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Angiogenesis Inhibition in the Treatment of Prostate Cancer

Ravi A. Madan^{1,2}, William L. Dahut^{2,*}

¹Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

²Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

For many men, prostate cancer is an indolent disease that, even without definitive therapy, may have no impact on their quality of life or overall survival. However for those men who are either diagnosed with or eventually develop metastatic disease, prostate cancer is a painful and universally fatal disease. Testosterone-lowering hormonal therapy may control the disease for some time, but patients eventually develop resistance and progress clinically. At this point, only docetaxel has been shown to improve survival, so clearly additional therapeutic options are needed. Angiogenesis inhibition is an active area of clinical research in prostate cancer. Without angiogenesis, tumors have insufficient nutrients and oxygen to grow larger than a few millimeters and are potentially less likely to metastasize. In prostate cancer in particular, angiogenesis plays a significant role in tumor proliferation, and markers of angiogenesis appear to have prognostic significance. Several different compounds have been developed to inhibit angiogenesis, including monoclonal antibodies, multitargeted kinase inhibitors, and fusion proteins. In addition, more traditional agents may also have an impact on angiogenesis. Trials studying antiangiogenic agents have been conducted in localized and advanced prostate cancer. There are several large, ongoing phase III trials in metastatic castration-resistant prostate cancer. The findings of these and future studies will ultimately determine the role of angiogenesis inhibitors in the treatment of prostate cancer.

Keywords

Antiangiogenesis; prostate cancer; bevacizumab; multikinase inhibitors; fusion proteins

CURRENT STATE OF PROSTATE CANCER THERAPY

Despite advances in medical oncology over the last decade, prostate cancer remains a commonly diagnosed and potentially lethal disease. With almost 200,000 new diagnoses annually and more than 27,000 deaths, prostate cancer treatments require continued investigation and enhancement [1]. In spite of aggressive prostate-specific antigen (PSA) screening, 20% to 40% of patients treated with definitive surgery or radiation will have

* Address correspondence to this author at the Medical Oncology Branch, National Cancer Institute, Building 10, Rm 12N226, 9000 Rockville Pike, Bethesda, MD 20892, USA; Tel: 301-435-8143; Fax: 301-435-3854; dahutw@mail.nih.gov.

disease recurrence, regardless of the type of primary intervention [2-5]. Patients with metastatic disease often receive sequential hormonal manipulations until symptomatic metastatic disease develops [6]. In 2004, docetaxel became the first chemotherapeutic agent approved by the U.S. Food and Drug Administration (FDA) for metastatic CRPC based on an improvement in survival compared to mitoxantrone and prednisone [7, 8]. Since that time, studies have attempted to improve on the standard docetaxel regimen, but without success. Given the clinical benefit demonstrated with angiogenesis inhibitors in other cancers and the sound scientific rationale for its use in prostate cancer, angiogenesis inhibition has become an active area of clinical research in the treatment of prostate cancer.

ANGIOGENESIS IN THE TUMOR MICROENVIRONMENT

Angiogenesis is a vital component of fetal development and wound healing, and may also play an important role in tumor progression. The concept that tumors require neovascularization to support their growth was first postulated by Dr. Judah Folkman in 1971 [9]. Since that time, our understanding of the role of angiogenesis in cancer has expanded. Tumors that are < 2 mm are likely able to acquire oxygen and other nutrients through simple diffusion from established capillaries. For tumors to grow beyond this rudimentary size, they need to develop their own vasculature. It is postulated that tumors undergo a transformation, or “angiogenic switch,” at some point in their development [10]. This angiogenic switch occurs at different points in tumor progression, based on tumor type and microenvironment. The end result is tumor neovascularization [10, 11]. Once tumors are able to recruit additional blood vessels, the increased oxygen and nutritional support can lead to significant tumor growth and the potential for metastasis.

