The Role of Modern Medical Imaging in Evaluation of Tumor Response to Vascular Targeting Therapy

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Abstract: The unique features of tumor vasculature represent an attractive target that can be utilized by vascular targeting therapy (VTT). The pharmaceuticals applied in VTT are classified into angiogenesis inhibiting agents (AIAs) and vascular disrupting agents (VDAs) according to their mechanisms of action. AIAs inhibit the formation of new vessels, while VDAs selectively destroy the existing tumor vessels. Both reduce the blood supply, cause the tumor necrosis, and delay the tumor growth, but they cannot eradicate tumor. This novel VTT challenges the traditional criteria for therapeutic evaluation based on tumor size. Functional and metabolic studies are thus necessary to monitor the early vascular alterations and to estimate the therapeutic efficacy for prompt justification and adjustment in oncological patients under the VTT regimen. In this article, we review the characteristics of tumor vessels, classification of VTT, and lead drugs in clinical development. We also envision, in addition to the conventional anatomy-based criteria, comprehensive imaging protocols for the assessment of tumor response to VTT combining morphological, functional and metabolic imaging biomarkers, applicable for magnetic resonance imaging, computed tomography, positron emission tomography, and ultrasound.

Key Words: Vascular targeting therapy; angiogenesis inhibiting agents; vascular disrupting agents; tumor response; imaging biomarkers; magnetic resonance imaging; computed tomography; positron emission tomography; ultrasound

1. Tumor Vasculature

A mature vascular network is a hierarchical structure of high efficiency. The blood supply to normal tissue is modulated with delicate balance between the inward perfusion of arterial blood with nutrients and oxygen and outward drainage of waste through veins and lymphatics. Angiogenesis is regulated via the tradeoff between pro- and anti-angiogenic molecular factors according to metabolic demands of the tissue. The hierarchical organization of vasculature suffices the blood supply in tissues for maintenance of structural and physiological requirements [1].

Solid tumors necessitate a functioning vascular network to sustain their metabolism. Tumors can develop various strategies, e.g. vessel co-option, intussusception of existing vessels and the recruitment of bone-marrow-derived endothelial progenitor cells into growing vessels [2], to acquire nutrients and oxygen, which only partially satisfy the ever increasing need of blood supply during tumor growth. Once a tumor expands beyond several milliliters in diameter, it has to initiate its own angiogenesis to maintain survival and accelerating growth. Tumor angiogenesis is non-self-limiting, a feature uncommon in normal tissues, has therefore been recognized as a hallmark of tumor. Ultimately it cannot match with the uncontrolled tumor expansion [3]. Tumor vessels do not share the same maturity with normal vessels; they are primitive and abnormal in structure [4, 5]. Tumor vasculature is poorly developed and hyperpermeable [1, 5]. The vessel walls are lined with discontinued monolayer endothelia with loose intercellular junctions, lacking sufficient structural investment with irregular vascular smooth muscle cells, pericytes and base membranes. These vascular defects lead to the hyperpermeability to macromolecules and consequent fluid effusion from tumor vessels. In addition, tumor vascular networks are chaotic. Nonhierarchical tumor vessels with asymmetric branching patterns, uneven length and inconsistent diameters increase the vascular geometric resistance and thus compromise the delivery of nutrients and oxygen, as well as therapeutic agents, to tumor cells, which causes the tumor hypoxia and decreases the therapeutic efficacy [5].

The micro-regional hypoxia in tumor, together with other factors, such as pH change and cytokine release
Angiogenesis or ocular angiogenic elements. The distinct abnormal vasculature. The two approaches are borne anticancer agents. Angiogenesis inhibiting agents (AIAs) like growth factor (IGF), tumor is often side effects with a narrow therapeutic margin. The specificity to tumor cells and can cause severe systemic minimal toxicity. Conventional chemotherapies lack the It has been a long quest in cancer therapy to locate the selective tumor targets with maximal specificity and minimal toxicity. Conventional chemotherapies lack the specificity to tumor cells and can cause severe systemic side effects with a narrow therapeutic margin. The targeting therapy distinguishing between malignant and nonmalignant cells is one of most important goals in anticancer therapy [7].

