The Value of Anti-angiogenics in Prostate Cancer Therapy

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Abstract

Prostate cancer, the most common cancer diagnosed in men, has been investigated extensively concerning the use of anti-angiogenics. There is a significant amount of preclinical and early clinical data about the potential value of this class of drugs as is the case with many other solid cancer types. Vascular endothelial growth factors and their receptors (VEGF/VEGFRs) seem to be key players in neo-angiogenesis and its expression can be regulated by androgen receptor signaling. Platelet-derived growth factor receptor alpha (PDGFR-α) is of lesser importance in primary prostate cancer; however, PDGFR-A might be involved in the formation of bone metastases. Other mechanisms of pro- and anti-angiogenic factors will be described herein.

The clinical development focused mainly on metastatic, castration-resistant prostate cancer. Phase I/II trials showed consistently interesting results in terms of response rates or reduction of tumor growth. Yet, randomized studies failed to demonstrate a significant overall survival benefit despite increased progression-free survival or clinical signs of activity, such as reduced need for analgesic drugs. This chapter will provide an overview of angiogenesis in prostate cancer and on the development of angiogenesis inhibitors, in particular bevacizumab, sunitinib, tasquinimod, lenalidomide, and cabozantinib.

Keywords
Castration-resistant • Prostate cancer • Angiogenesis • Bevacizumab • Sunitinib • Tasquinimod • Lenalidomide • Cabozantinib • Docetaxel

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Introduction

Prostate cancer is the most common cancer in men in the more developed regions. There are an estimated 1.1 million men newly diagnosed with prostate cancer each year and over 300,000 deaths directly related to metastatic prostate cancer. Seventy percent of cases occur in developed regions of the world. Globally, there are over five million men living with prostate cancer (Ferlay et al. 2015).

Prostate cancer is suspected if prostate-specific antigen (PSA) is elevated during the screening of healthy men. About 70% of men in western countries are diagnosed following screening procedures. Other patients may be diagnosed because of specific symptoms, such as urinary irritation, obstruction, or bone pain. Most of the time, men with localized prostate cancer are cured, but those with locally advanced or metastatic prostate cancer frequently relapse, progress, and die. Upon relapse, the first manifestation is usually the rise of the PSA. In this scenario, hormonal treatment, such as medical or surgical castration, is offered to the patient.

Unfortunately, patient progress after months or years of castration leads to the development of castration-resistant prostate cancer (CRPC). In this scenario, several treatment options are available to prolong survival and/or improve quality of life. In particular, there are new androgen-targeting agents, such as abiraterone or enzalutamide; taxane-based chemotherapy drugs, like docetaxel or cabazitaxel; radionucleotides, including Radium 223 for bone metastases; or immunotherapies, such as that with Sipulocel-T (Crawford et al. 2015).

Treatments targeting angiogenesis appear to be potential regulators of tumor growth in cancers. The role of angiogenesis in tumor growth was first described as early as the mid-1940s by Algire (Algire and Chalkley 1945; Algire and Legallais 1948) followed by the work of others, including Greene and Folkman (Folkman et al. 1971; Greene 1950); the latter of whom was also considered to have been the first to postulate in 1971 that angiogenesis may prove to be a valuable target for anticancer drugs (Schweizer and Carducci 2013).

Despite the high incidence of prostate cancer, the role of angiogenesis has only been evaluated late in comparison to other cancer types. A first report in the 1970s linked blood vessel invasion of prostate cancer to poor prognosis (Kwart and Sims 1978). Further studies that focused on angiogenesis in prostate cancer were only published roughly 15 years later, which represents a delay of half a century compared to other cancers (Furusato et al. 1994; Wakui et al. 1992). Consequently, nowadays, we have 25 years of hindsight regarding prostate cancer angiogenesis.

Several anti-angiogenic therapeutics developed and approved for other types of cancers have been studied within the context of prostate cancer. To better understand these results, it is of importance to first comprehend the mechanisms involved in prostate angiogenesis. Therefore, in the first part of this chapter, we will review the state of the art regarding physiological condition of the prostate, angiogenesis in prostatic benign hyperplasia, and angiogenesis in prostate cancer. The findings of different trials focused on antiangiogenics in prostate cancer will be described in the second part of the chapter.