Tumor angiogenesis begins on a genetic level. Hypoxia increases as tumors outgrow their existing blood supply, resulting in proangiogenic genetic expression [12]. This genetic activation leads to the production of growth factors that can enhance vasculature development, including vascular endothelial growth factor (VEGF), angiopoietin-1 (ANG1), and placental growth factor (PIGF) [13, 14]. Although VEGF plays a primary role in angiogenesis and can instigate the process on its own, in its absence, ANG1 and PIGF can lead to vascular development, a fact that may have therapeutic implications as angiogenesis inhibition strategies are developed [15].

As proangiogenic factors increase in the tumor microenvironment, existing capillary or post-capillary vasculature dilates and becomes more permeable, allowing for the efflux of proteins that lay down the provisional architecture for new vessels. Circulating or bone marrow-derived endothelial cells are recruited to these areas, forming a migrating column which ultimately becomes neovasculature [16, 17]. Several aspects of this process are still poorly understood, but the primary role of VEGF is apparent, and this factor is most commonly employed among different tumor types.

The resulting tumor neovasculature may be different from the vessels that serve the body's normal tissue. The new tumor-induced vessels are more tortuous and erratic in design and may have dead ends that do not lead to the tumor. Due to high levels of VEGF, they are often very permeable. A lower number of stromal cells than are present in normal vasculature and

the presence of tumor cells within the new vessel walls add to the inefficient, leaky nature of tumor neovasculature [18-21].

As with any complex biological process, angiogenesis can potentially be blocked at several points in an effort to limit tumor neovascularization. Such blocking mechanisms include decreasing endothelial cell proliferation, inhibiting proangiogenic factors through the use of neutralizing antibodies and fusion proteins, or intervening in signal transduction after proangiogenic factors bind to extracellular receptors (Table 1) [22]. The most studied proangiogenic factor is VEGF, which includes VEGF-A, -B, -C, -D, -E, and -F. VEGF-A has the most significant function in tumor angiogenesis [22]. VEGF-A binds to 3 different VEGF receptors: VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR-2 is expressed mainly by endothelial cells and plays a vital role in tumor angiogenesis [23, 24].

RATIONALE FOR ANTIANGIOGENIC THERAPY IN PROSTATE CANCER

Initial preclinical data indicate that angiogenesis inhibitors decrease tumor growth in both *in vitro* and *in vivo* models [25-27]. Further clinical data demonstrate the importance of angiogenesis in prostate cancer proliferation. Proangiogenesis serum factors are increased in patients with prostate cancer relative to healthy patients. Another way to assess angiogenesis activity is to determine the relative microvessel density in patients with prostate cancer. Increased microvessel density has been correlated with increased serum levels of proangiogenesis factors in prostate cancer patients [28]. Not surprisingly, microvessel density is increased in prostate adenocarcinoma compared with adjacent normal prostate tissue and prostate tissue that has undergone benign hypertrophy. Furthermore, patients with metastatic disease have higher microvessel density than patients with localized disease and no metastatic lesions [29].

Angiogenic activity may also have prognostic value in prostate cancer patients. A negative correlation has been seen between survival and patients with higher VEGF levels in both serum and urine [30, 31]. A study of over 1,000 men with prostate cancer suggested that microvessel density at the time of diagnosis was also prognostic in terms of overall survival [32]. This finding is consistent with previous data indicating that microvessel density correlates with high-grade primary tumors [29]. Although these findings are too preliminary to be useful in a clinical context, they demonstrate the potential influence of angiogenesis on disease progression and reveal the potential therapeutic benefit of angiogenesis inhibition in prostate cancer.

MECHANISM OF ACTION

The tumor microenvironment is greatly influenced by the erratic vasculature produced by the tumor's proangiogenic effects. The end result is heterogeneous blood flow to different areas of the microenvironment, leading to varying degrees of hypoxia. This may actually favor tumor growth, as there is decreased chemotherapy perfusion to the center of the tumor. In addition, diffuse hypoxia may decrease the local effectiveness of immune cells and radiation-based therapies [33, 34]. Also, central areas of the tumors often have high

interstitial pressure that further decreases chemotherapy penetration into the tumor and may result in an efflux of potentially metastatic cells into the circulation or lymphatics [35].

