review

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Is there a role for angiogenesis inhibition in prostate cancer?

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Abstract Prostate cancer is the most common male cancer and one of the most common causes of cancer death among men in European countries. In the last years, a large number of new drugs for treatment of castration-resistant prostate cancer (CRPC) have been approved, others are still in an advanced stage of clinical testing. In this review, we provide an overview on new substances which act via modulation or inhibition of angiogenesis. Results and limitations from clinical studies as well as future needs for improvement of those agents in CRPC are critically discussed.

Keywords Angiogenesis · Castration-resistant prostate cancer · Clinical studies

Abbreviations

CRPC	Castration-resistant prostate cancer
OS	Overall survival
PDGF	Platelet-derived growth factor
PFS	Progression-free survival
VEGF	Vascular endothelial growth factor

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Introduction

Prostate cancer remains a leading cause of male cancer-related death in the western world [1]. In the recent years, intensive research activities led to an increased understanding of the pathomechanisms of prostate cancer development and progression. One of the most crucial oncogenic factors in prostate cancer—through all disease stages—is the androgen receptor and its signaling network [2]. Therefore, androgen deprivation therapy either by surgical or hormonal treatment represents currently one of the most effective treatment options for advanced prostate cancer. Initially, most patients respond well to hormone therapy, however, resistance often develops rapidly, a status defined as castration-resistant prostate cancer (CRPC) [3]. Until recently, chemotherapy with docetaxel was the only treatment option in this stage of disease prolonging patients' overall survival (OS). However, in the last years several new compounds like new hormone synthesis inhibitors (abiraterone), antiandrogens (enzalutamide), the chemotherapeutic agent carbazitaxel, or the immunomodulator sipuleucel T have proven clinical efficacy and are now routinely used in clinical setting (except for sipuleucel T which is only used in the USA) [4]. Moreover, several other compounds like drugs targeting bone metastases and microenvironment, immunomodulators or growth factor inhibitors are currently proving their efficacy in large clinical trials [4].

Among these new substances, one of the most intensively investigated drugs for CRPC are inhibitors of angiogenesis.

In general, angiogenesis is a hallmark of tumor development and progression [5]. In the early 1970s Judah Folkman proposed the hypothesis of angiogenesis inhibition for tumor therapy [6]. Since then several concepts have been investigated and our knowledge of angiogenesis and tumor biology augmented significantly. As angiogenesis is a complex network regulated by several

pro- and antiangiogenic factors, plethora of targets were identified and investigated in preclinical and clinical models. For the first time tumor microenvironment and not the tumor cells themselves were used as target leading to a reduced tumor blood supply and finally tumor shrinkage and necrosis [7].

Most of the investigated agents or concepts inhibited the vascular endothelial growth factor (VEGF) signaling pathway either by neutralizing antibodies of the VEGF ligand or by blocking the tyrosine kinase of the VEGFR by small molecule [8–10]. Bevacizumab was the first monoclonal antibody against VEGF approved by the Food and Drug Administration for the treatment of colorectal cancer and in the following for other cancer entities as kidney, non-small cell lung cancer or brain cancer.

Consequent, intensive preclinical investigation also shows that in prostate cancer angiogenesis is involved in tumor initiation and progression. Therefore, several antiangiogenic agents were investigated with different results in metastatic prostate cancer. This review focuses on antiangiogenic concepts in advanced prostate cancer and critically discusses their future role in clinical practise.

Angiogenesis in prostate cancer

In the last years there is growing evidence that angiogenesis plays an important role also in prostate cancer. It has been reported that prostate cancer cells express higher VEGF9 levels compared with non-cancerous prostate tissue [11]. Moreover, VEGF serum levels were found to be elevated in prostate cancer patients with metastatic disease compared with those without metastatic prostate cancer [11]. Another study found a correlation between the VEGF levels in blood and urine in prostate cancer patients and survival [12]. In addition, microvessel density has been shown to correlate with Gleason score and may predict clinical or biochemical recurrence [13]. Recently our own group described for the first time that over expression of the receptors of the insulin-like growth factor axis (IGF1 receptor and insulin receptor) enhanced angiogenesis indicated by higher vessel density and increased number of desmin-immunoreactive pericytes [14].

Several strategies have been used to target angiogenesis in prostate cancer. These include blocking of pro-angiogenic factors via monoclonal antibodies or small molecule inhibitors targeting downstream signaling effector pathways, direct inhibition of endothelial cells, or targeting other receptors involved in cell adhesion, proliferation, and survival.