The tumor vasculature is an appealing therapy target, because it is the key route where nutrients deliver, metastases spread and blood-borne anticancer agents enter. Targeting one single tumor vessel may lead to the death of thousands of downstream tumor cells. Besides, the untransformed vascular endothelial cells are not susceptible to genetic mutation. Moreover, the alteration of vascular properties and subsequent morphological, functional and metabolic cellular events may be noninvasively monitored with quantitative imaging metrics, demonstrating the early therapeutic effects [8, 9].

According to targeting new or existing tumor vessels, vascular targeting therapy (VTT) can be divided into two groups [1]. Angiogenesis inhibiting agents (AIAs) suppress the angiogenic process in tumors, resulting in limited tumor growth by targeting VEGF and its receptor, as well as other pro-angiogenic elements including basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), placental growth factor (PIGF), insulin-like growth factor (IGF), mammalian target of rapamycin (mTOR), and histone deacetylases [2, 10-14]. Distinctively, vascular disrupting agents (VDAs) cause rapid selective shutdown of the established tumor vessels already present at the time of treatment. VDAs interfere with the integrity of endothelial cytoskeleton via signaling pathway or apoptotic induction, leading to secondary tumor necrosis [5, 15]. The two approaches are
Table 1. Reprehensive drugs of VTT in clinical development

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name</th>
<th>Company</th>
<th>Clinical developmental state</th>
<th>Description</th>
<th>Proposed action mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIA</strong></td>
<td>Bevacizumab</td>
<td>Genentech</td>
<td>Phase III/IV</td>
<td>Monoclonal antibody</td>
<td>Block VEGF factor A</td>
</tr>
<tr>
<td><strong>VDA</strong></td>
<td>L19-IL2</td>
<td>Darleukin</td>
<td>Phase II</td>
<td>Antibody fragment directed IL-2</td>
<td>Target extra-domain B of fibronectin</td>
</tr>
<tr>
<td><strong>Small molecule</strong></td>
<td>ASA404</td>
<td>Vadimezan</td>
<td>Phase III</td>
<td>Analogue of flavone acetic acid</td>
<td>Induce tumor necrosis factor α</td>
</tr>
<tr>
<td><strong>Tubulin-binding</strong></td>
<td>CA4P</td>
<td>Zybrestat</td>
<td>Phase III</td>
<td>Combretastatin</td>
<td>Disrupt the cytoskeleton of endothelia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OxiGene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVE8062</td>
<td>Ombrabulin</td>
<td>Aventis</td>
<td>Phase III</td>
<td>Combretastatin</td>
<td>Disrupt the cytoskeleton of endothelia</td>
</tr>
<tr>
<td>ZD6126</td>
<td>NA</td>
<td>Angiogene</td>
<td>Phase II</td>
<td>Colchicine analogue</td>
<td>Disrupt the cytoskeleton of endothelia</td>
</tr>
<tr>
<td>CA1P</td>
<td>NA</td>
<td>OxiGene</td>
<td>Phase I</td>
<td>Combretastatin</td>
<td></td>
</tr>
</tbody>
</table>

A number of VTT agents have undergone clinical trials in humans, either as single agent or in combination with conventional cytotoxic therapies [16]. Several representative drugs are listed in Table 1. Out of the agents in VTT, bevacizumab (a humanized anti-VEGF antibody) has been approved by the US Food and Drug Administration (FDA) as an AIA for the treatment of certain tumors in combination with other therapies. Its action mechanisms may lie in antiangiogenic effect and tumor vascular normalization, along with the inhibition of circulating endothelial cells and endothelial progenitor cells colonizing the tumor vasculature. Clinical trials have demonstrated that the normalization of abnormal vasculature may play a key role in its clinical effects, and combination therapy with other anticancer approaches can enhance the therapeutic efficacy [2, 17].

