

The efficacy and safety of zibotentan in the treatment of castration-resistant prostate cancer: a meta-analysis

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Abstract. – OBJECTIVE: Recently, novel endothelins like zibotentan and atrasentan and other novel taxanes have been introduced to treat prostate cancer. This study reviews zibotentan in the treatment of castration-resistant prostate cancer (CRPC) and derives a more precise estimate of their effect of treatment.

MATERIALS AND METHODS: Two reviewers searched and extracted data of the published trials and review articles on zibotentan for prostate cancer using the Medline, Embase and Cochrane Controlled Trials Register database. We used hazard ratios (HRs) to assess the effects on overall survival (OS), progression-free survival (PFS), or time to PSA progression (TTP), and relative risk (RR) for the different types of toxicity. Four randomized controlled trials were identified.

RESULTS: The pooled HR showed that zibotentan did not improve OS and PFS (HR = 0.92, 95%CI = 0.82-1.03, $p = 0.161$, HR = 0.98, 95% CI = 0.89-1.08, $p = 0.714$). Zibotentan had modest benefits on TTP (HR = 0.94, 95% CI = 0.91-0.97, $p = 0.001$). In addition, zibotentan led to more peripheral edema, anemia, cardiac failure and pneumonia.

CONCLUSIONS: Our study concludes that zibotentan is not an attractive option for CRPC patients. However, additional studies on other novel therapies are needed to improve patient outcomes.

Key words:

Zibotentan, Castration-resistant prostate cancer, Overall survival, Time to PSA progression.

agnosed in the USA with 28,170 estimated deaths^{1,2}. Non-metastatic tumors localized within the prostatic capsule could be treated with surgical castration or radiation, with a five-year survival rate. However, advanced PCa could achieve temporary disease control by androgen deprivation therapy. Most patients with PCa will later develop castrate-resistant prostate cancer (CRPC) and metastases. Castrate-resistant prostate cancer is defined as a rising prostate specific antigen (PSA) level, despite serum testosterone controlled below a castrate level. The vast majority of men with CRPC have radiological evidence of bone metastases, associated with a poor prognosis. Docetaxel-based therapy improves survival and quality of life in patients with metastatic disease^{3,4}. As the median improvement is 2-2.5 months and chemotherapy has associated toxicity, new treatments are needed for CRPC patients to delay disease progression.

The growth factor endothelin (ET)-1 is reported to play an important role in regulating the development and progression of various tumors, including prostate cancer⁵. Endothelin exerts paracrine and autocrine effects through the ET receptors, such as ETA and ETB. Activation of the endothelin A (ETA) receptor by ET-1 can promote prostate cancer growth through mediating processes like the inhibition of apoptosis, tumor invasion and metastasis⁶. However, signaling by the endothelin-B receptor (ETBR) may promote apoptosis and inhibit tumor progression. As a result, ETA receptor becomes an attractive therapeutic target for novel anti-cancer agents. Clinical trials of an oral selective ETA receptor antag-

Introduction

Prostate cancer (PCa) is the most common cancer and the second leading cause of cancer-related death in men. In 2012, 241,740 new cases were di-

onist, atrasentan (ABT-627, Abbott Laboratories, Abbott Park, CA, USA), has demonstrated benefit in PSA progression. Nevertheless, there was no significant improvement in overall survival (OS) or time to progression.

Zibotentan (ZD4054, Astra-Zeneca) is a specific ETA receptor antagonist and has no detectable activity of the ETB receptor. In recent years, several phase II and III randomized clinical trials have studied the effect of zibotentan in the treatment of CRPC⁷⁻¹¹.

Materials and Methods

The Medline (up to 2013), Embase (1980 to 2013), and Cochrane Controlled Trials Register databases were searched using the following keywords: endothelin, endothelin receptor antagonists, prostate cancer, zibotentan. The search was limited to “randomized controlled trial.” The reference lists of original and review articles were also examined for relevant clinical trials.