Completed studies of antiangiogenic agents

Bevacizumab (Avastin®) is a recombinant, humanized monoclonal antibody that blocks angiogenesis through binding and neutralizing VEGF-A. Two different phase II studies evaluated the effect of bevacizumab in prostate cancer with negative results: In a phase II study, 15 patients with chemotherapy-naïve metastatic CRPC were treated with bevacizumab. Results showed no objective responses and only 27 % of patients had pros-

Table 1 Overview about clinical studies with angiogenesis inhibiting agents. (Source: [19, 20, 22, 23])

Substance class	Targeting agent	Combination	Phase	Target	Status	Results	Reference/ study no.
Monoclonal antibody	Bevacizumab	Docetaxel	III	VEGF-A	Completed	Negative	NCT00110214
Tyrosine kinase inhibitor	Sorafenib	Placebo Bicalutamide	II	VEGFR1-3, PDGFRβ	Completed	Partial response	(19, 20)
Tyrosine kinase inhibitor	Subitinib	Placebo	III	VEGFR2, PDGFRβ, FLT-3, c-kit	Competed	Negative	(22)
Recombinant fusion protein	Aflibercept	Docetaxel + prednisolone	III	VEGF	Competed	Negative	(23)
Glutamic acid derivative	Lenalidomide	Docetaxel Prednisolone	III	TNFα, VEGF, bFGF, IL8	Completed	Negative	NCT00988208
Glutamic acid derivative	Thalidomide	Placebo Docetaxel	II	VEGF; bFGF, TNFα, NK Cells, regulatory T cells	Competed	Positive	NCT00988208 NCT00988208
Quinolone 3-carboxamide linomide	Tasquinimod	Placebo	III	Unknown (HIF1α discussed)	Completed	Awaiting	NCT01234311
Monoclonal antibody	TRC105	Placebo	I/II	CD 105 (endoglin)	Ongoing		NCT01090765
Tyrosine kinase inhibitor	Cabozantinib	Prednisolone Mitoxantrone	III	VEGFR2, c-MET	Ongoing		NCT01605227 NCT01522443
Small molecule inhibitor	Cediranib	Docetaxel Dasatinib	II	VEGFR1–3, PDGFR, c-kit	Ongoing		NCT00527124 NCT01260688
Fc fusion protein	Trebananib	Abiraterone	II/II	Ang1–2, Tie2R	Ongoing		NCT01552188

VEGF vascular endothelial growth factor, *PDGF* platelet-derived growth factor, *TNF* tumor necrosis factor, *HIF1α* hypoxia-inducible factor 1-alpha

tate-specific antigen (PSA) decline of less than 50 % [15]. The second phase II trial did not meet its primary endpoint of progression-free survival (PFS) [16]; however, the authors observed antitumor activity and favorable OS led to a phase III study of bevacizumab with docetaxel chemotherapy. CALGB 90401 was a phase III study that randomized 1050 patients to docetaxel with prednisone with or without bevacizumab. Final results of this study showed that the addition of bevacizumab did not improve OS (22.6 months in bevacizumab group versus 21.5 months in control group (HR 0.91; $P=0.1819$) [17].

Sorafenib (Nexavar®) is tyrosine kinase inhibitor inhibiting VEGF receptors VEGFR1–3 and platelet-derived growth factor receptor β (PDGFR). A phase II study of sorafenib evaluated the combination of sorafenib and bicalutamide in patients with chemotherapy-naïve CRPC. Thereby they reported a PSA response or stable disease for 6 months or longer in 47 % of the patients. The median time to treatment failure was 5.5 months [18]. Another phase II trial enrolled 57 chemotherapy-naïve CRPC. Among 55 patients, only two had PSA decline of more than 50 % and none had objective responses based on RECIST criteria [19]. Other phase II findings described that only 3.6 % of patients had PSA decline of more than 50 % [20].

Sunitinib (Sutent®) is a tyrosine kinase receptor targeting VEGFR2, PDGFRβ, FLT-3, and c-kit. This agent was assessed in combination with the chemotherapeutic agent docetaxel plus prednisolone in CRPC patients. Thereby this phase I/II study found that the combination of all three agents is well tolerated and has substantial benefits regarding response rates and OS benefits [21]. However, in 2014 the final results of the phase III study investigating sunitinib plus prednisone in patients with metastatic CRPC we published showing that the addition of sunitinib to prednisone did not improve OS compared with placebo in docetaxel-refractory CRPC [22].

Aflibercept (Eylea®) is a recombinant protein consisting of the Fc portion of human IgG1 which functions as a decoy receptor for VEGFs. A phase III multicenter double placebo-controlled study enrolled 1224 chemotherapy-naïve patients with metastatic CRPC. This study randomized 1224 patients to docetaxel and prednisone plus aflibercept in comparison with docetaxel, prednisone, and placebo. However, final analyses showed that aflibercept in combination with docetaxel and prednisone given as first-line chemotherapy for men with metastatic CRPC resulted in no improvement in OS and added toxicity compared with placebo [23].

