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Antiangiogenic agents and endothelin antagonists in advanced castration resistant prostate cancer

M. Merino *, *A. Pinto, R. González, E. Espinosa*

Medical Oncology Department, University Hospital La Paz, Madrid, Spain

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ABSTRACT

Despite multiple advances in prostate cancer therapy, treatment options for castration resistant disease are very limited. While data from recent studies are encouraging, there is no drug that has significantly improved results of standard chemotherapy. Some of the most consistent results are provided by antiangiogenic agents, showing high response rates and manageable toxicity. We describe some of the main therapeutic angiogenesis inhibitors in metastatic castration resistant prostate cancer. These agents include vascular endothelial growth factor inhibitors, tyrosine kinase inhibitors, antiangiogenic and inmunomodulatory agents and endothelin receptor antagonists.

1. Introduction

Prostate cancer is the most common tumour in men in Western countries, and the second cause of cancer-related death among them.[1] Almost 80% of cases are diagnosed as localised disease, and radiotherapy or surgery can be curative. However, despite current treatment options, there is still a relapse rate of 30–60%.

For locally advanced or metastatic disease, hormonal treatment with androgen deprivation therapy is a standard approach for the majority of patients, but in most cases the duration of response is limited to 15–20 months, and the disease will become castration-resistant. In this setting, we should consider treatment with chemotherapy.

The standard first line treatment combines docetaxel and prednisone. This is mainly based in the TAX 327 study,[2] a phase III trial that demonstrated an improvement in overall survival (OS) and quality of life (QoL) in patients with castration resistant prostate cancer (CRPC) when they were treated with every-3-week docetaxel and daily prednisone compared with weekly docetaxel or mitoxantrone (OS 19.2 versus 17.8 versus 16.3 months, $p < 0.004$). Apart from this standard therapy as first-line treatment, there are three agents that may improve disease outcomes: mitoxantrone, that achieves better pain control than placebo as first-line therapy, but without any survival improvement; cabacitaxel, that has demonstrated benefits in overall survival compared with mitoxantrone-based therapy after progression to docetaxel[3]; and abiraterone, which can improve overall survival when compared with placebo.[4] Unfortunately, when disease progresses on chemotherapy the prognosis is really poor, with median survival no longer than 10 months.

Angiogenesis has a very important role in prostate tumours, and there are several studies showing a correlation between angiogenesis biomarkers, such as microvessel density[5] or serum levels of vascular endothelial growth factor (VEGF),[6] and the development of metastatic disease. In this review, we summarise the main agents with a direct or indirect antiangiogenic action in prostate cancer.

2. VEGF inhibitors

Bevacizumab is a humanized monoclonal antibody, widely used in many solid tumours. Results from early studies in

* *Corresponding author:*
E-mail address: mariamesal@gmail.com (M. Merino).
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prostate cancer were quite disappointing. Reese et al. evaluated bevacizumab 10 mg/Kg every 14 days in 15 chemotherapy-naïve patients with CRPC, but no objective responses were seen based on RECIST criteria, although there was a PSA reduction (less than 50%) in 27% of patients.[7]

Bevacizumab has also been tested in combination with other agents. Di Lorenzo et al. published the results of a phase II trial with 20 CRPC patients previously treated with docetaxel, that received bevacizumab (10 mg/Kg) and docetaxel (60 mg/Kg) every 3 weeks. Objective responses were observed in 37% of patients, median progression free survival (PFS) was 4 months and median overall survival (OS) was 9 months.[8] The regimen was well tolerated, and the main adverse effects were neutropenia and nausea.

The phase II trial CALGB 90006[9] enroled 79 metastatic CRPC patients. In this study docetaxel (70 mg/m^2 iv) and bevacizumab (15 mg/kg iv) every 3 weeks were combined with estramustine (280 mg/8 h on days 1–5). They found a median PFS of 8 months, a median OS of 24 months and a PSA decline (higher than 50%) in 75% of patients. Among patients with measurable disease, 59% achieved objective radiologic response. Toxicity was slightly higher than in the previous study but manageable with medical treatment. The most common adverse effects were neutropenia (69%), asthenia (25%), thromboembolic events (9%) and grades 3–4 hypertension in 5% of patients.

