

# The emerging quest for the optimal angiostatic combination therapy

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## Abstract

Angiostatic therapies are now routinely embedded in the daily clinical management of cancer. Although these agents clearly benefit patient survival rates, the effect is only moderate with sometimes considerable side effects. A major cause of failure in this respect is the induction of resistance and tolerability against these drugs. Most angiostatic drugs are tyrosine kinase inhibitors that aim to inhibit or neutralize the activity of tumour-produced growth factors. Frustrating the tumour cells in this way results in genetic adaptations in the cells, turning them into mutants that are dependent on other growth mechanisms. It may therefore be necessary to shift to another class of drugs that directly target the tumour vasculature. It is evident that improvement of future angiogenesis inhibitors can only arise from two efforts. First, through the identification of better targets, preferably specifically expressed in the tumour vasculature. Secondly, through the development of combination therapies. The present review highlights the current efforts and challenges in trying to develop effective angiostatic combination therapies.

## Introduction

Angiogenesis inhibitors have firmly entered the current clinical practice for treatment of cancer [1–3]. Many of these agents, such as bevacizumab/Avastin®, sunitinib/Sutent®, and erlotinib/Tarceva®, have provided new treatment options for patients with, e.g., renal cell carcinoma (RCC) [3], non-small-cell lung carcinoma [4], colorectal carcinoma [1], and gastrointestinal stromal tumours [2]. However, when these drugs are used as monotherapies or in addition to existing treatment strategies, their contribution to patient survival is rather limited. This limited activity is most likely due to the heterogeneity that exists among patients, as well as in tumours [5], limited dose schedules due to drug toxicity and the development of drug-induced resistance [6].

It is very likely, and also generally realized, that considerable improvement of cancer therapy should be achievable through the combination of different treatment strategies. Similarly, the identification of a superior angiostatic strategy could come from combining different vascular targeting and angiostatic regimens. Like most intrinsic cell functions, angiogenesis is regulated through a system of highly robust and redundant cell signalling pathways aimed to maintain normal cell function [7,8]. Neutralizing one of these pathways

will probably lead to compensation by the cell through the up-regulation of other pathways in an attempt to maintain normal function [9]. These redundant cell signalling pathways, which play a role to facilitate the development of drug resistance, may also increase the likelihood of identifying combinations of drugs which can synergistically inhibit angiogenesis [10]. Although it seems a daunting task to find an optimal combination therapy due to the enormous number of possible options, much can be learned from recent experiences in combining different therapies. This experience originates from efforts to combine different angiogenesis inhibitors, but also from research on the combination of angiogenesis inhibitors with other treatment approaches with intrinsic angiostatic potential, such as chemo-, radio-, immuno- and photodynamic therapy (PDT) (Figure 1). Without trying to be exhaustive, the present review gives an overview of what is known about the development of angiostatic combination therapies and the challenges that are faced in trying to improve treatment of disease.

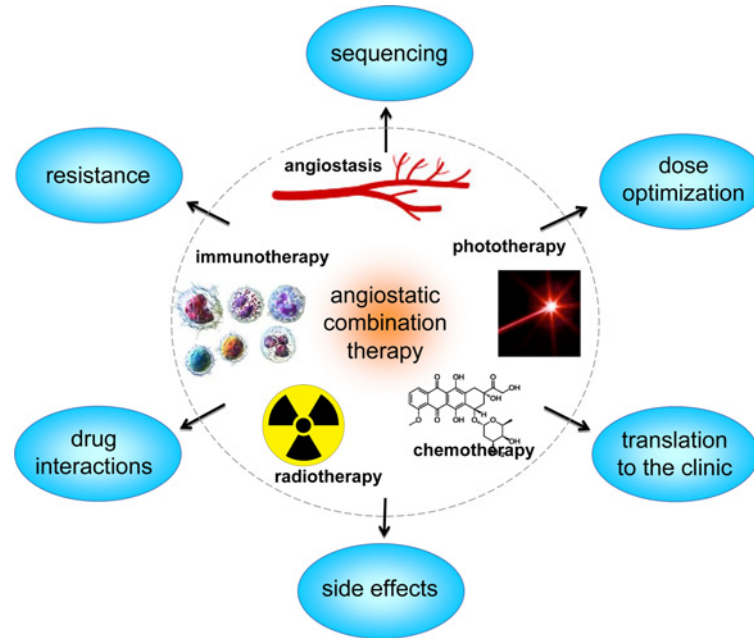
## Combination of angiogenesis inhibitors