3. VDAs

VDAs can be categorized into two subgroups: ligand-directed/biological and small molecule VDAs. Ligand-directed VDAs are antibodies, peptides or toxic proteins to target the tumor endothelial cells, while the small molecule VDAs selectively disrupt the rapidly-proliferating or newly-formed tumor vessels, inhibit tumor blood flow and induce vascular shutdown. Both approaches cause central necrosis of tumor, but always leave peripheral tumor residues, upon which the tumor unavoidably relapse [8]. Ligand-directed VDAs are endothelium-specific and directed toward tumor antigens or receptors expressed on tumor endothelia which are associated with angiogenesis and thrombosis [15]. Although they have shown to activate coagulation factors and thrombosis, leading to tumor necrosis in preclinical or early-phase clinical trials, the long-term efficacy and toxicity of ligand-directed VDAs are yet to be further evaluated [6, 18]. On the contrary, small molecule VDAs have demonstrated their antitumor
efficacy in extensive preclinical and clinical studies. Based on the drug mechanism, small molecule VDAs are further divided into flavonoids and tubulin-binding VDAs [19] (Figure 1).

### 3.1 Flavonoids

Led by ASA404 (5,6-dimethylxanthene-4-acetic acid/DMXAA), flavonoid VDAs have a structural variety. Their action mechanisms are tubulin-independent and have been speculated as two-fold: direct disruption of tumor vascular endothelial cells via the apoptosis induction, which has been evidenced by dose-dependent therapeutic effects in animal models within 30 minutes after treatment [20, 21]; and indirect upregulation of cytokines including tumor necrosis factor-α, interferon and interleukin, which leads to vascular collapse and decreased blood supply [22, 23]. In vitro study also showed that ASA404 reorganized the actin cytoskeleton of endothelial cells and compromised its integrity, resulting in endothelial deformation [5, 24].

In phase III clinical trials, ASA404 has been widely documented to selectively increase tumor vascular permeability, reduce tumor blood flow and induce endothelial apoptosis within a wide therapeutic window [21, 24, 25]. Dose-dependent blood perfusion drop was an early event in these studies, proceeded by vascular endothelial apoptosis. The suppressed blood flow and promoted endothelial apoptosis was correlated [20]. In an orthotopic model of human head and neck cancer, ASA404 induced a marked decrease tumor blood perfusion after 24 hours [26]. In a patient study, ASA404 caused the reduced blood perfusion up to 66% at 24 hours, consistent with the reported preclinical results [27].

ASA404 was well tolerated in patients without myelosuppression. Reversible dose-limiting toxicities included hypertension, confusion, tremor, slurred speech visual disturbance, anxiety, urinary incontinence, and cardiac events, etc [28, 29].

### 3.2 Tubulin-binding VDAs

Tubulin-binding/microtubule-destabilizing VDAs include a wide range of natural and synthetic compounds. The drugs undergoing clinical development are combretastatin A4 phosphate (CA4P), AVE8062, ZD6126, ABT751, CYT997, MPC6827, Dolastatin 10, MPC6827, NPI2358, EPC2407, combretastatin A1 phosphate (CA1P/Oxi4503), TZT1027, and MN029029 [16, 24]. They selectively bind to either the colchicine or vinblastine site of tubulin, destabilize the polymerization of microtubules, compromise the integrity of cytoskeleton, increase vascular permeability, obstruct the tumor blood flow and induce tumor hypoxia and necrosis [2, 19, 30]. However, the blood supply in normal tissues is less affected [31].

#### 3.2.1 CA4P

Combretastatin A4 is extracted from South African willow tree, *Combretum caffrum* [32, 33]. CA4P is the water-soluble phosphate prodrug of combretastatin A4 [34]. With endogenous phosphatases, CA4P is in vivo dephosphorylated into active form combretastatin A4, which binds to the colchicine site in β-tubulin of microtubule. Structurally similar with colchicine, CA4P mimics colchicine’s effect of inhibiting polymerization of tubulin and interference with tubulin assembly, but in a more rapid and reversible way with greater affinity [35, 36].