Paradoxically, the ultimate therapeutic mechanism of angiogenesis inhibition may not consist of decreasing blood flow to the tumor to starve it of oxygen and other vital nutrients. Although angiogenesis inhibitors may eliminate a small number of nascent vessels, emerging data suggest that the true benefit of these treatments may actually be in improved blood flow to the tumor [36-38]. Besides eliminating some inefficient vessels, angiogenesis inhibitors may also constrict vessels and decrease their permeability, thereby increasing blood flow to the tumor microenvironment [39, 40]. With the resulting stabilized interstitial pressure dynamics, chemotherapy and targeted molecular inhibitors may penetrate more regions of the tumor. Furthermore, improved tumor oxygenation may enhance the effects of radiation and immunotherapy.

Regardless of the ultimate mechanism of action, there is sound scientific rationale for employing angiogenesis inhibitors in the treatment of prostate cancer. Many antiangiogenesis strategies have been developed and investigated in an effort to improve the outcome for prostate cancer patients, with some intriguing results (Table 2).

MONOCLONAL ANTIBODIES

Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is the most studied antiangiogenic agent in clinical trials. It is a humanized monoclonal IgG1 antibody developed from a murine monoclonal antibody targeting human VEGF ligand. The antibody consists of 93% human protein sequences; the remaining 7% is a murine protein sequence residing chiefly in the complementary determining region [41-43]. Bevacizumab specifically recognizes and binds to all major isoforms of VEGF-A, making them unable to bind to VEGF receptors and thereby incapable of perpetuating the angiogenesis signal transduction cascade.

Initial preclinical studies demonstrated the effects of a murine monoclonal antibody targeting VEGF on several human cancer cell lines *in vivo*. These studies were the foundation of the subsequent development of bevacizumab and its ultimate use in the treatment of multiple tumor types [26, 41, 44]. In the United States, the FDA has approved bevacizumab in combination with chemotherapy for the treatment of metastatic colon, breast, and non-small cell lung cancer [45-49]. In addition, it was recently approved as a single agent in glioblastoma [50]. Promising studies also demonstrate the potential of bevacizumab in prostate cancer.

As has often been the case in clinical trials in other tumor types, the initial phase II study with bevacizumab alone did not result in significant clinical responses. In this study, 15 patients with metastatic CRPC were treated with 10 mg/kg of bevacizumab every 14 days for 6 total treatments. Half of the 14 evaluable patients had disease progression at 70 days. Only 4 patients had PSA declines, none > 50%. Common toxicities included fatigue, hyponatremia, and hyperkalemia [51].

This trial was followed by Cancer and Leukemia Group B 90006 for metastatic CRPC, in which bevacizumab (15 mg/kg every 21 days) was combined with docetaxel (70 mg/m² every 21 days) and estramustine (280 mg on days 1 to 5 of the 21-day cycle). In this trial, there appeared to be better antitumor activity compared to trials where patients were treated with docetaxel and estramustine without bevacizumab. PSA declines of > 50% were seen in 81% of patients, with time to progression of 9.7 months and an overall survival of 21 months [52].¹ The subsequent approval of docetaxel and prednisone as the standard treatment for metastatic CRPC led to the phase III investigation of docetaxel 75 mg/m² every 21 days vs. docetaxel 75 mg/m² and bevacizumab 15 mg/kg every 21 days. Both arms included prednisone 5 mg twice a day. The study completed accrual in December 2007 and results may be available by late 2009. The study was powered to detect a 25% improvement in overall survival in the bevacizumab arm [52, 53].

As oncologists await definitive phase III results in frontline metastatic CRPC, bevacizumab is also being investigated in other disease states. One phase II trial investigated metastatic CRPC patients who had progressed on docetaxel. Patients were re-treated with docetaxel at 60 mg/m² combined with bevacizumab at 10 mg/kg in a 3-week regimen. Preliminary findings were encouraging, with 3 patients having objective responses and 11 of 20 patients enrolled having a > 50% decline in PSA (7 patients had a > 50% decline on previous docetaxel, while 4 did not have substantial previous PSA responses) [54].