The trials were included if they had compared zibotentan to placebo regimens in patients with CRPC. The selected articles had to provide the following: (1) Studies in the mentioned databases with full text, (2) Sufficient published data for evaluating the overall hazard ratios (HRs) with 95% confidence intervals (CI). (3) Case-control design. The exclusion criteria were as follows: (1) No control population. (2) No usable data reported (3) Date duplicates. When studies from the same authors were published in different journals or years, the most recent publication was accepted for our study.

The following information was collected from each study: first author’s name and year of publication, median age, performance status, study design, number of the patients, HRs for OS, progression-free survival (PFS)/Time to PSA progression (TTP) and their 95% CI; data of main toxicities. The quantitative 5-point Jadad scale was used to assess the quality of the trials based on the methods and results of the studies¹². Data were extracted from each report using a standardized data recording form. Disagreements were resolved in consultation with an independent expert.

We analyzed the HRs for OS and PFS/TTP and relative risks (RRs) for grade 3 or 4 adverse events (AEs) using the Stata version 12.0 software (Stata Corporation, College Station, TX, USA). When OS, PFS or TTP could not be extracted from the reports, we deciphered them

from the survival curve as reported by Parmar et al¹³. A statistical test with a p value of less than 0.05 was considered significant. An HR less than 1 reflects more deaths, and a RR less than 1 indicates more toxicities in the placebo arms. Between-study heterogeneity was estimated using the χ^2 -based Q statistic¹⁴. Heterogeneity was statistically significant when $p < 0.05$ or $I^2 > 50\%$. If heterogeneity existed, calculations were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used. Publication bias was evaluated by the Begg and Egger tests^{15,16}. All p -values were two-sided. All CIs had a two-sided probability coverage of 95%.

Results

The search strategy retrieved 182 unique articles. Through screening of the titles and abstracts, 137 of these papers were excluded. An additional 41 articles were excluded for the following reasons: duplicate date, preliminary meeting reports, not reported/could not obtain usable data. As a result, we retrieved four studies based on the above search criteria^{7,9-11}. Amongst these trials, one was a phase II trials⁷ and three were phase III trials⁹⁻¹¹. There was only one trial that treated patients with zibotentan and docetaxel or placebo with docetaxel. In addition, enrolled patients received once-daily oral 10 mg zibotentan in the case group in all the trials and zibotentan 15 mg was investigated in only one trial. Characteristics of the four selected studies were shown in Table I.

Overall, the pooled HR didn’t show any significant differences in OS between zibotentan-based therapy and placebo-related therapy groups (HR = 0.92, 95% CI: 0.82-1.03, $p = 0.161$, Figure 1). There was no significant heterogeneity ($p = 0.451$), and the pooled HR was performed using fixed-effects model.

Begg’s funnel plot and Egger’s test were performed to assess the publication bias. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the two groups and the Egger’s test did not find any evidence of publication bias. Overall, the pooled HR for PFS showed that zibotentan could not prolong PFS significantly in patients with CRPC compared to placebo (HR = 0.98, 95% CI: 0.89-1.08, $p = 0.714$; Figure 1). There was no significant heterogeneity ($p = 0.643$) and fixed-effects model was used.

Table I. Baseline characteristics of included studies.

Authors	Country	Jaded scores	Patients	Treatment groups	N	Treatment regimen
Nelson et al (2012)	USA	3	mCRPC	Group A	299	Zibotentan: 10 mg q.d. po
				Group C	295	Placebo
James et al (2010)	UK	3	mCRPC	Group A	98	Zibotentan: 15 mg q.d. po
				Group B	107	Zibotentan: 10 mg q.d. po
				Group C	107	Placebo
Miller et al (2013)	Germany	3	Non-mCRPC	Group A	705	Zibotentan: 10 mg q.d. po
				Group C	716	Placebo
Fizazi et al (2013)	France	3	mCRPC	Group A	524	Zibotentan: 10 mg q.d. po
						Docetaxel: 75 mg/m ² iv on day 1, q.3.w
				Group C	528	Placebo
						Docetaxel: 75 mg/m ² iv on day 1, q.3.w