CA4P can exert an almost instant selective vascular collapse in tumors with as low as one-tenth of maximum tolerated dose (MTD) in spontaneous and transplanted tumor models. The effect in reducing blood flow was evident as early as 10 minutes after treatment [36], maximal during the following 1-6 hours and continuous for more than 24 hours [31, 37-39]. The half life of CA4P is just 3.6 minutes, while it has been known that the short duration of cutting blood supply may induce the dramatic reduction in tumor burden [1]. In sensitive tumors, CA4P caused the extensive central necrosis up to 90% of tumor mass with a unique peripheral viable rim [40].

As a lead tubulin-binding VDA, CA4P is the first agent approved for clinical trials in this group. In some studies of patients with advanced solid tumors, CA4P was systemically administrated with different regimens, and a wide range of response was observed in terms of dropped blood perfusion and tumor growth delay [41-44]. CA4P has demonstrated beneficial effects on some patients. For example, in a 55-year-old male patient with metastatic anaplastic thyroid cancer, a complete response was observed for more than 4 years after initial treatment. In a patient with non-small-cell lung cancer, the tumor burden was significantly decreased up to 34%. In three patients with colon cancer, medullary thyroid, and renal cancer respectively, the tumor progression was delayed for more than one year [18].

MTD for CA4P was estimated around 68mg/m² in patients [45]. In clinical studies, myelosuppression, stomatitis, and alopecia were absent. The predominant dose-limiting toxicities were hypertension, tumor pain, flushing, pruritus, headache, diarrhea, cramping abdominal pain, nausea, and vomiting [41-44].
Table 2. Comparisons between commonly used imaging modalities in VTT

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Cost</th>
<th>Invasiveness</th>
<th>Sensitivity</th>
<th>Morphological potential</th>
<th>Functional potential</th>
<th>Metabolic/molecular potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>High magnetic strength field</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>CT</td>
<td>Ionizing radiation</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>US</td>
<td>Sound waves</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>PET</td>
<td>Radiation decay</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
</tr>
</tbody>
</table>

The advantages and disadvantages are shown from lowest (+) to highest (+++) level.

3.2.2 AVE8062
Previously named as AC7700, AVE8062 is another promising synthetic analogue of combretastatin undergoing phase III clinical trials. Similar with CA4P, AVE8062 acts via selectively targeting tumor vessels and seems to have higher antivasculac efficacy than CA4P [46, 47]. In tumor models, AVE8062 at 10mg/kg caused almost complete vascular shutdown effect, and blood perfusion was not recovered until 8 hours. Lower doses at 1 or 3mg/kg also induced the drastic drop in tumor blood supply [48, 49]. In clinical studies, the recommended dose of AVE8062 was 50mg/m². In the combination treatment with cisplatin, AVE8062 at a range of doses all showed the antitumor effects including partial response and stable state of tumor in different tumor types [50]. The common side effects were tumor pain, hypertension, cardiac events and asthenia [50].

3.3 Therapeutic effectiveness and resistance of VTT
The effectiveness of VTT is dependent on the duration when the tumor blood supply is compromised and angiogenesis is prevented to sustain tumor growth. The tumor sparing still exists as a viable rim after VTT, because the tumor cells in the periphery can directly obtain the supply of nutrients and oxygen from neighboring normal tissues and engulfed-in normal vessels during the fast growth of malignancies [51]. Therefore, the tumor recurrence is almost inevitable after single-dose treatment [50, 52, 53]. In VTT, the tumor growth is only delayed and the tumor cannot be eradicated, which limits the use of AIA or VDA as monotherapy and necessities the combination therapy with each other or with other cytotoxic, hormonal or radiotherapy therapies to combat the treatment resistance [54-56].

4. Potentials of Multiparametric Imaging Biomarkers for Monitoring Tumor Response to VTT
Traditionally, antitumor efficacy has been evaluated with biomarkers from blood or other body fluids as well as the clinical endpoints including survival, mortality, morbidity, length of intensive care unit stay, etc, which can be difficult to quantify and may not be assessed until long after exposure to the therapy. Obviously, this is not well applicable particularly for new therapies such as VTT. Current evolving advances in multiple imaging modalities including magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET) or single photon emission computed tomography (SPECT), ultrasound (US) and optical imaging (OI), however, may offer reliable and reproducible metrics to develop imaging biomarkers for complementing or replacing the existing clinical endpoints in the evaluation of treatment response [57]. The use of imaging biomarkers has been acknowledged by the FDA in oncological drug development [58].