The Biology of Prostate Cancer

neo-Angiogenesis

The normal prostate gland is a well-vascularized organ; however, regional differences might be present (Scolnik et al. 1992). About 70% of prostate cancer initiates from the peripheral zone,
while the transition zone is home to the other 30%. Prostate cancer virtually never originates from the central zone. In contrast, benign prostatic hyperplasia initiates from the transition and central zones. It is not known if regional differences in angiogenesis might contribute to these differences, but more hypoxic microenvironments may accelerate cancer development and in suppressing immune surveillance (Anastasiadis et al. 2002).

Once the development of prostate cancer has been initiated because of the acquisition of genetic changes, prostate cancer, similar to most other cancers, requires the initiation of neo-angiogenesis to sustain tumor growth as well as to go beyond local disease and metastasize (Folkman and Hanahan 1991). The Gleason score of prostate cancer, which defines both varying degrees of biological aggressiveness as well as prognostic value, has been shown to correlate with microvessel density and histological evaluation of angiogenesis (Mehta et al. 2001). Constitutively activated androgen signaling downstream from the androgen receptor (AR) is key for prostate cancer development and maintenance as reflected by robust initial efficacy of androgen deprivation therapy in advanced treatment of naive prostate cancer (Perlmutter and Lepor 2007). The AR functions as a nuclear transcription factor, and among other important targets, it has been demonstrated that expression of FLT1 (FMS-related tyrosine kinase 1) encoding VEGFR-1 can be modulated by the AR (Sieveking et al. 2010). In addition, genetic polymorphisms in the AR-binding sites of the FLT1 promoter correlated with overall survival in a cohort of 601 advanced prostate cancer patients treated by androgen deprivation therapy (Huang et al. 2012a).

Although heightened VEGFR-1 is fundamental to cancer neo-angiogenesis, many other factors play important roles in the establishment, adaptation, and maintenance of abnormal neo-vasculature (Welti et al. 2013). In order to characterize the multifaceted regulation of neo-angiogenesis, the term “angiogenic switch” was coined by Folkman and Hanahan (1991). As in normal tissue regeneration, both pro- and anti-angiogenic factors influence the careful orchestration of blood vessel development. Cancers, including prostate cancer, corrupt the delicate balance of normal blood vessel formation, tipping it toward proangiogenic factors. Based on the chaotic, unregulated expression of a multitude of proangiogenic factors and suppression of anti-angiogenic factors, cancer-associated blood vessels are abnormal – they are fenestrated and leaky but with increased thickening of the vessel walls because of pericyte proliferation Ruoslahti (2002). In part, this abnormal angiogenesis also facilitates the maintenance of a hypoxic microenvironment that is preferred by cancer cells and sustains glycolytic metabolism, the so-called Wartburg effect (Koppenol et al. 2011). Furthermore, abnormal angiogenesis assists the creation of an immune-suppressive microenvironment, limiting cancer immune surveillance by the host immune system (Kim et al. 2007). In the following, we will elaborate upon the most important elements of angiogenesis that are modified in prostate cancer and offer potential rationale for the absence of benefits from angiogenic inhibitors in prostate cancer patients, which is similar to patients with other cancers whom also fail to benefit from anti-angiogenic therapies.

### Proangiogenic Factors

#### Vascular Endothelial Growth Factors (VEGFs)

The VEGF pathway includes five different ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E) and three cognate receptors, both of which modulate angiogenesis as well as lymphangiogenesis (Ferrara 2002). The most prominent and well-studied pair is VEGF-A and VEGFR-1/VEGFR-2. Like increased VEGFR-1 expression, the heightened expression of VEGF-A is also associated with poorer outcomes for prostate cancer patients (Green et al. 2007). ARs are also capable of transactivating VEGF-A promoters (Eisermann et al. 2013), but may additionally lead to alternative splicing of VEGF-A, potentially increasing expression of more potent proangiogenic VEGF-A splice variants (Bates et al. 2002; Mavrou et al. 2015). ARs can also affect the half-life of
VEGF-A transcripts; in the case of active AR signaling, the Wilms tumor suppressor gene \((WT-1A)\) may enhance VEGF-A transcript stability (Cash et al. 2007).

