Meta-analysis of efficacy and safety of custirsen in patients with metastatic castration-resistant prostate cancer

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Abstract

Custirsen is the second-generation antisense oligonucleotide (ASO), which can reduce cellular levels of clusterin to increase the cytotoxic effect of chemotherapeutic drugs. Our study assessed the efficacy and safety of custirsen in patients with metastatic castration-resistant prostate cancer (mCRPC). The reference lists of the retrieved studies were investigated.

Three publications involving a total of 1709 patients were used in the analysis. We found that overall survival (OS) ($P = .25$) was not statistically significant in the comparison. Safety assessments indicated custirsen were often associated with complications resulting from neutropenia ($P < .001$), anaemia ($P < .001$), thrombocytopenia ($P < .001$), and diarrhea ($P = .002$).

Our meta-analysis shows that custirsen has no obvious effect on improving the OS of patients with mCRPC. Adverse reactions were more common among those patients treated with custirsen as compared to those treated with placebo.

Abbreviations: ADT = androgen-deprivation therapy, ASO = antisense oligonucleotide, CCRC = clear cell renal carcinoma, CI = confidence interval, CRPC = castration-resistant prostate cancer, mCRPC = metastatic castration-resistant prostate cancer, OR = odds ratio, OS = overall survival, PAP-GM-CSF = prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor, RANKL = receptor activator of nuclear factor kB ligand, RCTs = randomized controlled trials, SMD = standardized mean difference, SREs = skeletal-related events.

Keywords: clinical efficacy, custirsen, meta-analysis, prostate cancer

1. Introduction

Prostate cancer is very common in modern times and it is the fifth leading cause of death from cancer in men.\textsuperscript{1,11} In the early stages of the disease, the prostate foci are more limited and most patients want to be cured. However, many cancer foci of the patients have metastasized at diagnosis. Although patients with cancer metastases are relatively sensitive to medical or surgical castration early in treatment, most patients eventually develop metastatic castration-resistant prostate cancer. Since 2004, docetaxel combined with prednisone has become the standard first-line chemotherapy for the treatment of metastatic castration-resistant prostate cancer.\textsuperscript{2} In recent years, there have been more and more treatment options for mCRPC which can improve overall survival (OS), mainly including abiraterone\textsuperscript{3,4} and enzalutamide\textsuperscript{5,6}—the androgen receptor axis-targeting agents, radium-223\textsuperscript{7} and cabazitaxel\textsuperscript{8}—the second generation taxane.

Clusterin is an anti-apoptotic protein that is upregulated in response to endocrine therapy, chemotherapy, or radiation therapy and that appears treatment resistance.\textsuperscript{11,12} It protects cells by conferring treatment resistance through several mechanisms, such as the prevention of protein aggregation,\textsuperscript{13,14} inhibition of the BCL-2 family member BAX\textsuperscript{15} and increased NF-κB.\textsuperscript{16} Since clusterin can also be expressed in prostate cancer (OGX-011)—the second-generation antisense oligonucleotide—enhances the anticancer efficacy by inhibiting the production of clusterin by binding to clusterin mRNA.\textsuperscript{19,12,17}

A phase 1 trial concluded that the expression of clusterin in prostate cancer tissues can be inhibited maximally when the biologically effective dose was 640 mg.\textsuperscript{18} A phase 2 study assessed the OS in patients who received treatments with docetaxel, prednisone, and custirsen as 15.8 months, which was longer than those who were treated with mitoxantrone, prednisone, and custirsen (11.5 months).\textsuperscript{19} A recently completed phase 3 trial (SYNERGY trial) concluded that the OS was not improved significantly for patients with mCRPC treated with custirsen, docetaxel, and prednisone compared with patients treated with docetaxel and prednisone alone (median OS 23.4 months [95% CI 20.9–24.8] vs 22.0 months [19.5–24.0], HR 0.93 [95% CI 0.79–1.0]).\textsuperscript{20} Another phase 3 trial (AFFINITY trial) indicated that there is no survival benefit in men...
with mCRPC with the addition of custirsen to cabazitaxel and prednisone treatment (median OS 14.1 months [95% CI 12.7–15.9] vs 13.4 months [12.1–14.9], HR 0.95 [95% CI 0.80–1.12]; \( P = .53 \))\(^{[21]} \).

However, there has been no systematic meta-analysis to evaluate the efficacy and safety of custirsen in patients with mCRPC. Therefore, we conducted this meta-analysis to investigate this issue.