4.1 Morphological, functional and metabolic evaluation with imaging
For monitoring the tumor therapy response, a reliable, standard and reproducible imaging protocol is critical in both preclinical studies and clinical practice. In 1981, the classical response criteria were proposed by World Health Organization (WHO) [59] and revised with the gauge of Response Evaluation Criteria in Solid Tumors (RECIST) in 2000 [60]. Based on the change of tumor size/volume with 1- or 2- or 3-dimensionai measurement on MRI or CT, the tumor therapeutic efficacy can be classified into complete response (total absence of disease), partial response (reduction of at least 50% of the product of two diameters), progressive disease (increase of 25%), and stable disease as every response between partial response and progressive
biological tissues. After being excited with biomarkers combine the different sets of readout from parameters that reflect specific aspects of the tumor become visible, serial dramatic intratumor functional and metabolic events have taken place, which, however, is imperative indication for prompt therapeutic justification and adjustment for oncological patients under the regimen of VTT. Therefore, traditional response evaluation criteria may not be sufficient to monitor the VTT efficacy or activity for achieving patient benefits, with the possible underestimation of immediate functional and metabolic changes after treatment, given the absence of size/volume change of tumor. According to the action mechanisms of VTT, other surrogates have to be used for providing the complementary information to anatomical data. Nonetheless, how to monitor the rapid vascular shutdown effect with imaging modalities remains a challenge. Thanks to the recent advances in imaging technologies, more prompt and sensitive imaging biomarkers have been under development for the anatomically-based functional and metabolic quantification of rapid vascular shutdown, necrosis formation and tumor recurrence (Table 2).

Multiparametric imaging biomarkers may document the early changes after treatment and obtain quantitative parameters that reflect specific aspects of the tumor response. More importantly, multiparametric imaging biomarkers combine the different sets of readout from morphology, function and metabolism, which goes beyond what can be yielded by using any single imaging technique and thus allows enhanced insights into biologic processes and responses to therapeutic interventions. With such advantages, multiparametric imaging biomarkers may accordingly be used as “surrogate endpoints” for comprehensive assessment of treatment response with greater predictability and precision than can the traditional clinical endpoints [9, 62, 63].

4.2 MRI

As a noninvasive imaging technique without ionizing radiation, MRI unitizes strong magnetic fields and spins of hydrogen proton of water abundantly occurring in biological tissues. After being excited with radiofrequency, these spins relax to their equilibrium state, producing the signal that can be detected and transformed into images [64]. First invented in 1973, MRI has rapidly evolved into a most widely used modality in evaluating tumor therapy response [65].

For the morphological evaluation, MRI can provide excellent contrast between the different soft tissues of the body. T1- (T1WI), T2-weighted imaging (T2WI) and contrast-enhanced T1WI are the routine sequences to provide the topographic information of tumor location, size/volume and necrosis [66, 67].

For the functional evaluation, dynamic contrast-enhanced (DCE)-MRI can be used for the evaluation of tumor vascular properties with the quantification of the blood-supply-related physiological parameter such as blood flow, blood volume, vascular permeability, and extravascular extracellular space. DCE-MRI involves the dynamic acquisitions at high temporal resolution before, during and after the intravenous bolus injection of a gadolinium-based contrast agent. By tracing the distribution of contrast agent in vascular and extravascular extracellular space, quantitative and semiquantitative kinetic analysis can be done [68, 69]. Since VTT aims at destroying or disrupting tumor vessels, DCE-MRI appears most relevant to document the related vascular alterations. Thus, DCE-MRI can detect early posttreatment changes in blood supply, and monitor the dynamic evolution or the recovery of perfusion, indicative of incomplete treatment effect or tumor relapse [52, 70-73].