Design of an effective angiostatic strategy may be achieved by combining drugs which inhibit a broad array of different angiogenic signalling pathways. Designing such a combination therapy, however, is not trivial, as two compounds may exert synergistic, additive or even antagonistic interactions on each other. In addition, synergy can also be dose dependent. So while two therapies result in synergistic activity in a given circumstance, this activity may be lost when drug doses and ratios are varied. Furthermore, the sequencing of drugs

**Key words:** angiogenesis, chemotherapy, combination therapy, immunotherapy, photodynamic therapy, radiotherapy, tyrosine kinase inhibitors.

**Abbreviations:** AML, angiomylipoma; CAM, chorioallantoic membrane; EGFR, epidermal growth factor receptor; ICG, Indocyanine Green; IFN, interferon; IL, interleukin; mTOR, mammalian target of rapamycin; MTD, maximum tolerated dose; PDT, photodynamic therapy; PEBBLE, probe encapsulated by biologically localized embedding; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

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**Figure 1** | Angiostatic combination therapy: different strategies, many challenges

can also be extremely important, as has been demonstrated in the treatment of RCC, where an effective sequence of drugs can be ineffective when the order of administration is changed [11]. Combination of drugs in the clinic is often based on the previous success of drugs when used as monotherapy or in combination with other drugs. It is clear that such an approach seems to rely on trial and error and, most importantly, fully ignores the biology of tumour and endothelial cells. However, combinations are continuously tested in preclinical research, and promising strategies are subsequently tested in the clinic.

Since the identification of the first angiogenesis inhibitors in the early 1990s, reports can be found on the combination of these initial angiostatic compounds. It was realized that certain inhibitors act through different signalling pathways, potentially giving synergism between the drugs. An early example of such a study was the identification of synergism between angiostatin and endostatin [12], two drugs with rather unknown working mechanisms. Later, a study with the galectin-1 targeting drug anginex with angiostatin showed clear synergism [13]. Therapeutic targets now being considered for new medications include vascular endothelial growth factor (VEGF), platelet-derived growth factor and the mammalian target of rapamycin (mTOR). A pivotal example of the clinical use of anti-angiogenic therapy is the treatment of advanced RCC where anti-angiogenic agents demonstrated significantly greater anti-tumour effects as compared with the standard first-line therapy with interferon- $\alpha$  (IFN $\alpha$ ) [14]. The success of these compounds resulted in the testing of other combinations in preclinical studies. Some of these combinations have already been clinically tested, e.g. the INTORACT trial

[15], but have turned out to induce severe toxicity and ultimately did not prove superior to individual agents. More studies resulted in the conclusion that the combination of angiogenesis inhibitors is heavily associated with toxicity, e.g. hypertension, hypothyroidism, hand-foot syndrome, and fatigue [tyrosine kinase inhibitor (TKI)-associated] and immunosuppression, and non-infectious pneumonitis (mTOR associated) [16–18]. The combination of everolimus with or without bevacizumab is currently being evaluated in the second-line setting (CALGB trial; NCT01198158) and the results are pending. Moreover, trebananib, an immunoglobulin G1 (synthetic human Fc domain fragment) fusion protein with angiopoietin 1/angiopoietin 2-binding peptide is currently in a Phase II trial (NCT01664182) for advanced kidney cancer, with or without bevacizumab, pazopanib, sorafenib, or sunitinib, whose results are also still pending. Summarizing, the optimized effective combination treatment protocols have yet to be identified and the balance between effectiveness and tolerability should be carefully considered. Nevertheless, promising responses and important lessons have emerged from already completed clinical trials.

