation, angiogenesis, motility and invasion to the formation of tumour emboli and circulation to distant anatomic locations.[1] Our current understanding of tumour biology illustrates the essential role of angiogenesis and vascularisation in the tumour's lifecycle. For decades, the tumour's vasculature was seen as an important substrate by which tumour cells were woven within a complex structural matrix. It has been long reported that there is a dependency of tumours to vasculature[2] that described tumour progression as the shift in reliance from diffusion to perfusion for tumours growing beyond 2 mm (Figure 1).

Vascularisation has an essential function in gas exchange, nutrient delivery and intercellular signalling.[1,3] In initial stages, tumours rely heavily on sourcing their nutrient supply by surrounding tissue through passive diffusion. As a tumour grows beyond 2 mm, its capacity to sustain its growth is unbalanced by inefficiencies in passive diffusion and therefore tumours respond by turning on the angiogenic 'switch' to induce vascular blood perfusion into the tumour compartment.[4,5] These physiological and biological processes often dictate the responsiveness of the tumour to anti-cancer agents and therefore have been the centre of many studies.[6–8] Previous investigations have explained changes in tumour response in association with vascular reorganisation through molecular targeting of the endothelial cells found within the tumour's vascular matrix.[9,10] However, there are varying limitations when vascular disrupting agents are delivered as a monotherapeutic agent. These limitations include drug efficacy, target specificity and delivery of an effective dose. However, when combined with other anti-cancer agents such as radiation, vascular targeting agents have shown some provocative results in enhancing tumour killing capacity.[10,11]

In radiation biology, it has been long reported that radiation exposure reorganises the tumour vasculature. At varying single fractions of doses up to 8 Gy, tumours exhibit some biological changes that include enhanced cell signals that are released into the tumour stroma in response to radiation injury. Many of these cell signals travel to the vasculature to initiate repair and repopulate damaged vessels. Higher doses of radiation exposure demonstrate different patterns of radiation injury in which vessels often succumb to endothelial cell death which subsequently retracts branching of the tumour's vascular configuration.[2,12,13] In principle, the combined use of vascular targeting agents and radiation would naturally infer a favourable tumour response as both mechanisms of action on endothelial cell targets can potentiate vascular atrophy.[10] The present review examines the role that endothelial cells play in tumourigenesis, vascularisation and tumour protection from radiation injury. We also examine the mechanisms of action for vascular targeting agents as anti-cancer agents and how this modality can be used as an effective combinative therapy to radiation therapy.

## ANGIOGENESIS AND THE TUMOUR'S VASCULAR ARCHITECTURE

Angiogenesis is described as the formation of new blood vessels in both neoplasms and normal tissue; existing in wound healing, normal growth, inflammation.[14] In tumourigenesis, the development of blood vessels that infiltrate the tumour mass can determine its viability, the success of the tumour's progression in situ, and



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*Table 1. Vascular signals involved in vascular growth and inhibition*

| Vascular signals | Inhibitor/promoter | Action |
|---|---|---|
| Vascular endothelial growth factor | Promoter | Acts on cultured endothelial cells to migrate and proliferate. Acts as a mitogen to endothelial cells |
| Fibroblast growth factor | Promoter | Induces proliferation, migration and differentiation of endothelial cells to tumour compartment |
| Angiopoietin 1 | Inhibitor/promotor | Blood vessel maturation and stability. Some reports demonstrate overexpression of Agiopoietin 1 can inhibit angiogenesis and cause tumour growth delay |
| Angiogenin | Promoter | Interacts with endothelial cells to activate the phospholipase pathway that subsequently promotes angiogenesis in tumours |
| COX-2 | Promoter | Promotes endothelial cell proliferation and homeostasis |
| Endostatin | Inhibitor | Suspected in inducing apoptosis in endothelial cells |
| Vasostatin | Inhibitor | Inhibits endothelial cell growth and neovascularisation |
| Angiotensin | Inhibitor | Inhibition of endothelial cell tubule formation |
| Angiostatin | Inhibitor | Inhibition of endothelial proliferation |
| Angiopoietin 2 | Inhibitor | Vessel destabilising agent. Can lead to permeability and dissociation of cell-cell contacts in cultured endothelial cells |

also plays an important role in haematogenous metastatic spread. Tumours begin their lifecycle without any vasculature and dependent on the diffusion of molecules from the surrounding microenvironment. Subsequently, there is a disparity between metabolic supply and demand and the tumour begins emitting signals that lead to the recruitment of endothelial cells to bridge vessels into the tumour's matrix.[15] The inadequate supply of oxygen that initiates this process produces several important signalling cascades, particularly, vascular endothelial growth factor (VEGF). VEGF is a signalling macromolecule that responds to hypoxia and oncogenesis. When bound to tyrosine kinase receptors on the cell surface of existing vessels, a surge of events initiate new vessel formation through endothelial cell proliferation as well as recruitment.[8]