Another important physiological parameter that can be provided by MRI is apparent diffusion coefficient (ADC) derived from diffusion-weighted imaging (DWI) [74, 75]. Being contrast-agent-free and easy-to-perform, DWI is the technique available for assessing the water diffusion at cellular level in vivo [76]. Quantified from DWI, ADC enables the depiction of change in water molecular diffusion from low ADC resulting from the hampered diffusion in cytotoxic edema to high ADC from less-disturbed diffusion in lytic necrosis [77, 78]. Besides, arterial spin-labeling (ASL) MRI [79, 80] and blood oxygen level dependent (BOLD) MRI [81, 82] are also explored with intrinsic contrast for the evaluation of tumor perfusion and hypoxia respectively.

For the metabolic evaluation, in vivo magnetic resonance spectroscopy (MRS) has been applied to noninvasively measure the metabolite contents of tumor in living organs and tissues. The same nucleus may encounter different magnetic environments in different molecular structures, known as chemical shift. Thus, different metabolites can be identified by their characteristic chemical shifts in the different chemical structures. Combined with structural information, MRS can be applied to monitor the cellular biochemical changes after VTT [83]. Different nuclei including $^1$H, $^{13}$C, $^{14}$N, $^{19}$F, $^{23}$Na, and $^{31}$P have been assessed, while proton ($^1$H) is the mostly explored in the tumor
4.3 DCE-CT, US, and PET
As the most often used imaging modality in the past decades, CT has a lot of advantages including fast imaging acquisition, widespread availability and high spatial resolution. Similar with DCE-MRI, DCE-CT can also be performed to quantify blood supply. Superior to DCE-MRI, CT generates the images of more uniform intensity with standardized Hounsfield unit, which facilities the intra- and inter-subject comparisons. Moreover, the concentration of injected iodine-based contrast agent has a linear relationship with the measured image intensity, thus allowing the simplified quantification of perfusion-related parameters [90]. In some studies, DCE-CT has been employed to monitor the tumor therapy response, showing the similar results with DCE-MRI [91-94]. Nonetheless, DCE-CT is less accepted than DCE-MRI in clinical practice due to large dose of ionizing radiation, suboptimal contrast resolution and a higher allergy incidence to CT contrast agents [95, 96].

US is another attractive imaging modality due to the cheap price, transportability, and easy accessibility in research and clinical work. US generates real-time images and enables the dynamic imaging of rapidly-moving organs such as heart and abdominal organs [97]. Recently, the advent of micro-bubble contrast agents has revolutionized the potential for US to probe the molecular target in VTT. Some studies have shown that targeted contrast-enhanced molecular US represents a promising tool for noninvasive longitudinal monitoring vascular effects in VTT in vivo [98-101].

Using short-lived radioactive isotopes linked to molecular probes, PET can reveal the spatial and temporal distribution of target-specific tracers. The acquired imaging data on time-dependent radiodecay can be yielded for the interpretation of tumor physiology and biology such as blood volume and flow, tissue uptake, glucose metabolism, receptor binding, and oxygen utilization [95, 102]. Despite their limited spatial resolution and the use of expensive cyclotron to produce radioactive pharmaceuticals, PET is the most sensitive imaging modality for the quantification of molecular function of biomolecules and biological process in vivo [103, 104]. Therefore, PET has been increasingly performed to monitor various molecular aspects of tumor response in VTT [42, 105-108].

5. Conclusions
Any ideal imaging modality has to be capable of measuring an immediate vascular collapse and subsequent morphological, functional and metabolic responses to VTT, in an accurate, sensitive and quantitative way. Unfortunately, no single method can satisfy all the requirements for routine use in patient care, although a variety of imaging modalities have been tested to reach this ultimate goal. In the long term, we envision that multiparametric imaging biomarkers integrating morphological, functional and metabolic metrics will evolve into qualified imaging protocols in clinical practice for assessing the tumor treatment response in different regimens. Thus, such increasing demands should encourage larger preclinical and clinical trials to validate the robustness of these imaging methodologies with the criteria of standardization and reproducibility.

6. References


[58] Medical imaging and drug development. US FDA.