In addition, AR-independent mechanisms also feature in the regulation of VEGF-A in prostate cancer. A single nucleotide polymorphism (SNP) in the VEGF-A gene has been linked with prostate cancer risk (Sfar et al. 2006). Specifically, this SNP causes a decrease in the usage of an alternative initiation codon (Lambrechts et al. 2003). MicroRNAs (miRNAs) can also regulate gene transcription, like miR-29b that can negatively regulate VEGF-A expression. In prostate cancer cell lines, miR-29b was significantly reduced, leading to elevated VEGF-A levels (Szczeryba et al. 2013). Other potential VEGF-modifying miRNAs that could be deregulated in prostate cancer are miR-145, miR-205, and miR-374b (Boll et al. 2013; Yue et al. 2012).

Finally, the role of VEGF-A is not limited to the development of primary, localized prostate cancer. VEGF-A promotes local tumor evasion, provides support to the development of niches for distant bone metastases formation (Kaplan et al. 2005), increases osteoblast activity and bone remodeling (Kitagawa et al. 2005), and diminishes immune surveillance by impairing the functions of cytotoxic T cells (Mellman et al. 2011), antitumoral M1 macrophages, and dendritic cells.

Together, VEGF-A-VEGFR-1/VEGFR-2 are crucial components of the angiogenic switch in prostate cancer.

**Platelet-Derived Growth Factors (PDGFs)**

PDGF signaling is composed of four ligands (PDGF-A, PDGF-B, PDGF-C, and PDGF-D) and two receptors (PDGFR-α and PDGFR-β) (Farooqi and Siddik 2015). Biochemically, ligands form homo- or heterodimers. PDGFR-β is upregulated in virtually all prostate cancers, and high PDGFR-β levels correspond to shorter prostate cancer recurrence-free periods (Paulsson et al. 2009). The PDGFR-β ligand, PDGF-B, is not overexpressed in most prostate cancers, though PDGF-D is frequently overexpressed and again correlates with prostate cancer aggressiveness (Ustach et al. 2010). Loss of PTEN is a very frequent event in prostate cancer and leads to upregulated PDGF-D expression (Christensen et al. 2014). PDGF-D is also important in the metastatic process – it promotes differentiation of osteoclasts by increasing NFAT-1, the master regulator of osteoclastogenesis (Huang et al. 2012b). PDGFR-A is of lesser importance in primary prostate cancer; however, it may be involved in the formation of bone metastases (Sulzbacher et al. 2009).

**Fibroblast-Derived Growth Factors (FGFs)**

FGF signaling features 22 ligands and four receptors and FGFRs are frequently mutated in cancers (Turner and Grose 2010). With this, recurrent FGFR3 mutations have been identified in prostate cancer (Hernandez et al. 2009), while several of the ligands, including FGF2, FGF6, and FGF10, are known to be overexpressed in prostate cancer (Giri et al. 1999; Ropiquet et al. 2000). Beyond mutations, the receptor, FGFR1-IIIc, has been demonstrated to be upregulated (Giri et al. 1999). In addition, negative regulators of FGF signaling, including SPRY1, SPRY2, and SEF, can be lost, resulting in increased FGF signalling (Fritzsche et al. 2006). It was suggested that most of the changes in FGF signaling are AR independent (Kwabi-Addo et al. 2004).

**Angiopoietins (Angs)**

Ang signaling includes four ligands and several angiopoietin-like ligands (ANGPTLs), the latter of which bind to two receptors (TIE-1 and TIE-2) (Fagiani and Christofori 2013). Angiopoietin-2 is highly expressed in primary prostate cancer as well as in liver, bone, and lymph node metastases, whereas angiopoietin-1 is minimally expressed (Lind et al. 2005). Inhibition of Ang-2 in preclinical models of prostate cancer has been seen to
result in blockade of prostate cancer development and progression (Morrissey et al. 2010).

**Anti-Angiogenic Factors**

There are multiple endogenous anti-angiogenic factors. Angiostatin, endostatin, osteopontin, vasostatin, thrombospondin, and prothrombin are among many other more or less potent molecules but, when acting in combination, are capable of blocking the angiogenic process rather effectively (Nyberg et al. 2005). Of note is that these molecules are not absent in primary or metastatic prostate cancer; however, the higher levels of proangiogenic factors override them, being anti-angiogenic. Potential enhancement of anti-angiogenic molecules in tumors could help in diminishing angiogenesis; however, tumor-specific overexpression remains a challenge for clinical feasibility.