Intriguing findings came out of a trial performed in patients with a rising PSA after initial definitive therapy, but without metastatic disease. The treatment combined bevacizumab (10 mg/kg) with the cellular-based therapeutic cancer vaccine sipuleucel-T (Provenge®; Dendreon, Seattle, WA) [56]. Sipuleucel-T has recently been shown to improve survival when compared to placebo in a phase III trial in advanced disease [55, 56]. A total of 3 sipuleucel-T infusions were given over 4 weeks. Bevacizumab was given every 14 days until disease progression. The rationale for the combination arose from preclinical data suggesting that VEGF may inhibit immune (dendritic) cell function in the tumor microenvironment, and that VEGF inhibitors such as bevacizumab may prevent such immune suppression, leading to enhanced immune responses against the tumor [57-59]. The preclinical data also suggested that improved perfusion increased immune cell trafficking to the tumor. In the sipuleucel-T/bevacizumab trial, median PSA doubling time increased from 6.9 months on-study to 12.7 months ($P = 0.01$). Nine of 20 patients had PSA declines ranging from 6% to 72%, and all evaluable patients demonstrated specific immune responses [55]. These provocative preliminary data indicate that follow-up evaluations of vaccines plus antiangiogenic therapy, perhaps in combination with chemotherapy, may be warranted. Other clinical investigations of antiangiogenic agents are ongoing in early disease states, including combinations with chemotherapy, hormonal therapy, or radiation.^{2,3}

¹Picus, J.; Halabi, S.; Rini, B.; Vogelzang, N.; Whang, Y.; Kaplan, E. The use of bevacizumab with docetaxel and estramustine in hormone refractory prostate cancer: initial results of CALGB 90006 [abstract]. *Proc. Am. Soc. Clin. Oncol.*, **2003**, *22*, 392.

²Vuky, J.; Madsen, B.; Hsi, A.; Song, G.; Badiozamani, K.; Warren, S.; Pham, H. Phase II trial of bevacizumab in combination with androgen deprivation and intensity modulated radiation therapy (IMRT) in patients with high risk prostate cancer [abstract]. *Genitourinary Cancers Symposium*, **2008**, 145.

³Oh, W.; Febbo, P.; Rickie, J.; Fennesy, F.; Scibelli, G.; Hayes, J.; Choueiri, T.; Tempany, C.; Taplin, M.; Ross, R. A phase II study of neoadjuvant chemotherapy with docetaxel and bevacizumab in patients (pts) with high-risk localized prostate cancer: a Prostate Cancer Clinical Trials Consortium trial [abstract]. *ASCO Meeting Abstracts*, **2009**, *27*, 5060.

Another strategy currently being investigated is the use of fully humanized monoclonal antibodies to target the VEGF receptor in order to diminish endothelial cell proliferation, and thus angiogenesis [60]. Phase I studies of a potent anti-VEGFR-2 antibody, IMC-1121B, were well tolerated, with observed toxicities including anorexia, vomiting, fatigue, insomnia, depression, and anemia [61]. A phase II study is currently enrolling docetaxel-resistant, metastatic CRPC patients and evaluating IMC-1121B in combination with mitoxantrone and prednisone [62].

MULTITARGETED RECEPTOR KINASE INHIBITORS

After binding to serum VEGF, the cellular receptors VEGFR-1, VEGFR-2, and VEGFR-3 initiate a signal transduction cascade that ultimately leads to epithelial cell proliferation, angiogenesis, and tumor growth. These VEGF receptors are kinases that activate the downstream PI3-K/AKT pathway and components of the RAF/MEK/ERK pathway [63]. Blocking these cellular receptors within the cell could prevent or impair the proliferative and angiogenic downstream effects of VEGF binding. Several such inhibitory agents have been investigated in the treatment of prostate cancer and are FDA-approved in the treatment of other cancers.