Preliminary data of CALGB 90401 trial have been shown at the American Society of Clinical Oncology (ASCO) meeting in 2010.[10] In this phase III study 1050 metastatic CRPC patients were randomized to first line treatment with docetaxel (75 mg/m^2/3w) and prednisone (5 mg/d) with or without bevacizumab (15 mg/kg/3w). The analysis has been performed with 748 events and the study was powered to show a 21% difference in the risk of death reduction. Although median PFS and response rate (RR) were higher in the bevacizumab arm, the combination did not show statistically significant superior OS ($p = 0.181$), and there was a higher toxicity and drug-related mortality in the experimental arm.

Despite the evaluation of several combinations of bevacizumab with other drugs, including cytotoxic agents and immunotherapy,[11] at the present time no schedule has shown results that might change the current standard treatment. However, there are several ongoing trials combining bevacizumab with other agents.

Another way of targeting VEGF is by binding its receptors. VEGF-trap is a fusion protein of VEGF receptor that binds VEGF-A, and blocks all its isoforms and also placental growth factor (PIGF). Even though this agent is at an early development stage, the standard dose has already been established as 6 mg/kg in phase I studies and there is currently a randomized phase III trial to evaluate the efficacy and safety of VEGF-trap versus placebo (NCT00519285).

3. Tyrosine kinase inhibitors

Tyrosine kinases (TK) are key enzymes that modulate several intracellular pathways of growth and proliferation of tumoural cells. Although there are many drugs that act through this mechanism, the most studied in prostate cancer are sorafenib, sunitinib and cediranib.

3.1. *Sorafenib*

This agent exerts its antiangiogenic effect targeting RAF kinase, VEGFR-2 and platelet-derived growth factor receptor (PDGFR-β). It is currently approved for renal cell carcinoma and hepatocellular carcinoma, but clinical experience in prostate cancer is limited to phase II studies. Steinbild et al. treated 57 metastatic CRPC patients in first line therapy with sorafenib (400 mg/12 h), obtaining a biochemical response in two of them, and 15 patients got stable disease, with no partial or complete response following RECIST criteria.[12] Median PFS was 12 weeks and 26% of participants in the study had some kind of toxicity, although no severe (grade 4) adverse effects were reported.

Dahut et al. conducted another study with sorafenib (400 mg/12 h) in CRPC patients.[13] Preliminary results were quite controversial because there was no objective biochemical response and there was an important difference between PSA evolution and radiologic response: among 21 patients with radiologic progression only 13 of them had biochemical progression and among two patients with clear response based on RECIST, both of them had an important PSA increase. In a second stage 24 patients were added to the study, and progression was redefined following just clinical or radiographic criteria. Stable disease was observed in one patient and there were two partial responses (PR). Median PFS was 3.7 months and median OS was 28.3 months.[14] Taking into account these findings sorafenib may be an active drug in the CRPC setting, although PSA evaluation does not seem to be the ideal way to test its efficacy.

After these results were published, there has been a controversy about using PSA levels to determine a response in CRPC clinical trials, and the Prostate Cancer Clinical Trials Working Group (PCCTWG) does not recommend excluding patients from a study only because of an isolated PSA increase.[15]

3.2. *Sunitinib*

Sunitinib is an oral tyrosine kinase inhibitor with activity against VEGFR-2, PDGFR β and KIT, currently approved for renal cell carcinoma and gastrointestinal stromal tumour (GIST). Results from a phases I–II study[16] were presented at the ASCO meeting in 2009. In this trial 55 metastatic CRPC patients were enroled for first line treatment to evaluate safety and efficacy of sunitinib (37.5 mg/d on days 1–14), docetaxel (75 mg/m^2/21 d iv) and prednisone (5 mg/d p.o daily). Objective biochemical RR (the main aim of study) was 56%, RR based on RECIST was 39%, and time to progression (TTP) was 42 weeks. This regimen was well tolerated and main toxicity was asthenia (15%) and haematologic events (75% of patients had neutropenia, and 15% of them had febrile neutropenia).

Another phase II study by Michaelson et al. was published in 2009.[17] In this trial, patients with no previous treatment (group A) or with previous docetaxel therapy (group B) were treated with sunitinib. There was one confirmed PSA

response in each group, and there were also responses following RECIST criteria that were not concordant with PSA levels, indicating that maybe radiographic assessment should be taken into consideration for future trials.