Another option of designing angiostatic combination therapies is with the combined use of conventional treatment strategies that have an intrinsic angiostatic activity. It has been known for some time now that certain chemotherapeutic compounds have an angiostatic effect as well [19], especially when given in low-dose long-term regimens [20,21]. Radiotherapy and PDT have also been known to have a major effect on the tumour vasculature, suggesting the potential for its successful use in combination with angiogenesis inhibitors [22,23]. In addition, the reciprocal interactions between the immune system and angiogenesis

suggest that angiogenesis inhibition can be reinforced by immunotherapy [24].

## Angiogenesis inhibition in combination with chemotherapy

Conventional chemotherapeutic agents are usually administered at their maximum tolerated dose (MTD) and exert their anti-tumour effects by killing cells that divide rapidly. In general, these agents are not considered to possess anti-angiogenic properties. In contrast, angiogenesis inhibitors do not show primary anti-tumour activity but rather act on endothelial cells. Although clear differences between chemotherapeutics and angiogenesis inhibitors exist, there are chemotherapeutics with anti-angiogenic properties. Browder et al. [20] were the first to propose anti-angiogenic chemotherapy by showing that cyclophosphamide-resistant murine tumours were strongly inhibited by frequent low-dose cyclophosphamide administration while the conventional MTD schedule was ineffective. In addition, they showed that the strong decrease in tumour size was correlated to increased endothelial cell apoptosis. This concept of targeting tumour vasculature endothelium with frequent low-dose chemotherapy was later called 'metronomic' therapy. The chemotherapeutics used for metronomic therapy include (among others) cyclophosphamide, capecitabine, topotecan and vinorelbine, and are currently being used for breast cancer, glioblastoma, gastric cancer, prostate cancer, colorectal carcinoma and several other malignancies [25].

Ruthenium-based chemotherapeutics are also of particular interest, since these compounds show intrinsic anti-angiogenic properties and are in both clinical and preclinical development. For instance, NAMI-A (imidazolium trans-[tetrachloro(dimethylsulfoxide)imidazole ruthenium(III)]) [26] and the anti-tumoral KP1019 (indazolium trans-[tetrachlorobis(1*H*-indazole)ruthenium(III)]) [27] completed Phase I and are currently in Phase II clinical trials. Another ruthenium complex called RAPTA-C  $[\text{Ru}(\eta^6\text{-arene})\text{X}_2(\text{PTA})]$  (PTA = 1,3,5-triaza-7-phosphaadamantane), exhibited interesting anti-metastatic [6–8] and anti-angiogenic *in vivo* properties [23].

Since metronomic therapy consists of frequent and well-tolerated low-dose chemotherapy administration, combination with other treatment modalities may be of clinical benefit [25]. It was previously proposed that by combining metronomic therapy with angiogenesis inhibitors, enhanced anti-tumour efficacy could be achieved [20,21]. In recent years, many preclinical studies confirmed this hypothesis. For example, a study that evaluated the combination of metronomic topotecan and pazopanib in a murine model of human ovarian carcinoma showed that the anti-tumour activity of topotecan was significantly enhanced by pazopanib [28]. Another study showed that metronomic gemcitabine in combination with sunitinib inhibited primary tumour growth and metastasis in an orthotopic mice model for pancreatic carcinoma, whereas both individual treatments were less effective [29].

Apart from the conventional chemotherapeutics used for metronomic therapy, ruthenium compounds were also studied for their activity in combination with angiogenesis inhibitors. KP-1339, for instance, showed synergistic activity *in vitro*, as well as in *in vivo* models in combination with sorafenib. It was proposed that NKP-1339 potentiates the anticancer activity of sorafenib by increased apoptosis and G<sub>2</sub>/M arrest [30].

Several clinical trials have been performed, or are still in progress, to further investigate the potential of metronomic chemotherapeutics in combination with anti-angiogenic agents. A study assessing the combination of metronomic capecitabine and cyclophosphamide in combination with bevacizumab and erlotinib in adult patients with metastatic HER2 (human epidermal growth factor receptor 2)-negative breast cancer showed an overall clinical benefit of 75% and a prolonged median time to progression [31]. This treatment regimen was well tolerated and showed only mild toxicity. In contrast, a study that evaluated the combination of metronomic vinorelbine in combination with bevacizumab in adult patients with metastatic breast cancer was cancelled due to a lack of efficacy, although the therapy was very well tolerated [32]. In addition, a Phase II trial was conducted that tested the combination of bevacizumab with metronomic cyclophosphamide in patients with recurrent ovarian carcinoma and revealed significant activity of the treatment regimen [33]. Currently under clinical evaluation is the combination of pazopanib and metronomic cyclophosphamide in patients with recurrent ovarian carcinoma (PACOVAR trial, NCT01238770) [34].