Sorafenib (Nexavar®; Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ) is a bi-aryl urea agent (see Fig. 1) that inhibits the activity of multiple tyrosine kinases, including those on the intracellular domain of VEGF-2 and VEGF-3. Sorafenib has been extensively studied in solid tumors and is FDA-approved as a secondline agent in metastatic clear-cell renal-cell carcinoma [64]. Several phase II trials with sorafenib have been conducted in patients with prostate cancer. A multicenter trial conducted by the Central European Society for Anticancer Drug Research enrolled a heterogeneous population of chemotherapy-naïve CRPC patients, 13% of whom had no metastatic disease. Sorafenib was administered at a dose of 400 mg twice daily. Median time to progression was 8 weeks. At one year, 68% of patients were still alive and 13% were progression-free. Common toxicities included fatigue, diarrhea, and dermatologic reactions [65]. Two other trials conducted in metastatic CRPC patients demonstrated similar findings [66, 67].

Another trial of sorafenib was conducted by the National Cancer Institute (NCI) in metastatic CRPC patients. Of the 46 patients enrolled, 33 had been previously treated with chemotherapy. Although time to progression was found to be similar to that observed in previous trials, median overall survival was 18.3 months. Toxicities were generally as anticipated; however, some of the dermatologic (hand-foot) reactions were significant and may have been associated with cumulative dose [68-70]. An interesting finding in these trials was that while sorafenib actually increased PSA levels in patients, this increase was not necessarily related to increased tumor volume. Preclinical studies confirmed that the agent actually led to increased secretion of PSA by prostate cancer cells on a percell basis [69]. The NCI trial altered its progression criteria in the midst of the trial, which could account for the improved clinical benefit relative to other studies that used strict PSA progression criteria and therefore discontinued the agent sooner. In light of these findings, future trials with sorafenib and similar agents should include progression criteria that do not

include PSA. Trials are currently investigating sorafenib in early-stage disease and in combination with chemotherapy [71-73].

Another FDA-approved agent that has been investigated in the treatment of prostate cancer is sunitinib malate (Sutent®; Novartis, East Hanover, NJ), see Fig. (2). Also approved for the first-line treatment of metastatic clear-cell renal-cell carcinoma, this molecular inhibiting agent has broad activity against all 3 VEGF receptors [74, 75]. One phase II study enrolled 34 patients, half of whom were chemotherapy-naïve patients with metastatic CRPC and the other half were metastatic CRPC patients who had progressed on docetaxel. The dosing schedule was 50 mg/day in 6-week cycles of 4 weeks of treatment, then 2 weeks off. Among patients enrolled, 41% had PSA declines; one patient in each group had a PSA decline > 50%. Nineteen of 34 patients had stable disease after 12 weeks. Common observed side effects were nausea, diarrhea, fatigue, and significant levels of myelosuppression. Results indicated that serum VEGFR-2 decreased while on sunitinib, but increased when the drug was stopped, suggesting evidence of a VEGFR blockade in study patients [76].

A second trial assessed sunitinib in metastatic CRPC patients who had progressed on 1 to 2 previous chemotherapy regimens. Nineteen patients were enrolled, with a median progression of 2.8 months. Four patients had PSA declines of 30%. Again, myelosuppression was a significant toxicity, a side effect that could complicate potential chemotherapy combinations in future studies.⁴ Nonetheless, trials evaluating sunitinib in prostate cancer are accruing in both early- and late-stage disease in combination with chemotherapy [77, 78].

Cediranib (Recentin®; AstraZeneca, London, UK) is another agent that inhibits the tyrosine kinases of VEGF receptors. This indole-ether quinazoline compound has activity against all 3 VEGF receptors, but is most potent against VEGFR-2, which may have the greatest role in tumor propagation [79]. Phase I studies suggested a safe dose level of 45 mg/day, but 20 mg/day was the recommended dose in patients with metastatic CRPC based on a subset of patients. Toxicities included hypertension, diarrhea, fatigue, vomiting, myalgia, and prolonged QTc complexes on ECG [80, 81]. Preliminary studies have indicated a discordance between clinical response and PSA, similar to those described with sorafenib [69].⁵ Preliminary findings from a phase II study in docetaxel-resistant metastatic CRPC are encouraging, with 13 of 23 evaluable patients having decreases in soft tissue lesions, 4 of which meet criteria for partial responses.⁵ If these findings remain consistent in the phase II study, cediranib may warrant further investigation, perhaps in combination with docetaxel or in an earlier disease state.