Encouraging results were also shown by a phase II trial conducted by Sunpavde et al.[18] Sunitinib, with a standard schedule of 50 mg/day, 4-weeks-on/2-weeks-off, was administered to 36 patients with CRPC who had progressed after one or two chemotherapy regimens including docetaxel. Four patients (12.1%) had a >50% decrease in PSA levels and seven (21.2%) had a >30% PSA decline, with a median PFS of 19.4 weeks.

A phase III trial comparing sunitinib and prednisone versus placebo has been recently interrupted because of futility in an interim analysis (NTC00676650). Nevertheless, it must be emphasised that sunitinib dosing in this trial was 37.5 mg/day continuously, and not the usual schedule of 50 mg/day, 4-weeks-on/2-weeks-off, so this may have influenced the results.

3.3. *Cediranib*

Cediranib is a tyrosine kinase inhibitor that acts by binding VEGFR 1 and 2, and is currently being tested in many neoplasms. In the prostate cancer setting, there are updated results from a phase II trial presented at the ASCO meeting in 2010. The study enroled 53 CRPC patients previously treated with docetaxel[19] and had two stages: in the first one cediranib 20 mg/d was administered to 35 patients, observing four PR; and in the second one, 23 patients received the same treatment, with two PR achieved. Furthermore, there was a decrease in size of metastatic sites (lung, liver, bones and lymph nodes), although without reduction in PSA levels. It seems to be an active agent, but still in an early phase of research.

3.4. *Other tyrosine kinase inhibitors*

There are other drugs with similar mechanism of action in an initial development phase, such as Vandetanib, which inhibits VEGFR, epidermal growth factor receptor (EGFR) and RET; Pazopanib, which inhibits VEGFR, PDGFR and KIT; and Enzastaurin, a seronine/threonine kinase inhibitor of protein-kinase C (PKC). This last agent showed safety results from a phase II study presented at the ASCO meeting in 2009,[20] and efficacy results are pending.

Semaxinib is a synthetic TK inhibitor with activity against VEGFR-2 and KIT. This drug investigation was interrupted because of the results from a phase II trial that showed no significant activity.[21]

4. Antiangiogenic and inmunomodulatory agents

4.1. *Thalidomide*

It is an oral agent with dual activity; its antiangiogenic activity could be due to inhibition of VEGF and fibroblast growth factor (FGF) secretion from tumour and stroma cells, but it also has an immunomodulatory effect by stimulating T-cells, inhibiting T-regulatory cells and increasing Natural Killer cells activity. Although it has been studied mainly in haematologic tumours, it has also demonstrated to be active in solid tumours, including prostate cancer either as monotherapy or in combination.

Despite the fact that RR observed in monotherapy regimens[22,23] are quite average (between 15% and 18% of patients achieve more than 50% PSA decrease), these results get better when combined with other cytotoxic agents. Results from a randomized phase II trial were published in 2004: 75 metastatic CRPC patients were treated with docetaxel 30 mg/m^2 on days 1, 8 and 15 each 21 days with or without thalidomide 200 mg/d.[24] Docetaxel was administrated weekly because the study design was previous to TAX327,[2] which showed superiority of every-3-weeks administration. Although results were superior for the combination arm, statistical signification was not achieved (PFS 5.9 versus 3.7 months, $p = 0.32$ and biochemical RR 53% versus 37%, $p = 0.32$). However, when analysis was performed with median follow up of 46 months, there was a statistically significant improvement in OS for patients treated with thalidomide, with a median OS 25.9 versus 14.7 months ($p = 0.0407$). Adverse effects were similar to other regimens using docetaxel (asthenia, nausea, vomiting, diarrhoea, constipation and oedema), with the addition of neurologic events (dizziness, instability), dry mouth and thrombotic events (18% of patients) in the thalidomide arm. Despite this finding, when low-molecular-weight heparin was used as prophylaxis, there was no difference in thrombotic events between the two arms of the trial.