Increasing preclinical and clinical data suggest a great potential for combining anti-angiogenic chemotherapeutics with angiogenesis inhibitors. A major advantage could be a well-tolerable treatment regimen due to low drug doses. However, more clinical trials are necessary to reveal the true value of this anti-angiogenesis strategy.

## Angiogenesis inhibition in combination with radiotherapy

In general, anti-angiogenic therapy has the potential to induce structural and functional normalization of tumour vasculature. Additionally, angiostatic drugs may improve the tumour microenvironment [35]. During this normalization window, the efficacy of conventional treatments is significantly enhanced, including concomitant radiotherapy [35–37]. Hence, administration of angiostatic drugs may increase the effectiveness of radiotherapy.

When radiotherapy is combined with angiogenesis inhibitors, a synergistic effect has been shown. For example, Dings et al. [36] described the synergistic effect of combining radiotherapy and a direct anti-angiogenic peptide (anginex) or bevacizumab. As a result of normalized tumour vasculature, improved oxygen delivery is achieved, and hypoxic conditions are eliminated, resulting in a tumour microenvironment with enhanced therapeutic potential for radiotherapy. It is generally realized that the effects of

high- and low-dose radiotherapy vary. Sofia Vala et al. [38] found that low doses of radiotherapy (0.5 Gy) induced rapid phosphorylation of several endothelial cell proteins, including VEGF receptor (VEGFR)-2 and induced VEGF production in hypoxia mimicking conditions. This effect may explain why they found that low-dose irradiation actually enhanced angiogenesis and endothelial cell migration. Hence low-dose radiotherapy may result in a progressive tumour growth and increased metastatic spread, in contrast with high-dose radiotherapy [39].

The clinical applicability of combining radiotherapy with anti-angiogenic drugs has also been studied. Bevacizumab, in particular, was subject to several clinical trials in different types of tumour tissue, including head and neck and colorectal tumours [40,41]. The Phase I clinical trial by Czito et al. [41] showed promising results. This group combined bevacizumab, capecitabine, oxaliplatin and radiation therapy for treatment of rectal cancer. Of the 11 included patients, six experienced a significant response. In the remaining five patients, the disease was progression-free during this study. Despite these encouraging results, some patients did experience minor adverse side effects, including bleeding and duodenal ulcers. Gasparini et al. [37] who continued research on the combination of bevacizumab and radiotherapy in a Phase II trial, also found a clinical benefit of additional angiostatic treatment. Overall, most Phase I/II trials with bevacizumab and radiotherapy found a decrease in tumour progression, although toxicity of this combination remains an issue.

The combination of anti-angiogenic and radiotherapy has also been tested in brain tumours. For example, Knisely et al. [42] combined thalidomide, an inhibitor of bFGF activity, with whole brain radiotherapy. Unfortunately, these trials showed no increase in overall survival in the combination therapy groups. Moreover, 48% of patients were excluded due to severe side effects. The authors argue that angiostatic drugs that directly act on endothelium may be more effective. It is evident that future research is required to determine the benefit of combining radiation with angiostasis. Kleibeuker et al. [22] have provided a comprehensive review on the combination of radiotherapy with anti-angiogenesis.

## Angiogenesis inhibition in combination with immunotherapy

Immunotherapy is a rapidly growing field in the treatment of cancer. It involves stimulation of the components of either the innate or adaptive immune system to target tumour cells. This strategy not only enhances anti-tumour immunity but has also been shown to affect tumour angiogenesis. Immunotherapy is considered a double-edged sword since the immune system regulates both pro-angiogenic and anti-angiogenic factors. One approach to enhance the angiostatic activity of immunotherapy is to set the switch towards angiostatic components of the immune system involving specific cytokines, such as interleukin (IL)-2, IL-4, IL-12, IL-21 and IFN $\alpha$ . The cytokine IL-2,