N: number of patients

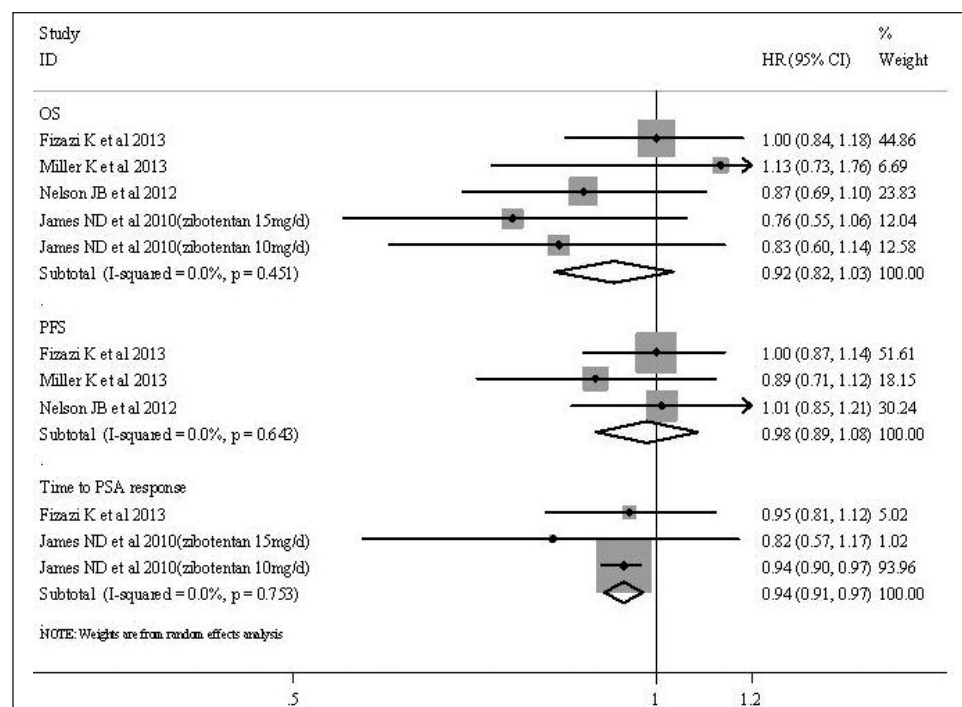
Modest benefits were seen in the zibotentan groups compared to the placebo group (HR = 0.94, 95% CI: 0.91-0.97, $p = 0.001$; Figure 1). There was no significant heterogeneity ($p = 0.248$). Publication bias was not found according to Begg's funnel plot and Egger's test.

All trials reported the total adverse events. In addition, adverse events that were reported most often included headache, fatigue, neutropenia, peripheral edema, anemia, constipation, and back pain. An analysis was made to combine the results of these trials and derive a more precise estimation on toxicities between the two groups.

The results showed that zibotentan-based therapy group led to more peripheral edema, anemia, cardiac failure and pneumonia than placebo (RR = 3.216, 95% CI: 1.731-5.974, $p < 0.001$; RR = 1.487, 95% CI: 1.009-2.191, $p = 0.045$; RR = 3.277, 95% CI: 1.983-5.415, $p < 0.001$, RR = 2.151, 95% CI: 1.093-4.233, $p = 0.027$, respectively, Figure 2). The fixed-effects model was used (Table II).

The results of headache, fatigue, neutropenia, constipation and back pain didn't display a difference between the two groups. In addition, publication bias was not found according to Begg's funnel plot and Egger's test.

Figure 1. The pooled HR for OS or PFS failed to display a difference between zibotentan and placebo groups. However, zibotentan only had modest benefits on TTP.