Thalidomide has also been evaluated in earlier stages of disease, when there is a biochemical relapse after radical treatment. Figg et al. conducted a study with 159 patients to evaluate if the addition of thalidomide could improve TTP and hormonotherapy efficacy.[25] In this study patients were randomized to receive a gonadotropin analogue for 6 months and then thalidomide 200 mg/d (stage A). Stage B started when biochemical relapse happened, and then patients crossed over to the opposite arm. In spite of showing a trend to better results in the thalidomide arm, the difference was not statistically significant during stage A (15 versus 9.6 months, $p = 0.21$). On the other hand, after analysing stage B results, there was a clear impact on TTP in the combination arm (17.1 versus 6.6 months, $p = 0.0002$).

Regarding combination of thalidomide with other antiangiogenic agents, we have results of a phase II study with 60 metastatic CRPC patients who received thalidomide 200 mg/d, docetaxel 75 mg/m^2/3w and bevacizumab 15 mg/Kg/3w.[26] RR was surprisingly high, achieving PSA decrease (more than 50%) in 90% of patients, and radiologic RR in 67.7%. The median PFS was 18.3 months and median OS 28.2 months. With respect to toxicity, all patients had grades 3–4 neutropenia, and there were also some adverse events due to bevacizumab (perforation, nephritic syndrome, bleeding), although manageable with medical treatment. The importance of these data warrants further confirmation studies.

4.2. *Lenalidomide*

In an attempt to avoid thalidomide adverse effects, agents with a more favourable toxicity profile have been studied,

such as lenalidomide. This drug was evaluated in a phase I trial obtaining objective radiologic response in 38% of patients and biochemical response in near 50% of them.[27] On the other hand, the combination with paclitaxel showed low activity and important toxicity.[28]

Results from a phases I–II trial evaluating efficacy and tolerability of lenalidomide have been presented at the 2010 ASCO meeting. The study compared lenalidomide 5 versus 25 mg/d, administered during 6 months or until progression in 60 patients, without hormonotherapy, after a biochemical relapse. Main toxicity was neutropenia, thrombotic events, asthenia and rash, with more grades 3–4 events in the 25 mg dose arm. Despite higher toxicity, PSA decline curve was favourable to patients receiving the 25 mg/d dose.[29]

The first results of a phase II trial combining bevacizumab, lenalidomide, docetaxel and prednisone in CRPC patients were presented at the 2011 ASCO Genitourinary Cancer Symposium.[30] With 24 patients having completed four or more cycles, 22 patients (91.7%) had a >50% PSA decline, and 20 patients (83.3%) had a >75% PSA decline. 14 patients with measurable disease showed two complete responses, nine partial responses and three stabilizations (overall response rate of 78.6%). Therefore, this combination seems to be associated with a high response rate, showing manageable toxicity. A phase III trial comparing different doses of lenalidomide combined with docetaxel–prednisone versus placebo is currently underway (NCT00988208).

5. Endothelin receptor antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor, that binds to its receptors A or B (expressed in near 50% castration-resistant prostate tumours). According to preclinical models, when osteoblasts are stimulated by ET-1, growth factors are produced, enhancing tumour cells proliferation and ET-1 production, thus maintaining a cycle that leads to disease progression and morbidity. In addition, it has been shown that serum ET-1 concentration is higher in patients with bone dissemination than in patients with localised disease. Therefore, ET-1 and its receptors could be a therapeutic target in this disease.

5.1. *Atrasentan*

Atrasentan is an oral ET-A receptor antagonist that inhibits ET-1 activity. Carducci et al. initially evaluated this agent in a randomized, placebo-controlled phase II trial. 288 metastatic CRPC were enroled and received 2.5 or 10 mg/d. Median TTP was significantly superior for the 10 mg/d dose arm versus placebo arm (196 versus 129 days, $p = 0.021$), and so was TTP based on biochemical criteria (155 versus 71 days, $p = 0.002$). The most frequent adverse events were headache, rhinitis and edema.[31]

Results from a randomized phase III trial with 809 CRPCm patients were published afterwards, comparing atrasentan 10 mg/d with placebo.[32] The main objective of the study was PFS, and despite the results from the above mentioned phase II trial, atrasentan did not show any benefit. This was possibly correlated with the large number of patients that were classified as disease progression based on radiologic studies but without clinical progression. However, patients achieved an improvement in their quality of life, and in a late meta-analysis with 1002 pooled patients, a statistically significant improvement in PFS for patients receiving atrasentan was found.[33]