**Mechanisms of Resistance to Angiogenesis Inhibition**

Multiple compounds targeting the neo-angiogenic process of prostate cancer have been developed, including inhibitors of ligands or receptors, but to date none of these have shown promise. Worthwhile noting is that, similar to other cancers, angiogenic inhibitors have limited efficacy, and, eventually, all patients progress. This apparent lack of efficacy is linked to two major processes – innate and adaptive resistance (Bergers and Hanahan 2008).

**Adaptive Resistance**

Despite the apparent lack of long-term efficacy of angiogenic inhibitors, these compounds actually do perform what they were designed for. VEGF-A neutralizing antibodies and VEGFR-2 blockers along with kinase inhibitors can potently inhibit signaling and consequently block angiogenesis. However, under therapeutic pressure, cancer cells will adapt. Shutting down angiogenesis creates tumors with increased hypoxia as well as necrosis (McIntyre and Harris 2015). Cancer cells are used to hypoxia and managed to activate several alternate pathways to alleviate the acute crisis of drops in blood flow and nutrient supply (Rapisarda and Melillo 2009).

When only one aspect of angiogenesis, for example, the VEGF pathway, is blocked, cancer cells are capable of upregulating other factors, including FGFs (Rapisarda and Melillo 2009), angiopoetins (Rigamonti et al. 2014), and ephrins (Pircher et al. 2014). Furthermore, in cases of increased hypoxia by inhibition of angiogenesis, cancer cells recruit bone marrow-derived cells that aid restoring angiogenesis (Asahara et al. 1997). Finally, pericyte coverage of blood vessels that remains after potent angiogenic inhibition might also save tumor cells (Song et al. 2005).

A very severe consequence of potent angiogenic inhibition is that cancer cells can become more aggressive to escape nutrient deprivation, and this tragically could bring about increased metastatic potential, e.g., more metastases (Pennacchietti et al. 2003). It has been previously shown that during angiogenic therapy, cancer cells are capable of activating pro-metastatic pathways, including, c-MET, Axl, and TGF-β (Sennino et al. 2012).

**Innate Resistance**

In the case of innate resistance, cancers are straightforwardly insensitive to angiogenic inhibition. This could be primarily because of the absence, or relative deficiency, of the particular pathway that is being targeted. Analysis of tumor-associated biomarkers could better identify patients who might be insensitive to a given anti-angiogenic therapy.
Anti-Angiogenic Therapies of Advanced Prostate Cancer

Bevacizumab

The first anti-angiogenic treatment that arrived in the clinic was bevacizumab. The humanized monoclonal antibody targets VEGF-A and has been registered in a number of countries for the treatment of colorectal, lung, and renal cell cancers. Other indications with approval in several countries are breast cancer, glioblastoma, ovarian carcinoma, and carcinoma of the cervix. It has been among the most successful anticancer drugs and its global sales were worth about seven billion US dollars in 2015.

In early studies, bevacizumab did not exhibit single-agent activity in prostate cancer. There were, however, promising results in combination with docetaxel. Di Lorenzo reported a phase II study with 20 heavily pretreated patients, and 11 (55%) showed major PSA responses and 3 had objective responses (Di Lorenzo et al. 2008). One phase II study featuring a combination of bevacizumab, docetaxel, and estramustine included 79 patients with docetaxel-naive CRPC. A 50% PSA decline was observed in 58 patients (75%) and 23 of 39 patients with measurable disease had a partial response (59%) (Picus et al. 2011). While these response rates were encouraging, the combination had significant toxicity with a high rate of neutropenia and thromboembolic events.

CALGB90401 was a large, phase III trial with 1,050 men randomized to receive docetaxel either with bevacizumab at 15 mg/kg (DP-B) or placebo (DP). The primary endpoint was overall survival which was not significantly different among the two arms – 22.6 months for DP-B compared with 21.5 months for patients treated with DP (HR, 0.91; 95% CI, 0.78–1.05; stratified log-rank p = 0.181). The median PFS time was superior in the investigational arm (9.9 vs. 7.5 months, p < 0.001). Grade 3 or greater treatment-related toxicity was more common with DP-B (75.4% vs 56.2%; P <= 0.001), as was the number of treatment-related deaths (4.0% vs 1.2%; P = 0.005) (Kelly et al. 2012). The difference in cardiovascular events was particularly important regarding the increased risk of arterial thromboembolism (Patel et al. 2015).