2. Materials and methods

2.1. Search strategy

In order to determine the randomized controlled trials (RCTs) regarding the efficacy of custirsen in treating patients with mCRPC, we searched MEDLINE (1966 to June 2018), Embase (1974 to June 2018), Cochrane Controlled Trials Register databases, and reference lists of the retrieved studies. The search terms are custirsen, metastatic castration-resistant prostate cancer, and randomized controlled trial.

2.2. Inclusion criteria and trial selection

Eligible study designs for inclusion were RCTs, and the participants were men with mCRPC; the study group was treated with docetaxel or cabazitaxel and prednisone plus custirsen and the control group with docetaxel or cabazitaxel and prednisone alone. The included studies should also meet the following criteria: (1) the selected study can provide full text; and (2) the study should offer accurate date, including the total number of subjects, the OS, and the number of adverse events of each study group. In addition, each study was included when the same group of researchers performed various experiments on the same subject. As shown in Figure 1, the study selection process is illustrated in a flow chart.

2.3. Quality assessment

We used the Jadad scale to evaluate the quality of the retrieved RCTs.\(^{[22]} \) The risk-of-bias assessment tool—outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)—was used to assess the methodological quality of each study. The tool focuses on the following domains: the generation of random sequence and the concealment of allocation procedures, blinding, the data loss resulting from attrition, and other sources of bias. Each study is rated according to the quality assessment criteria and then assigned to the quality categories: A, the study is considered to have a lower risk of bias once all quality criteria are adequately met; B, if the quality criteria are only partially met or ambiguous, the study is considered to be at risk of moderate bias; C, the study is deemed to have a higher risk of bias if one or more criteria are barely met or included. Differences were resolved by discussion among the authors. The quality of the studies is demonstrated in Table 1.

2.4. Data extraction

The following information was extracted from each included study: the first author, publication year, study design, the number of participants in each group, the therapy that the patients received, the country where the study was conducted, the data including the changes in OS, and the number of adverse events of each study group.

2.5. Statistical analysis and meta-analysis

The REVMAN V.5.3.5 (Cochrane Collaboration, Oxford, UK) was used to complete meta-analysis of the extracted data. The standardized mean difference (SMD) for continuous outcomes and the relative risk for dichotomous outcomes were estimated by the DerSimonian and Laird random-effects model\(^{[23]} \) and we adopted a 95% confidence interval (CI). If the analytic result suggested that \( P > .05 \), the studies were seen as homogeneous and then a fixed-effect model was used for the analysis. Otherwise, the random-effect model will be selected. We also quantified the inconsistency through the \( I^2 \) statistic, thereby illustrating the degree of true inconsistency in results across trials\(^{[24]} \). The \( I^2 \)
statistic was used to quantify the inconsistency, thus the degree of true inconsistency in results can be illustrated accurately. $I^2 < 25\%$ reflects small inconsistencies while $I^2 > 50\%$ reflects significant inconsistencies. We used a funnel plot to evaluate the presence of publication bias (Fig. 2). All data from our meta-analysis were derived from previously published studies, and this meta-analysis has no original data. Therefore, no ethical approval and patient consent are required.

3. Results

3.1. Studies characteristics

The process of literature search is shown in Figure 1. We found 51 original documents retrieved from the commonly used database. Based on the abstract of the articles and the inclusion and exclusion criteria of our meta-analysis, 45 articles were excluded. Three articles were excluded due to lack of useful data. In total, 3 RCTs\(^{[20,21,25]}\) were included in the analysis: 2 RCTs\(^{[20,25]}\) compared docetaxel and prednisone plus custirsen with docetaxel and prednisone alone, and 1 RCT\(^{[21]}\) compared cabazitaxel and prednisone plus custirsen with cabazitaxel and prednisone alone. The baseline characteristics are shown in Table 2.

3.2. Quality of individual studies

All of the 3 RCTs included in the analysis followed the randomization process and included a power calculation to determine the optimal sample size. The quality level of each identified study was A (Table 1). The funnel plot suggested that there is no evidence of bias was found (Fig. 2).