Atrasentan has been evaluated in combination with other drugs, such as docetaxel. Security of this regimen has been confirmed in a phase I trial with full doses of both agents.[34] A randomized phase III trial comparing docetaxel (75 mg/m^2/3w) and prednisone (10 mg/d), with or without atrasentan (10 mg/d), in CRPC patients with bone disease is currently underway.[35]

5.2. *Zibotentan*

It is another oral and selective ET-A receptor antagonist. James et al. recently published a randomized, placebo-controlled phase II trial with 312 patients. The study compared 10 and 15 mg/d doses with placebo. Although not showing a significant impact on TTP, there has been a trend to better OS for all patients treated with zibotentan (zibotentan 15 mg HR 0.76; IC 80% 0.61–0.94; $p = 0.103$ and zibotentan 10 mg/d HR 0.83; IC 80% 0.67–1.02, $p = 0.254$). Most common toxicities were peripheral oedema, nasal congestion and headache.[36] These are encouraging results, and there are several ongoing phase III trials for confirmation.

6. Conclusions

Nowadays, treatment options for CRPC are quite limited and none of the drugs under evaluation have overwhelmed the standard chemotherapy with docetaxel. Bevacizumab in combination with other cytotoxic drugs has high RR and better PFS when compared with docetaxel alone, although with higher toxicity, and it has not been able to improve OS data. Thalidomide is an active agent in this setting, but it does not seem to significantly improve results of standard treatment. Some TK inhibitors and ET antagonist have shown a very interesting activity, although results are not conclusive and more data are needed (Table 1).

Targeting angiogenesis is a very promising approach for the treatment of CRPC patients, as there is evidence of the influence of angiogenesis in the prognosis and clinical course of this disease. Nevertheless, there is lack of a phase III trial that confirms a consistent overall survival advantage with this strategy. Research about predictive factors for antiangiogenic agents is an unmet need in this setting; we must identify these factors to better select patients most likely to benefit from these drugs, so we can tailor their treatment. Also, a combinational approach can obtain better results than each drug tested in monotherapy. As an example, trials with endothelin antagonists have shown poor results when used alone, but promising activity when explored in combination, mainly with chemotherapy. Combination of different antiangiogenic drugs, with distinct mechanisms of action that can influence the proangiogenic stimuli at different levels, may also be of interest.

We should take into account the toxicities of these agents, that are used mainly in elderly population with different

Table 1 – Summarised view of the activity of the different antiangiogenic agents.

Agent	Phase	Biochemical RR	Radiologic RR	PFS (months)	OS (months)
Bevacizumab 10 mg/Kg/14 d[7]	II	27%	0%		
Bevacizumab + docetaxel[8]	II		37%	4	9
Bevacizumab + docetaxel + estramustine[9]	II	75%	59%	8	24
Bevacizumab + docetaxel + prednisone[10]	III	69%	53%	9.9	22.6
Sunitinib + docetaxel + prednisone[16]	I/II	56%	39%	10	NR
Thalidomide + docetaxel[24]	II	53%	NR	5.9	25.9
Thalidomide + docetaxel + bevacizumab[26]	II	90%	67.7%	18.3	28.2
Lenalidomide + docetaxel[27]	I/II	50%	38%	NR	NR
Atrasentan[32]	III	NR	NR	NR	20.5

comorbidities. We have to monitor very closely the imbalance between efficacy, toxicity and cost of these agents in their different combinations to ensure that they really help our patients to live longer and with a better quality of life.

We also have to consider the potential role of immunotherapy in the treatment of advanced prostate carcinoma. Sipuleucel-T (Provenge®) has been recently approved in this setting, and some other immune approaches, such as dendritic cell vaccines (PROSTVAC, DCVax, GVAX) and antibodies against the T-cell inhibitory receptor CTL-associated antigen 4 (ipilimumab) will probably emerge as future standard therapies for this disease. Understanding the best combinations, the most appropriate therapeutic sequence, and the patients that are most likely to benefit from every distinct approach, will enhance the efficacy and safety of these agents.

Conflict of interest statement

None declared.

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