FUSION PROTEIN

A fusion protein is similar to a monoclonal antibody in function, but not in the formulation process. Like monoclonal antibodies, fusion proteins function as a decoy to bind ligands

⁴Periman, P.; Sonpavde, G.; Bernold, D.; Weckstein, D.; Williams, A.; Zhan, F.; Boehm, K.; Asmar, L.; Hutson, T. Sunitinib malate for metastatic castration resistant prostate cancer following docetaxel-based chemotherapy [abstract]. *ASCO Meeting Abstracts*, May 20, 2008, 5157.

⁵Karakunnel, J.; Gulley, J.; Arlen, P.; Mulquin, M.; Wright, J.; Turkbey, I.; Choyke, P.; Figg, W.; Dahut, W. Cediranib (AZD2171) in docetaxel-resistant, castration-resistant prostate cancer (CRPC) [abstract]. *J. Clin. Oncol.*, 2009, 27(15S), 5141.

such as VEGF, preventing them from binding to receptors and initiating a signaling cascade. Monoclonal antibodies are generated by another animal, usually a mouse, after exposure to a human protein. After significant processing, these xenographic antibodies can be “humanized” by replacing portions of the antibody with human antibody components, resulting in a more tolerable antibody with minimal side effects. Fusion proteins are generated entirely from human molecules, often through the binding of the Fc portion of an IgG1 human antibody to molecules similar to the binding domain of a receptor. Since fusion proteins are entirely human, they often have more favorable side effect profiles and pharmacokinetics [82].

VEGF Trap (Aflibercept®; Sanofi Aventis, Paris, France and Regeneron, Tarrytown, New York), a human fusion protein developed as an antiangiogenic agent, binds with great affinity to VEGF-A, VEGF-B, and another prominent angiogenesis factor, PlGF. In preclinical models, VEGF Trap decreased microvessel density and tumor size, as well as the size and number of metastases [83-85]. A phase I study demonstrated tolerability, with major side effects including hypertension, proteinuria, leucopenia, and thrombosis.⁶ Based on promising phase II data in solid tumors, a phase III trial is randomizing approximately 1,200 metastatic CRPC patients to either VEGF Trap in combination with standard docetaxel and prednisone or standard docetaxel and prednisone alone [86].

OTHER AGENTS WITH ANTIANGIOGENIC PROPERTIES

Several agents influence angiogenesis, although their exact mechanisms are poorly understood. One such agent is thalidomide (Thalomid®; Celgene Corporation, Summit, NJ), whose antiangiogenic properties led to birth defects in Europe 5 decades ago [87-89]. Preliminary evidence from *in vitro* and *in vivo* animal models suggests that thalidomide may have proapoptotic effects or may reduce angiogenic factors in patients with prostate cancer [90]. Thalidomide has overcome its ignominious history to become an FDA-approved treatment for multiple myeloma; investigations are ongoing in prostate cancer [91].

An open-label, phase II, randomized trial of thalidomide in prostate cancer found that doses of 200 mg/day were tolerable and effective. A total of 28% of all patients had a > 40% decline in PSA, and 18% of patients had a > 50% PSA decline [92]. Another trial combined thalidomide with weekly docetaxel at 30 mg/m² in patients with metastatic CRPC and compared the results to patients treated with weekly docetaxel alone [93, 94]. The combination was well tolerated except for an increase in thromboembolic events subsequently attributed to thalidomide. Prophylactic anticoagulation drugs have been administered in subsequent trials. Other toxicities included fatigue, peripheral neuropathy, and constipation. There was a greater incidence of PSA declines of > 50% in the combination group (53% compared to 37% in the docetaxel-alone group). Progression-free survival also favored the combination treatment group (5.9 months versus 3.7 months), as did overall survival (25.9 months in the combination group versus 14.7 months in the