3.3. Efficacy and safety

The included 3 RCTs\(^{[20,21,25]}\) represented 1709 participants (857 in the experimental group and 852 in the control group). According to our analysis, there was no heterogeneity among the trials (Fig. 3), thus our analysis chose the fixed-effects model. The odds ratio (OR) was selected to assess the effect size for the meta-analysis.

| Study | Therapy in experimental group | Therapy in control group | Country | Sample size | Inclusion population | Exclusion population | Drug |
|-------|-------------------------------|--------------------------|---------|-------------|----------------------|----------------------|------|
| CN 2010 Docetaxel and prednisone plus OGX-011 (custirsen) | Docetaxel and prednisone | Canada, British Columbia, Jamaica, and USA | 41 | mCRPC, PSA > 5 ng/ml, received no prior chemotherapy or radiopharmaceuticals. A history of other malignancy, received other anti-cancer therapy less than 28 days before protocol treatment. | Docetaxel with prednisone plus OGX-011. | Docetaxel with prednisone. | 10 cycles of therapy, one cycle last for 21 days |
| CN 2017 Docetaxel and prednisone plus custirsen | Docetaxel and prednisone | Belgium, Canada, France, Germany, Hungary, Israel, Italy, Netherlands, Republic of Korea, Spain, UK, and USA | 501 | mCRPC, PSA > 5 ng/ml, received no radiotherapy or chemotherapy or investigative agent for at least 28 days. Receipt of any other cytotoxic chemotherapy, receipt of any hormonal treatment 28 days before randomization, active second malignancy. | Docetaxel with prednisone plus custirsen. | Docetaxel with prednisone. | 10 cycles of therapy, one cycle last for 21 days |
| Beer 2017 Cabazitaxel and prednisone plus custirsen | Cabazitaxel and prednisone | Australia, Canada, Czech Republic, France, Hungary, Russia, the UK, and the USA | 315 | mCRPC, previous first-line treatment with docetaxel. Brain or meningeal metastases, active second cancer, any notable concurrent medical illness. | Cabazitaxel with prednisone plus custirsen. | Cabazitaxel with prednisone. | 10 cycles of therapy, one cycle last for 21 days |

mCRPC = metastatic castration-resistant prostate cancer, PSA = prostate-specific antigen.
The indicator OS (Fig. 3A) was used to assess the efficacy of custirsen in the treatment of mCRPC. The analysis showed that the pooled estimate of SMD was 0.99, and the 95% CI was 0.71 to 2.69 (P = .25). It suggests that custirsen has no significant improvement in the OS.

Treatment-related adverse reactions are mainly manifested in the hematological and digestive systems (Fig. 3B–E); it contains neutropenia (OR = 1.59, 95% CI = 1.28–1.98, P < .001), anemia (OR = 1.86, 95% CI = 1.50–2.31, P < .001), thrombocytopenia (OR = 2.62, 95% CI = 1.82–3.77, P < .001), and diarrhea (OR = 1.35, 95% CI = 1.11–1.63, P = .002). The analysis concluded that the incidence of adverse reactions in patients treated with custirsen was significantly higher than that in patients without the treatment of custirsen.

4. Discussion
At first, the control of prostate cancer was mainly achieved by androgen-deprivation therapy (ADT). Most patients were sensitive to ADT with a median progression-free survival of 12 to 33 months and a median overall survival of 23 to 37 months. However, a small number of cancer cell subpopulations can survive the androgen deprivation, and finally show signs of cancer progression in biochemical, imaging, and clinical
symptoms. This stage of the disease is known as castration-resistant prostate cancer (CRPC), and some patients will progress to mCRPC in the further, which is the ultimate common pathway to death from prostate cancer.

Extending the lifespan for patients and improving their quality of life are the final goals of therapy in mCRPC, and the purpose of many trials in recent years is to achieve the above goals. Docetaxel and cabazitaxel are used as first-line and second-line drugs, and many other drugs have been applied to the treatment of mCRPC. Androgen-mediated signaling has been discovered, and thus the CYP17, abiraterone acetate, and potent androgen synthesis inhibitors have been approved for the treatment of mCRPC. Custirsen is a second-generation ASO intended to reduce cellular overexpression of clusterin should be considered as a cellular process of lipid transport, cell adhesion, and programmed cell death, etc. When the cell is under the stress conditions, the overexpression of clusterin should be considered as a cellular response to the tissue insults like radiation, cytotoxic chemotherapy, or ADT, etc. Clusterin is implicated in treatment resistance and it would be highly expressed in treatment-resistant poor prognostic disease. Clusterin has been shown to be expressed in a variety of malignancies including prostate, non-small-cell lung, renal, breast, urothelial, and pancreatic cancers. It has been confirmed that the clusterin is an intracellular protein which can be secreted by normal tissue cells, so the serum clusterin concentrations and the intratumoral clusterin concentrations may not be related. Direct measurement of the intratumoral clusterin concentrations has important clinical significance, but the test has not been widely carried out because it is technically demanding and susceptible to prostate cancer tissue.

Inhibition of clusterin can enhance the cytotoxic effects of chemotherapeutic drugs, while custirsen can exert anticancer effects by inhibiting the production of clusterin.