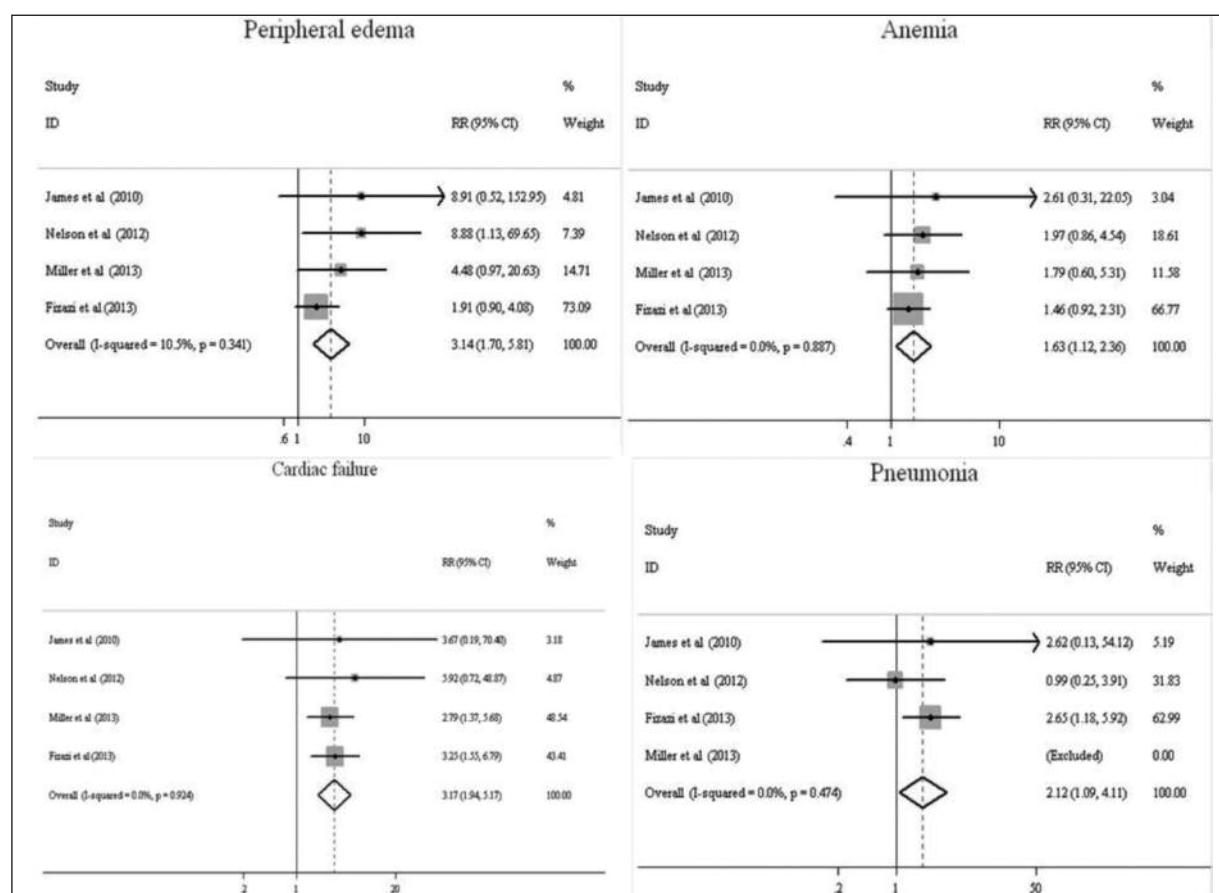


Figure 2. Forest plot showed that zibotentan related therapy led to more peripheral edema, anemia, cardiac failure, pneumonia than placebo.

Discussion

Overexpression of the ET-A receptor is found in several cancers, including PCa. Overexpression of the ET-1 is accompanied by increased expression of ET-A receptor in PCa cells, which correlates with an increase in stage and grade of the PCa lesions. The activation of the ET-A receptor by ET-1 causes the manifestations of cancer, such as the modulation of angiogenesis, nociception, and bone deposition. Therefore, the blockade of the ET-A may inhibit cancer growth, proliferation, and metastasis.

Zibotentan (ZD4054) is an oral and selective ET-A receptor antagonist in development for the treatment of CRPC. The ENTHUSE program of phase III clinical trials was designed to evaluate the efficacy and safety of zibotentan as monotherapy in metastatic CRPC (mCRPC, ENTHUSE M1)⁹, non-metastatic CRPC (non-mCRPC, ENTHUSE M0)¹¹ and combination with docetaxel in patients with mCRPC (ENTHUSE M1C)¹⁰.