approved as a first-line therapy in RCC, has been shown to inhibit blood vessel formation in the chick embryo chorioallantoic membrane (CAM) through nitric oxide induction [43]. In a more recent study, antibody-based IL-2 delivery was performed in C1498 murine leukemia-bearing immunocompetent mice, and subsequent targeting of tumour neo-vasculature abrogated tumour growth [44]. This method of delivery also led to a decrease in angiomyolipoma (AML) lesions of an AML patient with disseminated extramedullary manifestation. Another interesting study used antibody-based delivery of IL-4 and IL-12 to the tumour endothelium, causing tumour eradication in murine tetracarcinoma, colon carcinoma and lymphoma models [45]. Despite the fact that IL-4 and IL-12 have different immunological functions, it was quite intriguing that together they prevented tumour growth through angiogenesis inhibition. Synergy between cytokines at inhibiting vascular growth was demonstrated by Coughlin et al. [46] already in 1998, showing that the combined action of IL-12 and IL-18 in a murine model led to strong angiogenic regression compared with treatment with only one of either cytokine [46]. In later studies, the possibility to improve IL-12 as a therapeutic agent was explored by co-injecting mice with IL-12 and IL-18 cDNA. Surprisingly, this resulted in the rapid induction of IL-10, neutralization of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) and reduction in toxicity while anti-tumour activity of IL-12 was still retained [47]. Synergism was also shown in the clinic when patients with colorectal cancer were treated with pre-operative IL-2 immunotherapy resulting in increased IL-12 activity and decreased levels of VEGF in patient sera [48].

Future clinical benefit may come from the fact that each individual cytokine elicits angiogenic targeting via different mechanisms. For instance, IL-21, another anti-angiogenic cytokine, seems to act through down-regulation of signal transducer and activator of transcription 3 (STAT3) phosphorylation in endothelial cells [49], whereas IL-4 was recently shown to target hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) translation, consequently leading to reductions in the proangiogenic activity of macrophages in the tumour environment [50]. IL-12 has been shown to mediate its action by up-regulating angiostatic molecules such as IFN $\gamma$  and angiostatin [51]. The cytokine IFN $\alpha$  is claimed to block angiogenesis by directly down-regulating VEGF expression [52].

Pre-clinical data show encouraging results *in vitro* and *in vivo*, but clinical trials have yet to progress with IFN $\alpha$  and IL-2, being the only immunomodulating agents to have been approved by the Food and Drug Administration. Various efforts have been made to combine IL-2 and IFN $\alpha$  in a clinical setting, but these have not been proven to be very successful due to severe toxicity. For example, in a randomized Phase III trial high-dose IL-2 was compared with subcutaneous IL-2 and IFN $\alpha$ ; however, the response rate to high-dose IL-2 therapy was markedly better in the patients although not significant [53]. On the other hand, a Phase I study showed minimal toxic effects when patients received IL-12 before IFN $\alpha$  [54]. In patients with melanoma or RCC

concurrent low-dose IL-2 combined with IL-12 was well tolerated and IL-2 seemed to enhance the immunological functions of IL-12 by maintaining IL-12-induced IFN $\gamma$  levels supporting the results from pre-clinical data [55]. IL-4 and IL-21 have been tested in Phase I/II trials as single agents; however, there are no trials combining the two with other cytokines [56].

To conclude, cytokine-based immunotherapy in a monotherapy setting is not sufficient to prolong the survival of patients and great measures have to be taken to improve the patients' quality of life. Combination of these strategies with direct angiogenesis inhibitors may be of future benefit.

### Angiogenesis inhibition in combination with photodynamic therapy

PDT is a form of therapy based on the systemic administration of a photosensitive agent and its local activation with a wavelength-specific light source [57]. Photosensitizers, selectively excited with an appropriate light wavelength, react with environmental oxygen to produce highly reactive oxygen species (ROS) that damage surrounding tissues and lead to blood flow stasis. PDT is clinically used in the treatment of various superficial cancer types, including squamous cell carcinoma [58], early stage (*in situ* and microinvasive) cancer of the bronchi and the esophagus [59] basal cell carcinoma. Although a large portion of the effect of PDT is on the vasculature, a major limitation of PDT remains the secondary induction of angiogenic pathways in response to tissue hypoxia resulting from blood vessel closure. This process is believed to result in enhanced tumour recurrence and accelerated tumour growth after treatment [60]. A promising strategy to overcome these secondary effects is through the combination of PDT with anti-angiogenic drugs [61]. PDT has routinely been implemented in the clinical management of neovascular based eye disorders, such as age-related macular degeneration [62] or polypoidal choroidal vasculopathy (PCV) [63]. In both disorders, it has been demonstrated that its therapeutic benefits are prolonged through the co-administration of VEGF-targeted antibodies, with or without anti-inflammatory compounds [64].