Bevacizumab has therefore not been registered for the treatment of prostate cancer. Interestingly, with similar results in terms of progression-free survival (PFS) benefit, the addition of bevacizumab to chemotherapy has led to different conclusions for different types of tumors. For example, the AVADO trial compared docetaxel alone or with bevacizumab at two different doses for the treatment of first-line therapy for human epidermal growth factor receptor 2-negative, locally advanced, or metastatic breast cancer (Miles et al. 2010). There was no difference in overall survival between the three arms, and only a minimal PFS benefit was detected in one of them, being the combination of docetaxel with bevacizumab at 15 mg/kg, but not with 7.5 mg/kg, demonstrating superior median PFS to placebo plus docetaxel in an unstratified analysis (placebo mPFS, 8.2 months; 7.5 mg/kgmPFS, 9.0 months [HR, 0.86; P = 0.12]; 15 mg/kg mPFS, 10.1 months [HR, 0.77; P = 0.006]). Despite similar median PFS benefit, this trial was considered positive. This is an example how similar data can yield varied conclusions and different solid tumor types (Ocana et al. 2011).

Aflibercept

Aflibercept (also known as VEGF-Trap) is a recombinant fusion protein consisting of the extracellular domains of the human VEGF receptor 2 (VEGFR-2) fused to the Fc portion of human immunoglobulin G1. Aflibercept has high binding affinity to the isoform, VEGF-A, and also binds VEGF-B, PDGF-1, and PDGF-2, thereby inhibiting angiogenesis (Chu 2009). Aflibercept has been assessed alone and with other chemotherapies, including docetaxel, in preclinical models and exhibited activity in a DU145 prostate cancer cell line xenograft model. Aflibercept has also been assessed in phase I and III clinical trials with docetaxel, though no phase II trial of this combination has been conducted for men with metastatic CRPC (mCRPC) (Isambert et al. 2012).
The Venice trial was a phase III multicenter randomized double-blind placebo-controlled trial for patients with mCRPC (Tannock et al. 2013). Patients were randomized to docetaxel 75 mg/kg and aflibercept (6 mg/kg) or placebo every 3 weeks. 1224 men were randomly allocated to treatment. Median overall survival (the primary endpoint) was 22.1 months (95% CI 20.3–24.1) in the aflibercept group and 21.2 months (19.6–23.8) in the placebo group (stratified hazard ratio 0.94, 95.6% CI 0.82–1.08; \( p = 0.38 \)). A higher incidence of grades 3–4 gastrointestinal side effects, hemorrhagic events, hypertension, fatigue, infections, and treatment-related fatal adverse events (21 [3.4%] vs. 9 [1.5%]) in the aflibercept group was recorded. Therefore, aflibercept has not been approved for the treatment of metastatic prostate cancer. In contrast, aflibercept was tested as a second-line treatment for metastatic colorectal cancer (in combination with 5-FU and irinotecan). Medium improvement of overall survival was 6 weeks, and this led to the approval of aflibercept in certain countries for the treatment of colon cancer (Van Cutsem et al. 2012).

**Tyrosine Kinase Inhibitors (TKIs): Sunitinib, Sorafenib, and Cabozantinib**

TKIs targeting both the VEGF and PDGF pathways revolutionized the treatment of metastatic kidney cancer in early 2000. Much efforts have also been placed into the development of this class of drugs for the treatment of metastatic prostate cancer.

**Sunitinib** blocks the VEGFR-2 and PDGF receptors, FLT3, and c-kit. A phase II trial that enrolled 36 patients who were progressing after docetaxel found that 4 patients (12.1%) had a ≥ 50% PSA decline and 7 (21.2%) had a ≤ 30% PSA decline (Sonpavde et al. 2010).

Another phase III trial featured 873 men with progressive mCRPC after docetaxel-based chemotherapy; patients were randomly assigned in a 2:1 ratio to receive sunitinib 37.5 mg/d continuously or placebo. Median OS was 13.1 months and 11.8 months for sunitinib and placebo, respectively (HR, 0.914; 95% CI, 0.762–1.097; \( p = 0.168 \)). PFS was statistically significantly improved in the sunitinib arm (median 5.6 v 4.1 months; HR, 0.725; 95% CI, 0.591–0.890; \( P < 0.001 \)). This difference was not deemed to be a clinically significant advantage, however, when considering the toxic side effects, such as fatigue (Michaelson et al. 2014).