Our study includes three ENTHUSE-related trials and another trial. Our results suggest that zibotentan could not prolong OS and PFS significantly in patients with CRPC compared to placebo. However, zibotentan had a modest benefit on TTP and increased the incidence rate of peripheral edema, anemia, cardiac failure and pneumonia. The limited number of trials, dissimilar methodologies and criteria might affect the results.

Both the ETA and ETB receptors have been reported to be important in different cardiovascular disorders. Therefore, dysregulation of the ET axis has been implicated in the development of vascular dysfunction and cardiovascular disease^{17,18}. The small and asymptomatic reductions in blood pressure and hemoglobin levels may be due to the vasodilatory activity of zibotentan, and consequent hemodilution¹⁹. There was no evidence that zibotentan was the leading cause of cardiac-related AEs. In James et al study¹⁹, 10 patients who received zibotentan developed cardiac failure, compared with none in the placebo

Table II. Grade 3 or 4 toxicities in the treatment of castration-resistant prostate cancer (zibotentan vs. placebo).

Toxicity (Grade ≥ 3)	No. of Trials	$P_{\text{heterogeneity}}$	RR(95%CI)	P
Peripheral edema	4	0.349	3.216 (1.731-5.974)	<0.001
Headache	4	0.007	1.326 (0.563-3.120)	0.519
Fatigue	4	0.733	0.562 (0.306-1.034)	0.064
Anemia	4	0.703	1.487 (1.009-2.191)	0.045
Neutropenia	4	0.868	0.782 (0.590-1.038)	0.088
Cardiac failure	4	0.929	3.277 (1.983-5.415)	<0.001
Pneumonia	4	0.467	2.151 (1.093-4.233)	0.027
Constipation	4	0.683	1.381 (0.436-4.376)	0.583
Back pain	4	0.624	0.736 (0.249-2.181)	0.581

$P_{\text{heterogeneity}}$: p for heterogeneity

group. However, ten of these patients had a history of cardiovascular disease at baseline. Therefore, a clear causal relationship cannot be established due to the small number of patients.

The combination of zibotentan 15 mg and docetaxel was well tolerated in patients with mCRPC¹⁹. There was no evidence that zibotentan treatment could increase the toxicity burden of docetaxel. In our analysis, only one trial⁹ contained zibotentan-based therapy with or without docetaxel. In addition, no significant differences were found. As known, docetaxel plus prednisone is the current treatment for patients with mCRPC²⁰. Effect of the combination of docetaxel and zibotentan in patients with the mCRPC needs further investigation.

The dose of zibotentan was defined to be 15 mg as the maximum tolerated dose in a multicenter, open-label, non-randomized Phase I trial⁸. Zibotentan 10 mg dose was selected because it showed comparable efficacy to the 15 mg dose.

Atrasentan (ABT-627) is another orally selective antagonist of the endothelin A (ET-A) receptor that inhibits ET-1 activity. Previous studies showed that Atrasentan had no benefit on OS and failed to delay disease progression in patients with metastatic or non-metastatic CRPC^{21,22}. There is currently one ongoing phase 3 trial, which compares the OS and PFS in patients with mCRPC treated with docetaxel and prednisone or docetaxel, prednisone and atrasentan (NCT00134056). This study is ongoing, but is not recruiting any participants.

Although zibotentan's results were reassuring, there were still a few ongoing challenges. 1) There was controversy about the appropriate time to initiate such treatment. 2) The disease state (pre-docetaxel, in combination with or without docetaxel needs further assessment).

The influence of bias in this article could not be completely excluded. Only published studies were included in our analysis, as non-significant

or negative findings may not be published. In addition, the researchers in the trials were different and our investigation only included four studies.

However, our study shows some advantages. Firstly, the statistical power of the analysis was greatly increased as numbers of cases and controls were pooled from different studies. Secondly, the quality of the studies included in our analysis met our inclusion criterion. Thirdly, this analysis included the most comprehensive and latest trials related to zibotentan in treating CRPC.

Conclusions

Our investigation revealed that the zibotentan-based regimen had only a modest benefit on TTP, compared with placebo-related regimen. Based on no improvement in OS and high AEs, our analysis suggests that zibotentan is not an attractive option for CRPC patients.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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