Although such combinations have yet to be applied in the clinical treatment of cancer, a large body of pre-clinical evidence indicates a potential for the enhancement of the therapeutic benefits of both treatments strategies through their combination. This may be of therapeutic value in the treatment of ocular tumours. Case studies have indicated the potential of using PDT in combination with bevacizumab/Avastin<sup>®</sup> in the treatment of benign ocular tumours, such as circumscribed choroidal hemangiomas, to help minimize disease related vision loss [65]. A potential role for the use of PDT in combination with angiogenesis inhibitors has also been suggested in the treatment of peritoneal metastasis of various cancer types, including ovarian carcinoma [66]. The study by Piatrouskaya et al. [67], for example, used an orthotopic model of peritoneal carcinomatosis in rats to show a significant increase in

the percentage of necrosis in disseminated tumour cells in tumours treated with a combination of intraperitoneal PDT and bevacizumab.

Additionally, we have previously investigated the potential of prolonging the angio-occlusive effects of verteporfin-PDT through its combination with angiogenesis inhibition in both physiological angiogenesis in the chicken CAM [68] and in tumour angiogenesis in human ovarian carcinoma (A2780) xenografts in the same model [69]. In the latter study, we reported the synergistic inhibition of tumour growth through the combination of sub-optimal doses of three anti-angiogenic TKIs (axitinib, sorafenib and sunitinib) and low-dose verteporfin-PDT [69]. In another study, Ferrario and Gomer [70] showed a significant prolongation in tumour response when Avastin<sup>®</sup> was added to Photofrin-PDT in the treatment of nude mice bearing Kaposi's sarcoma tumours, as compared with either treatment alone.

Others have also investigated the potential to enhance the selectivity of PDT by increasing the delivery of photosensitizer to tumour tissue through their conjugation with molecules targeting angiogenic growth factors. Gamal-Eldeen et al. [71] encapsulated Indocyanine Green (ICG) dye in polymeric nanoparticles using probe encapsulated by biologically localized embedding (PEBBLE) technology to make ICG-PEBBLE photosensitizers which were then conjugated to an anti-epidermal growth factor receptor (EGFR) molecule. The treatment of CD1 mice bearing induced skin squamous cell carcinoma (SCC) tumours with the ICG-PEBBLE-anti-EGFR photosensitizer showed increased inhibition of VEGFR and an increase in caspase-3 activity, as compared with the free ICG-PEBBLE. Gamaleia et al. [72] investigated whether the efficacy of PDT could be enhanced by using a hematoporphyrin photosensitizer conjugated to an anti-VEGFR antibody and administering it at the time of day that coincides with maximal tumour concentrations of VEGF, based on the variation of VEGF production in tumours due to circadian rhythms. They showed the increased accumulation of immunoconjugated photosensitizer and a significant enhancement in the efficacy of therapy in mice with Lewis lung carcinoma and sarcoma 180, when treatment was performed during the time of maximal tumour VEGF concentration as compared with the time when minimal levels of VEGF were measured in the tumour.

### Concluding remarks

The current overview makes it clear that there are major opportunities to improve angiostatic treatment. However, it also becomes evident that there is an almost infinite number of possibilities for the development of efficient angiostatic treatment regimens. Because of this enormous parametric space, it is obvious that the current clinical trial and error approach will not result in optimal improvement of angiostatic treatment. Therefore it may be necessary to call upon mathematical modelling systems to systematically screen for optimal combinations. Several initiatives in this

regard have been proposed, for example, to predict the effects of combining anti-angiogenic and chemotherapeutic agents [73,74].

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