**Sorafenib** has been studied in a phase II combination trial with bicalutamide. Eligible patients had rising PSA and minimal symptoms and were chemotherapy-naïve. PSA declines of ≥50% took place in 12 (32%) of the 38 assessable patients, including 7 of 27 patients (26%) with prior anti-androgen use (Beardsley et al. 2012). While these results were encouraging, no large follow-up study has ever been reported.

**Cabozantinib** is a second-generation TKI that inhibits VEGFR-2 as well as MET, hence potentially preventing the development of resistance mechanisms. Cabozantinib also has important effects on the tumor microenvironment, particularly against bone metastasis impacting the balance of osteoclast/osteoblast differentiation. Cabozantinib was tested in two phase II trials with 171 and 144 patients each.

In one randomized, phase II discontinuation study, 171 men were treated with cabozantinib – 72% of patients had regression in soft tissue lesions, whereas 68% of evaluable patients showed improvement upon bone scanning, including complete resolution in 12% (Smith et al. 2013). In addition, a second trial demonstrated significant improvements in clinically relevant parameters, like pain relief (57% of patients) and reduction or discontinuation of narcotic analgesics (55% of patients), along with improvements in measurable soft tissue disease, circulating tumor cells, and bone biomarkers (Smith et al. 2014).

Given these very encouraging results, cabozantinib was evaluated in two, randomized controlled, phase III trials. In particular, the so-called “Comet 1” and “Comet 2” studies investigated patients with mCRPC before or after treatment with docetaxel.

The Comet 1 trial randomly assigned 1,028 patients in a 1:1 ratio to either cabozantinib or prednisone. Median OS was 11.0 months with
cabozantinib and 9.8 months with prednisone (HR, 0.90; 95% CI, 0.76–1.06; \( P = 0.213 \)). Radiological PFS was improved in the cabozantinib group (median, 5.6 vs 2.8 months; HR, 0.48; 95% CI, 0.40–0.57; stratified log-rank \( P < 0.001 \)). Cabozantinib was associated with improvements in circulating tumor cell (CTC) conversion, bone biomarkers, and postrandom assignment incidence of serial skeletal events (SSEs) but not in PSA outcomes (Smith et al. 2016).

Considering that Comet 1 failed the primary endpoint (OS), the Comet 2 study (docetaxel-naive CRPC patients) was abandoned.

On the contrary, cabozantinib has yielded positive results with other tumor types. For example, cabozantinib has been approved for the treatment of medullary thyroid cancer as well as for second-line treatment of metastatic clear cell carcinoma of the kidney (Choueiri et al. 2016; Elisei et al. 2013).

Tasquinimod

Tasquinimod is a quinoline-3-carboxamide derivative with anti-angiogenic activity. The inhibition of anti-angiogenesis has been demonstrated in a variety of assays, including the in vitro endothelial capillary tube formation assay. Human prostate cancer xenograft models also exhibited diminished tumor growth by at least 50% compared to control-treated animals (Dalrymple et al. 2007).

Tasquinimod can also inhibit regulatory myeloid-derived suppressor cells (MDSCs), possibly resulting in a decrease in the immune-suppressive tumor microenvironment. The agent has therefore a dual mechanism of action – immune regulation and anti-angiogenic effects (Olsson et al. 2015).

A phase I trial for men with CRPC established the maximum tolerated dose of tasquinimod at 0.5 mg per day, but when a stepwise intra-patient dose escalation was employed, 1.0 mg per day was also well-tolerated. Several disease stabilizations were seen (Bratt et al. 2009).

One randomized phase II trial with 201 male participants (134 assigned to tasquinimod, 67 to placebo) exhibited a 6-month PFS rate (the primary endpoint) for tasquinimod and placebo groups at 69% and 37%, respectively (\( P < 0.001 \)), and PFS was 7.6 versus 3.3 months (\( P = 0.0042 \)) (Pili et al. 2011). Based on these results, two randomized phase III studies were performed.

1245 men with chemotherapy-naive mCRPC and evidence of bone metastases were assigned (2:1) to receive tasquinimod once per day or placebo until progression or toxicity. The patient population was typical with a median age of 71 years, Karnofsky performance status \( \geq 90\% \) close to 80%, and median PSA levels around 50 ng/l.