Endothelial cells also have a critical role in the formation of tiny capillaries and are organised to enable free gas exchange, nutrients and waste products. In normal tissues, the vasculature is well defined, has predictable organisation and controls the exchange of molecules adequately. In contrast, tumour vasculature is highly disorganised and inefficient. The vasculature has weak endothelial cell junctions and is typically porous. The vascular structure also does not support adequate oxygen supply into the tumour's core and therefore explains the predominance of hypoxia within this region. As a result of hypoxia, cellular signals such as those leading to VEGF production are over-expressed leading to an overpopulation of vessels within tumour stroma. Though initially counterintuitive, this abundance of blood vessels does not lead to an increase in efficiency and delivery of essential molecules to the tumour compartment and is explained by the structural abnormalities associated with such vessels.[16] Jain[17] characterised the blood blockade as a result of abnormal growth and organisation of the vasculature. Tumour vasculature was seen as immature and often leading to 'dead ends' which resulted in blood flow heterogeneity. From a clinical stand-point, this erratic scaffolding of vessels can result in difficulty in properly delivering drugs into tumours. In radiation therapy, these conditions often lead to hypoxia, which is known to be a major contributor to radiation resistance.[10,18]

## VASCULAR DISRUPTING AGENTS

The abnormal vessel structure associated with cancers has been identified as a possible limitation to the therapeutic success of cytotoxic agents.[16] In order to address these limitations, investigators have examined ways of alleviating the malformation of vessels through molecular targeting approaches (Table 1). Such vascular disrupting agents are ideal in their use as anti-cancer agents because they do not discriminate between different neoplasms and specifically target the endothelial cells, which can be found



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in vasculature formations within the all tumour types. Other studies have looked into how pro-angiogenic biomolecules affect vasculature and tumour cell dependence to such vascular promoting agents such as VEGF.[19] As a monotherapeutic agent, vascular disrupting agents have been shown to significantly modulate tumour blood flow and oxygenation following 1–6 hours of administering a combretastatins vascular disrupting agent to CaNT mammary carcinoma bearing mice.[20]

## Tyrosine kinase inhibitors

The 'angiogenic switch' is controlled by a fine balance between competing proangiogenic and angiogenic inhibitory signals.[17] VEGF, a pro-angiogenic factor, is a glycoprotein that works by binding to tyrosine kinase receptors on endothelial cells and is implicated in radiation resistance.[21] It belongs to a family of glycoproteins (VEGF-A, VEGF-B, VEGF-C, and VEGF-D) although not all members of this family are solely involved in angiogenesis but can also play a role in other physiological processes.[22] VEGF works by initiating the MAPK–Raf–MEK–ERK pathway[8] subsequently activating gene expression and initiating cell differentiation. Although VEGF can act as a potent mitogen,[5] it also has the ability to recruit pre-existing endothelial cells into the tumour vasculature.[19,23] In normal vessel formation, VEGF is counterbalanced by endogenous angio-inhibitory proteins that create homeostasis in vessel formation. However, abnormal cell signalling in tumour progression can deactivate the expression of these inhibitory signals and therefore result in inhomogeneities in vascular growth. Tyrosine kinase inhibitors are competitive binding molecules to the VEGF receptor on the cell surface of endothelial cells. These molecules were directed to interfere with initiating the mitogenic effects of VEGF binding inasmuch as inhibiting endothelial cell conscription to the tumour stroma. Sutent (SU11248) is such an example of a tyrosine kinase inhibitor currently approved by Health Canada and the FDA as an anti-cancer agent.[24]