Clusterin is involved in many biological processes and represents the multifunctional protein. It participates in the process of lipid transport, cell adhesion, and programmed cell death, etc. When the cell is under the stress conditions, the overexpression of clusterin should be considered as a cellular response to the tissue insults like radiation, cytotoxic chemotherapy, or ADT, etc. Clusterin is implicated in treatment resistance and it would be highly expressed in treatment-resistant poor prognostic disease. Clusterin has been shown to be expressed in a variety of malignancies including prostate, non-small-cell lung, renal, breast, urothelial, and pancreatic cancers. It has been confirmed that the clusterin is an intracellular protein which can be secreted by normal tissue cells, so the serum clusterin concentrations and the intratumoral clusterin concentrations may not be related. Direct measurement of the intratumoral clusterin concentrations has important clinical significance, but the test has not been widely carried out because it is technically demanding and susceptible to prostate cancer tissue.

Inhibition of clusterin can enhance the cytotoxic effects of chemotherapeutic drugs, while custirsen can exert anticancer effects by inhibiting the production of clusterin. Custirsen has been proved that it can enhance cytotoxicity when combined with docetaxel in prostate cancer, with platinum compounds and gemcitabine in lung cancer, with cisplatin in clear cell renal carcinoma (CCRC), with paclitaxel in ovarian cancer, and with sorafenib in CCRC.

Antisense oligonucleotides (ASOs) are single-strand DNA fragment complementary to the mRNA region of the target gene, which forms RNA/DNA duplexes to inhibit translation, thereby reducing mRNA and protein levels of the target gene. Custirsen is a second-generation ASO intended to reduce cellular levels of clusterin. One of the included RCTs suggested that treatment with custirsen and docetaxel can improve survival.

Another two RCTs (SYNERGY trial and AFFINITY trial) indicated that there is no survival benefit in men with mCRPC with the addition of custirsen to docetaxel or cabazitaxel and prednisone treatment. This meta-analysis summarizes the evidence from the three RCTs regarding the efficacy and safety of custirsen for treatment of mCRPC and revealed that custirsen has no significant improvement in the OS of patients with mCRPC. A post-hoc analysis noted an improvement in OS in the poor prognosis patients when treated with custirsen, docetaxel, and prednisone, compared with docetaxel and prednisone alone, suggesting the inhibition of clusterin might be more pronounced in patients with poor prognosis. However, the findings of the subsequent trial found that the survival rate did not improve in patients with poor prognosis. So, this conclusion requires confirmation from further studies.

There are many factors that cause the custirsen to be ineffective in patients with mCRPC. The clusterin gene might be homozygously deleted in about 20% of elderly male with mCRPC. Custirsen could be ineffective in patients in which the clusterin gene of tumors is deleted. Prostate cancer patients included in the study may have different progressions of disease. At different stages of prostate cancer, the concentration of clusterin in tumor cells is different. Although the dose of custirsen which is used in the trials can inhibit the production of clusterin, its inhibition of intratumoral clusterin may not be enough to produce a detectable clinical effect in the trial. And whether the patient’s previous treatment has an effect on the biological role of the clusterin is unknown.

The treatment-emergent adverse events were primarily localized to the hematological and digestive systems, including neutropenia (OR = 1.59, 95% CI = 1.28–1.98, P < .001), anemia (OR = 1.86, 95% CI = 1.50–2.31, P < .001), thrombocytopenia (OR = 2.62, 95% CI = 1.82–3.77, P < .001), and diarrhea (OR = 1.35, 95% CI = 1.11–1.63, P = .002). The incidence of adverse reactions in patients treated with custirsen was significantly higher than that in patients without the treatment of custirsen.

The studies included in our meta-analysis are all findings from multicenter, randomized trials. According to the quality assessment scale, the quality of each study was conforming. The results of this analysis not only acquire great importance from the scientific standpoint, but also in the clinical practice. However, this meta-analysis only included three studies and unpublished studies’ data were not included in our analysis. In addition, the lack of uniform patient cohorts, the differences in the doses and efficacy between docetaxel and cabazitaxel, and inconsistent/unavailable recording of data may have resulted in bias. However, these limitations were unlikely to affect the results of this analysis. After the heterogeneity among each RCTs is taken into account, this meta-analysis remains crucial for assessing the efficacy and safety of custirsen in patients with mCRPC. Therefore, more high-quality RCTs are proposed to learn more about the combination therapy for the treatment of mCRPC.

5. Conclusion

Our meta-analysis shows that custirsen has no obvious effect on improving the OS of patients with mCRPC. Adverse reactions were more common among those patients treated with custirsen as compared to those treated with placebo.

Author contributions

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