⁶Dupont, J.; Camastra, D.; Gordon, M.; Mendelson, D.; Murren, J.; Hsu, A. Phase 1 study of VEGF Trap in patients with solid tumors and lymphoma [abstract]. *Proc. Am. Soc. Clin. Oncol.*, **2003**, *22*, 776.

docetaxel-alone group; $P = 0.0407$) [95]. Further studies of combination regimens involving thalidomide and thalidomide analogs such as lenalidomide are ongoing.⁷

Although primarily marketed as an anti-inflammatory agent, selective cyclooxygenase-2 (COX-2) inhibitors have previously been investigated in the treatment of various stages of prostate cancer [96, 97]. Preclinical evidence suggests that COX-2 inhibition has a negative effect on angiogenesis in prostate cancer [98, 99]. The clinical development of COX-2 inhibitors in the treatment of cancer was curtailed after rofecoxib (Vioxx®; Amgen, Thousand Oaks, CA) was implicated in increased cardiovascular morbidity [100]. Further investigation into COX-2 inhibitors suggests that celecoxib (Celebrex®; Pfizer, New York, NY) may have fewer antihypertensive and prothrombotic effects, making it safer than rofecoxib. With appropriate patient selection, celecoxib may be a more viable anticancer therapy [101-103]. A current trial is investigating celecoxib in metastatic CRPC patients in combination with chemotherapy and androgen suppression [104].

A targeted molecular therapy currently in clinical development is ZD4054. This agent was designed to inhibit the endothelin axis, a group of peptides that have been implicated in tumor growth and proliferation [105]. Although it does not directly inhibit angiogenesis, preclinical models suggest that its effects on the endothelin axis decrease new blood vessel formation and serum VEGF levels [106, 107]. After a phase II study suggested a survival benefit in patients with metastatic CRPC after treatment with ZD4054, the agent has entered phase III trials in the same advanced disease state [108, 109].

Docetaxel is another agent with antiangiogenic properties. This drug has important implications for patients with metastatic CRPC. In addition to being the only chemotherapeutic agent to show a survival benefit in prostate cancer, docetaxel is toxic to endothelial cells and may impact angiogenesis in the tumor microenvironment. Notably, when administered in standard doses, docetaxel is cytotoxic to new endothelial cells. In fact, docetaxel has been found to be up to 10 times more effective at inhibiting angiogenesis than paclitaxel [110, 111]. These antiangiogenic characteristics of docetaxel add to the rationale for combining angiogenesis inhibitors with docetaxel in patients with prostate cancer.

COMBINING ANTIANGIOGENESIS INHIBITORS

As targeted monoclonal antibodies and molecular agents have evolved in the last decade, it has become evident that although tumors may respond initially to one agent, tumor cells often develop mechanisms to compensate for the singular point of inhibition in a given pathway. This was observed in a phase II trial of sunitinib in metastatic CRPC, where VEGFR-2 was effectively blocked but increases in the proangiogenesis factor PlGF were found, likely to compensate for the decreased effectiveness of circulating VEGF ligand [76]. In order to circumvent this type of compensatory mechanism, multiple antiangiogenesis inhibitors are being investigated in prostate cancer with the goal of minimizing such tumor escape mechanisms.

⁷Moss, R.; Mohile, S.; Shelton, G.; Melia, J.; Petrylak, D. A phase I open-label study using lenalidomide and docetaxel in androgen-independent prostate cancer (AIPC) [abstract]. *Prostate Cancer Symposium*, **2007**, 89.