## Monoclonal antibodies for anti-angiogenic targeting

Tumour vasculature can be created through mechanisms that elicit mitogenic reactions in existing endothelial cells within the tumour stroma. However, endothelial cells may also be recruited through angiogenic signals such as VEGF, however, their ability to migrate into the tumour microenvironment is reliant on associations with cell adhesion molecules known as integrins.[25] Integrins are receptors found in the extracellular matrix and are involved in cell signalling, motility and can mediate the cell cycle, and of particular importance, is the $\alpha_v\beta_3$ integrin in oncogenesis.[25,26] Monoclonal antibodies, which are designed as specific antibodies to the $\alpha_v\beta_3$ integrin has been demonstrated to inhibit the recruitment of endothelial cells into the tumour matrix.[25] Another study conducted by Takahashi et al.[27] demonstrated the effectiveness of introducing monoclonal antibodies specifically targeted for cell surface antigens in endothelial cells. This group showed that anti-EDG monoclonal antibodies could be used to control angiogenesis in vivo.

## Receptor anti-sense inhibition

Cell signalling receptors are responsible for the activation of many molecular signalling cascades that can lead to promoting angiogenic processes during tumour development[28,29] One such example is epidermal growth factor receptor (EGFR) activation which has a key role in vascular development in neoplasms which has been inhibited by anti-sense methods. Targeting strategies involved in anti-sense inhibition rely on understanding the sense oligonucleotides involved in pathway reactions. In these methods, a synthesised construct (anti-sense) is created to be complimentary to the sense sequence (i.e. receptor) and blocks its transcription and subsequent translation, blocking gene expression, and in this instance inhibiting signal cascading downstream. Li et al.[30] demonstrated that EGFR-anti-sense administration was successful in blocking tumour angiogenesis in human head and neck squamous cell carcinomas although these results were modest when this approach was used as a monotherapy. However, when used in combination with endostatin, a significant difference in tumour response was observed. Kamiyama et al.[31] explored anti-angiogenesis behaviour in human gastric (NUGC-4 in vivo) and prostate (PC-3 in vitro) cancers and found decreases in



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tumour dissemination after treatment with phosphorothioate anti-sense oligonucleotides.

## COMBINING ANTI-VASCULAR AGENTS AND RADIATION

The effects of radiation on tumour vasculature have been well documented. Canonical radiobiology explains tumour response as a function of direct and indirect effects on the bulk tumour without emphasis on its supporting network (i.e. vascular components).[32] However, reports have elucidated effective vascular modulation through these indirect and direct radiobiological effects to endothelial cells of tumour blood vessels, possibly through molecular factors.[9,33] Some reports have demonstrated changes to the vasculature that described radiation treatment transformations in tumour leakiness, oxygen perfusion and abundance of vascular structures. A study by Park et al.[34] linked vascular response to radiation. The investigators tested radiation response in glioblastoma and primary astrocytes in vitro and evaluated mitogen-activated protein kinase (MAP-K) activity responsible for inhibiting radiation damage in vasculature and showed its effect on tumour vasculature.

With recent attention given to vascular targeting agents as a possible approach to eradicating a tumour, increased attention is being placed on using anti-vascular agents in combination with ionising radiation because of the potential effects that both modalities have on vasculature. Since both mechanisms have vascular destructive properties, it would appear that combining these two modalities may also potentiate tumour killing ability. It is important to mention that although vascular targeting agents and ionising radiation share destructive effects and mechanisms, they do not completely overlap in mechanism and achieving the same tumour toxicities.[35] There are several reasons why combining vascular targeting agents would be beneficial to radiation coupling. First, radiation response may upregulate several angiogenic factors such as VEGF, the factors targeted are also believed to be involved in radiation resistance, and have been the foundation of some anti-vascular drugs as such as Avastin (Bevacizumab), angiostatin and endostatin. Pre-clinical trials have demonstrated that blocking VEGF can enhance radiation efficacy in human squamous cell cancer xenografts,[6] possibly because the vascular architecture contributes to regenerative properties to the tumour. Second, it is also believed that combining anti-vascular agents with radiation may alleviate hypoxic tumour conditions thereby making radiation therapy administration more effective. It may appear counterintuitive that eliminating vasculature enhances tumour oxygenation. However, a study by Teicher et al.[36] measured increased oxygenation after administration of TNP-470 and minocycline, believed to be involved in vascular modulation. Increased oxygenation could possibly be explained by vascular normalisation.[17] Tumour vasculature was believed to be a matrix of immature, leaky and inefficient vessels that contributed to an obstructive delivery path to blood flow. Jain's[17] model proposed that eliminating these ineffective vessels would enhance delivery of blood (and therefore oxygen) to the tumour compartment. In the radiotherapy context, this would serve as a good approach to mitigate hypoxia and therefore optimise radiation biological effects. Lastly, combining vascular targeting agents and radiation establishes a good concomitant modality because both approaches cause endothelial cell aberrations. Endothelial cells can modulate radiation response because of their role in upregulated cell signals that contribute to radiation resistance.[10] Their destruction or inhibition by such agents then may diminish radiation resistance. Furthermore, endothelial cells bridge vessels to cancer stem cells that are often most resistant to radiation.[10,37] Therefore, anti-vascular agents could potentially create very favourable conditions for radiation toxicity to cancer stem cells.