Estimated median mPFS by central review was 7.0 months (95% CI 5.8–8.2) with tasquinimod and 4.4 months (95% CI 3.5–5.5) with placebo (HR 0.639 [95% CI 0.544–0.751]; \( P < 0.001 \)). With a median follow-up of 30.0 months for tasquinimod and 30.7 months for placebo, the median OS was 21.3 months (95% CI 19.5–23.0) with tasquinimod but 24.0 months (95% CI 21.4–26.9) with placebo (HR 1.097 [95% CI 0.938–1.282]; \( p = 0.247 \)). The authors concluded that in chemotherapy-naive men with mCRPC, single-agent tasquinimod statistically significantly improved mPFS versus placebo. With this, no OS benefit was observed with tasquinimod (Carducci et al. 2015) However, a randomized placebo-controlled maintenance study after docetaxel did indicate there was a mPFS benefit for tasquinimod; OS data is not yet mature (Fizazi et al. 2016).

Taking into account these relatively disappointing results, further development of tasquinimod has been put on hold.

Thalidomide

The anti-angiogenic effect of thalidomide was accidentally discovered more than 20 years ago. The drug was initially marketed in 1957 to relieve morning sickness in pregnant women. Subsequently, it was linked to over 10,000 cases of phocomelia and other deformations, such as that of the heart or internal organs, and its use is widely thought to be one of the dark chapters in modern medicine (Vargesson 2015). In 1994, it was
demonstrated that thalidomide inhibits basic lym-
phoblast growth factors (BLGF) that induce
angiogenesis (D’Amato et al. 1994). Since then,
thalidomide has been evaluated as an anticancer
drug with anti-angiogenic properties.

Thalidomide and eight thalidomide analogues
have been tested in human prostate cancer xeno-
graft models (Ng et al. 2004). Clinical develop-
ment has included a randomized phase II study
employing combination with docetaxel. Seventy-
five patients with chemotherapy-naive metastatic
CRPC were randomly assigned to receive three
weekly docetaxel doses with or without daily
thalidomide at 200 mg orally (n = 50). The pro-
portion of patients with a greater than 50% decrease
in PSA was higher in the docetaxel/thala-
domide group (53% in the combined group, 37%
in the docetaxel-alone arm). The median PFS in
the docetaxel group was 3.7 months, while it was
5.9 months in the combined group (P = 0.32). At
18 months, OS in the docetaxel group was 42.9%
and 68.2% in the combined group (Dahut et al.
2004).

Similar activity has been described by Figg and
colleagues. Fifty-nine patients were treated with
the combination, and responses increased to 53%
for those receiving the combination treatment ver-
sus 36% with docetaxel alone. A greater number
of thromboembolic event rates with the combina-
tion were documented in both trials (Figg et al.
2001; Chen et al. 2014).

The combination of docetaxel, thalidomide,
and bevacizumab was tested in a single-arm,
phase II trial that enrolled 60 patients. Eighty-
eight percent of patients experienced a drop in
PSA of at least 50%. The time to progression
(TTP) was 18.3 months and the OS was
28 months. This was double the survival of his-
torical controls based on the Halabi nomogram
(Ning et al. 2010).

Despite these motivating findings, no phase III
trials have been initiated. The additional toxicity
of thalidomide and the increased rate of signifi-
cant toxicities (grades 3–4) of neutropenia, addi-
tional thrombosis and vascular events,
neuropathy, constipation, and fatigue have ham-
pered continued development.

Lenalidomide

Lenalidomide is an analogue of thalidomide,
selected for its better tolerance and side effect
profile. It is thought to be both an immune mod-
ulator and an anti-angiogenic compound.
Lenalidomide was studied in preclinical models,
including prostate cancer cell lines, and demon-
strated single-agent activity as well as synergism
with docetaxel (Henry 2012).

Phase I and phase II clinical trials have been
carried out in patients with solid tumors. With this,
it has been seen that men with mCRPC had a 25%
response rate (Sanborn et al. 2009). Responses
reflected by PSA declines were observed when
lenalidomide was combined with docetaxel in
47% of patients that had not received docetaxel
prior and in 50% of patients that did.