Thalidomide (Thalomid®) and its second generation analog **Lenalidomide** (Revlimid®) are both glutamic acid derivatives with immunomodulatory and antiangiogenic effects. In generally, thalidomide targets VEGF; bFGF, TNFα, NK cells, regulatory T cells, while lenalidomide acts via targeting or modulating TNFα, VEGF, bFGF, and Interleukin 8 (IL8). A phase II randomized study investigated the combination of docetaxel with or without thalidomide. Therefore, they found that the median OS for the combined arm was 25.9 months versus 14.7 months for docetaxel alone, which was statistically significant ($P=0.04$) [24]. After similar positive results from phase I/II clinical trials also with lenalidomide, a randomized phase III clinical trial of lenalidomide in combination with docetaxel and prednisone as first-line therapy for metastatic CRPC was initiated (MAINSAIL trial). However, the primary endpoint data presented at the ESMO meeting 2012 shows that the primary endpoint of the study (OS) had not been reached, however, final results of the study are not published yet.

Moreover, **dual antiangiogenic therapy (bevacizumab and thalidomide)** in combination with docetaxel and prednisone has also been evaluated in a phase II trial. In this study, the median OS was 28.4 months, which was longer than the historical controls. However, this combination therapy was very toxic. All patients developed grade 3 and 4 neutropenia, 20 % had grade 3 and 4 thrombocytopenia or anemia. Grade 3 and 4 non-hematologic toxicities occurring in more than 10 % of the patients were syncope and hypertension [25].

Tasquinimod (ABR-215050®) is a quinoline-3-carboxamide linomide whose exact mechanism of action is still unclear, however, preclinical findings suggest an interaction with hypoxia-inducible factor 1-alpha (HIF1α). A phase II study found that the median PFS was 7.6 versus 3.3 months ($P=0.0042$) compared with placebo in CRPC patients [26]. These findings led to a randomized, double-blind, placebo-controlled phase III clinical trial in men with metastatic CRPC recently completed the enrollment (1200 patients) (NCT01234311). The final results of this study are awaited within this year [27].

Ongoing studies of antiangiogenic agents

TRC105 is a therapeutic human/murine chimeric monoclonal antibody to CD105 (endoglin), a TGF-β accessory receptor that is highly expressed on tumor vessel of endothelial cells. By binding to CD105, TRC105 may inhibit angiogenesis. A phase I study enrolled 50 patients with advanced solid tumors who were treated with escalating doses of TRC105. First analyses revealed that 6/45 patients were progression free for 18 to 48 months [28]. A second stage I/II trial evaluating TRC 105 as a single agent in metastatic CRPC is ongoing (NCT01090765) [27].

The tyrosine kinase inhibitor **Cabozantinib** (Cometriq®) is acting via inhibition of VEGFR2 and c-MET. Two phase III studies are currently underway in patients with CRPC affected by bone metastases who have received prior docetaxel and abiraterone or enzalutamide (NCT01605227, NCT01522443). One study randomizes patients to cabozantinib versus prednisone and evaluates OS, whereas the second study randomizes patients to cabozantinib versus mitoxantrone [27]. Both studies are still recruiting patients.

Cediranib (Recentin®) is an oral small molecule inhibitor of VEGFR1-3, PDGF receptor, and c-kit. Currently, cediranib is evaluated in two phase II studies: NCT01260688 investigates the use of cediranib with

dasatinib in patients with docetaxel-refractory metastatic CRPC [27]. The other phase II study is evaluating docetaxel with or without cediranib in chemotherapy-naïve patients with CRPC (NCT00527124) [27].

The peptide-Fc fusion protein **Trebananib** (AMG 386) disrupts tumor endothelial cells proliferation and angiogenesis by preventing interaction between angiopoietins (Ang) 1 and 2 and Tie2 receptors. A phase I/II study investigating the use of abiraterone with or without trebananib in patients with chemotherapy-naïve metastatic CRPC is currently underway (NCT01553188) [27] (Table 1).

Conclusion

In the recent years, a large number of antiangiogenic strategies have been developed for treatment of CRPC. Mostly monoclonal antibodies or tyrosine kinase inhibitors were tested in clinical studies with or without standard treatment options. However, most clinical studies were disappointing as the OS, which was the primary endpoint of all phase III studies was not reached. However, in the last few years new substances have been evaluated targeting multiple angiogenic factors or acting by new modes of action. Currently these substances are still under investigation, results from these clinical trials will hopefully clarify the role of angiogenesis inhibitors in the prostate cancer. Moreover, role of combination therapies may also be explored.

Take home message

Currently several substances have been evaluated in CRPC however, the role of angiogenesis inhibitors in prostate cancer is still a matter of debate.

Conflict of interest

All authors have no conflict of interest regarding this article.

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