### Combining a vascular disrupting agent (5,6-Dimethylxanthenone-4-acetic acid [DMXAA]) and radiation

As an anti-tumour agent, DMXAA has been tested in pre-clinical and clinical trials as a monotherapeutic agent and also combined with radiation therapy.[7] DMXAA is a compound that is similar to flavone acetic acid[7] and targets tumour vasculature by modifying cellular response pathways that control apoptosis, particularly suspected in triggering tumour necrosis factor.[7,35]



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When DMXAA is combined with radiation, the result is a morphological transformation in the endothelial cell, reorganisation of the endothelial cell matrix and finally the initiation of apoptosis. Murata et al.[7] tested combination therapy in pre-clinical C3H mammary and KHT sarcomas with DMXAA and radiation. The results demonstrated some varying limitations such as administration time, DMXAA dose given, radiation doses delivered and also sequencing between the drug and the administration of radiation.[7] Tumour effects in preclinical murine models were seen ~30 minutes after treatment with DMXAA.[38] In another study by Wilson et al.,[35] response was measured after administration with DMXAA in RIF-1 tumours and showed progressive growth delay in time lapsed measurements.

## OBSTACLES IN OPTIMISING TREATMENT EFFICACY

The prospects of combining anti-vascular agents with radiation are promising. However, there are many obstacles in planning for effective delivery of these two modalities together in order to attain a desired therapeutic ratio. Anti-vascular agents may impose several toxicities because of the physiological dependence to vessel formation and vascularisation. Although vascularisation plays an essential role in tumourigenesis and cancer biology, it is also engaged in many other functional processes such as wound healing, inflammatory response, normal cellular growth and repair mechanisms.[14] Therefore, clinical and preclinical data have reported adverse reactions such as tachycardia, blood pressure changes[39,40] and delayed wound healing.

Engaging in combination therapies requires close attention to the administration sequence of both agents.[7] Wilson et al.[35] report the potential problems of DMXAA administration as a precursor to radiation treatment in their pre-clinical trials. These researchers propose that DMXAA may alter the oxygen state of the tumour and therefore may have a negative effect when radiation is delivered after. Furthermore, because radiation therapy is often delivered in fractionated regimens, obstacles in timing vascular targeting agents between radiation fractions would be important considerations as biological responses may potentially hinder radiation treatment effectiveness.

One new form of anti-vascular treatment that may prove useful and bypass the risk of systemic side effects is the focussed biophysical perturbation of blood vessels through the use of microbubbles and ultrasound. In this mechanism microbubbles are used to mechanically disrupt endothelial cells in blood vessels through cavitation. This then results in endothelial cells becoming sensitive to radiation-induced cell death and short-term tumour responses macroscopically consistent with vascular disruption. Such methods have demonstrated 40–60% tumour cell death 24 hours after the administration of 2 Gy doses of radiation with a priori treatment of tumour vasculature with microbubble-enhanced ultrasound which otherwise on its own causes no appreciable macroscopic damage.[40,41]

## CONCLUSION

There is an immense opportunity to explore the clinical applications of vascular targeting agents and radiation. Close consideration must be put into application techniques and toxicities related to combining both treatments. Vascular targeting agents can enhance radiation treatments through the multitude of biological approaches and strategies to reduce hypoxia, starve cancer stem cells and reduce the angiogenic signals that induce radiation resistance are all undergoing serious considerations in pre-clinical and clinical trials. It is possible that when optimal conditions are reached, vascular targeting agents will work in symphony with radiation to deliver a desired synergistic effect on tumour control.

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