In a phase II, single-arm study with
lenalidomide before chemotherapy in men with
mCRPC, 32 patients were enrolled; stable disease
was observed for 20 patients suggesting a clinical
benefit rate of 63%. The median time to radi-
ographic progression was 4 months (2–16 months);
the median OS was 20 months. Of 27 PSA-
evaluable patients, 13 (48%) had a reduction in
PSA levels; 3 (11%) had >50% PSA decrease; the
median time to PSA progression was 3 months
(2–9 months) (Nabhan et al. 2014).

In considering these preliminary but promising
results, a phase III study was undertaken (Main-
sail). Patients were administered 75 mg of
docetaxel and 5 mg prednisone twice daily with
either 25 mg lenalidomide or placebo daily. The
study included overall 1.059 patients. Unfortu-
nately, the study was ceased early because of
futility. The OS was 17.7 months in the
lenalidomide group and had not been reached in
the placebo group. Additionally, in the investiga-
tion arm, there were more grades 3–4 side effects,
such as neutropenia, febrile neutropenia, diarrhea,
neuropenia, dyspnea, asthenia, and pulmonary
embolism. The authors ultimately felt that further
research of the combination was not warranted
(Petrylak et al. 2015).
Conclusion

Overall, prostate cancer can utilize multiple proangiogenic pathways, making it a promising target for anti-angiogenic therapy. Unfortunately, so far, all attempts to introduce anti-angiogenic drugs into the treatment algorithm for prostate cancer have failed. Thousands of men have taken part in clinical trials, and in contrast with other types of cancers, few approvals have been granted. While most agents have elicited a PFS benefit (see Table 1), this did not translate into an OS benefit. In actual fact, lenalidomide lessened survival significantly compared to placebo. Several explanations have been posed to explain these failures.

First, prostate cancer manages to rapidly activate multiple adaptive resistance mechanisms, leading to failure of these therapies. A better understanding and description of patients failing angiogenic drug administration could result in personalization of the therapy regimens. In clinical studies, to date, no particular patient population was enriched based on any biomarkers, and deciphering intra-patient, population heterogeneity is currently not considered for the treatment of CRPC (Dayyani et al. 2011).

Another issue in prostate cancer is the lack of intermediate or surrogate endpoints. While PSA, radiological responses, and CTCs decline, and others have been studied to serve as surrogates for OS, none have been shown to possess

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of phase III trials with anti-angiogenic agents in men with prostate cancer</th>
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<tbody>
<tr>
<td>Agent</td>
<td>n/Population</td>
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<tr>
<td>Bevacizumab (Kelly et al. 2012)</td>
<td>1050, chemotherapy-naive CRPC</td>
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<tr>
<td>Sunitinib (Michaelson et al. 2014)</td>
<td>873, progressive mCRPC after docetaxel</td>
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<tr>
<td>Tasquinimod (Carducci et al. 2015)</td>
<td>1245, chemotherapy-naive CRPC</td>
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<tr>
<td>Cabozantinib (Smith et al. 2016)</td>
<td>1028, progressive mCRPC after D and abiraterone and/or enzalutamide</td>
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<tr>
<td>Lenalidomide (Petrylak et al. 2015)</td>
<td>1059, chemotherapy-naive CRPC</td>
</tr>
</tbody>
</table>
significant power to predict OS benefit and hence are not recognized by regulatory agencies (Scher et al. 2011).

Another problem is the side effect profile of anti-angiogenic drugs. The increase of thrombo-embolic events is a constant problem and limits their use. Fatigue and increased neutropenia rates when in combination with other chemotherapeutic agents are particularly relevant for the elderly and frail prostate cancer patient population.

Currently, the development of anti-angiogenic drugs alone or in combination with existing chemotherapy (docetaxel) is restricted by the many negative clinical trial findings. Further research, however, should be considered in combination with immunological agents in select patient populations driven by relevant biomarkers.

Cross-References

▶ Anti-Angiogenic Cancer Therapy: Development of Resistance
▶ Anti-Angiogenic Targets: Angiopoietin and Angiopoietin-Receptors
▶ Anti-Angiogenic Targets: VEGF and VEGF-Receptors
▶ Mechanisms of Anti-Angiogenic Therapy
▶ Mechanisms of Tumor Angiogenesis

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The Value of Anti-angiogenics in Prostate Cancer Therapy