A promising phase II study has built upon the standard docetaxel treatment for prostate cancer by adding 2 antiangiogenic agents. In this study, 60 chemotherapy-naïve patients with metastatic CRPC were treated with docetaxel 75 mg/m² and bevacizumab 15 mg/kg every 21 days, in addition to daily thalidomide 200 mg and prednisone 5 mg twice daily. Fifty-eight of 60 patients had PSA declines, with 88% having declines > 50% and 71% having declines > 80%. Among 32 patients with measurable disease, there were 18 partial responses and 2 complete responses. The median estimated progression-free survival was 18.2 months. The treatment was well tolerated, with toxicities including febrile neutropenia (8%), syncope (8%), thrombosis (5%), and fistula/gastrointestinal perforation (5%).⁸ This study demonstrates promising evidence that multiple antiangiogenic agents can be combined with enhanced clinical benefits. A subsequent trial will investigate docetaxel and prednisone in combination with bevacizumab and lenalidomide.

FUTURE DIRECTIONS

With several ongoing trials of angiogenesis inhibitors in metastatic CRPC, the potential role of these targeted therapeutics in prostate cancer continues to evolve. By early 2010, the role of bevacizumab in metastatic CRPC should be clarified. Regardless of the results of that trial, several areas of investigation remain. The potential of angiogenesis inhibitors in early-stage disease will also continue to be evaluated. As new angiogenesis inhibitors come to market, they too may be evaluated alone and in combination with standard therapies. Also, as demonstrated by the bevacizumab/thalidomide/docetaxel combination, there is both scientific and clinical merit for the use of multiple antiangiogenic agents in the treatment of prostate cancer. Almost 4 decades after Dr. Folkman first proposed the role of angiogenesis inhibitors in cancer, cancer patients are reaping the benefits of improved clinical responses. In the years to come, perhaps prostate cancer patients will also benefit from Dr. Folkman's insight.

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Fig. (1).
Sorafenib

Fig. (2).
Sunitinib

Table 1.

Mechanism of Angiogenesis Inhibition by Targeted Agents

Modality	Mechanism of Inhibition
Monoclonal antibodies	<ul style="list-style-type: none"> Antibodies are able to bind to proangiogenic factors such as VEGF in serum. These factors are thus prevented from activating cellular receptors or initiating angiogenesis at the cellular level. Antibodies can also bind to receptors and prevent factor-receptor interactions that initiate a proangiogenic signal transduction cascade.
Fusion protein	<ul style="list-style-type: none"> Fusion proteins bind soluble factors, preventing the factors from activating cellular receptors. Unlike monoclonal antibodies, the fusion protein is composed entirely of human-derived molecules and therefore has a better side effect profile and longer half-life.
Multitargeted receptor kinase inhibitors	<ul style="list-style-type: none"> These molecular agents inhibit the cytoplasmic domains of cellular receptors. Once proangiogenic factors bind to cellular receptors, a cascade of reactions occurs that leads to new vessel growth. One of the primary events in this cascade is the phosphorylation of certain proteins. Kinase inhibitors prevent this phosphorylation and therefore may prevent angiogenesis signaling within the cell.

VEGF: Vascular Endothelial Growth Factor.

Important Trials in the Clinical Development of Angiogenesis Inhibitors in Prostate Cancer

Table 2.

Disease state	n	Findings
mCRPC (chemotherapy-naïve)	15	Initial phase II trial of bevacizumab in prostate cancer demonstrated tolerability. (Ref. #51)
mCRPC (chemotherapy-naïve)	17	A combination of bevacizumab, docetaxel, and estramustine demonstrated the benefits of chemotherapy and angiogenesis inhibition in prostate cancer. Overall survival was 21 months. ¹
mCRPC (chemotherapyrefractory and naïve)	46	A trial of sorafenib suggested efficacy of angiogenesis inhibition in docetaxel-refractory CRPC. Also noted were altered PSA kinetics post-therapy that were incongruent with clinical responses. (Ref. #69)
mCRPC (chemotherapy-naïve)	60	A combination of antiangiogenesis inhibitors (thalidomide and bevacizumab) plus docetaxel demonstrated significant clinical responses, including 71% of patients with a > 80% PSA decline and median time to progression of 18.2 months. ²
mCRPC (chemotherapy-naïve)	Results pending	A phase III trial of docetaxel with and without bevacizumab that will determine the drug's role in mCRPC therapy. This trial has completed accrual and results are expected by early 2010. (Ref. #53)