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The influence of prior novel androgen receptor targeted therapy on the efficacy of cabazitaxel in men with metastatic castration-resistant prostate cancer

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Abstract ***Introduction:*** The treatment armamentarium for metastatic castration-resistant prostate cancer (mCRPC) has expanded with the introduction of several new therapies. In this treatment continuum, it is unclear whether the efficacy of cabazitaxel is affected by prior novel androgen receptor targeted therapies (ART) such as abiraterone and enzalutamide. In this study, we investigated the influence of prior ART on the efficacy of cabazitaxel in men with mCRPC.

Patients and methods: Data from an ongoing multicentre, phase II trial were used comprising 114 men with mCRPC treated with cabazitaxel in the post-docetaxel setting. The primary endpoints of the current analysis were prostate-specific antigen (PSA) response ($\geqslant$50%), and overall survival (OS). Univariate and multivariable analyses were conducted to investigate the influence of prior ART on the efficacy of cabazitaxel.

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Results: From the 114 patients included in this analysis, 44 men received prior ART and 70 men did not receive prior ART before treatment with cabazitaxel. PSA response rates while on cabazitaxel treatment were similar in patients with and without prior ART (34% versus 40%, respectively, $P = 0.53$). Likewise, median OS was not significantly different between men with and without prior ART (13.0 versus 14.0 months, respectively, logrank $P = 0.65$). In multivariable analysis, the only variables significantly associated with OS were performance status, serum albumin and alkaline phosphatase.

Conclusion: Our study showed that prior treatment with ART may not influence the efficacy of cabazitaxel in men with mCRPC. With emerging evidence of cross-resistance in the treatment of mCRPC, cabazitaxel provides a good treatment option irrespective of prior ART.

1. Introduction

The treatment armamentarium for metastatic castration-resistant prostate cancer (mCRPC) has changed considerably over the past few years, with the introduction of several new drugs that provide substantial survival benefits [1–6]. Cabazitaxel, abiraterone, enzalutamide and radium-223 all demonstrated to prolong life in the post-docetaxel setting and subsequently became approved for the treatment of this disease. Moreover, the novel androgen receptor (AR)-targeted therapies abiraterone and enzalutamide have shown survival improvement when used in chemotherapy-naïve mCRPC [5,6]. These advances also come with new challenges. Although there are emerging biomarkers such as the androgen receptor splice variant AR-V7 [7], no established biomarkers for treatment selection exist at the current time and the optimal treatment sequence in mCRPC is still undetermined.

Retrospective studies suggested that overall survival benefit obtained by the new therapies cannot be added up, as cross-resistance between docetaxel and AR-targeted agents has been observed [8–10]. Reduced efficacy of docetaxel was observed in men with mCRPC who had previously been treated with abiraterone, suggesting clinical cross-resistance [8–10]. In a post-hoc analysis of the COU-AA-302 study, a prostate-specific antigen (PSA) response rate of 45% was observed in patients treated with taxane chemotherapy after abiraterone [11]. This was slightly higher as compared to previous reports of docetaxel in this setting, with PSA response rates ranging from 26% to 40% [8–10]. However, the observed response rates were lower as compared with a contemporary cohort of abiraterone-naïve patients treated with docetaxel (PSA response rate $\geqslant$50%: 64%), which might support the hypothesis of cross-resistance [12].

Preclinical studies revealed that the AR may confer cross-resistance between enzalutamide and docetaxel *in vivo*, which is induced by an overlapping working mechanism on AR nuclear translocation [13,14]. These findings are confirmed in clinical studies [15], and raise concern whether prior treatment with abiraterone or enzalutamide may affect the efficacy of subsequent cabazitaxel treatment. Emerging preclinical and retrospective clinical data suggested that cabazitaxel, in contrast to docetaxel, has sustained efficacy in men with mCRPC after prior abiraterone treatment [16,17]. In two retrospective studies, cabazitaxel efficacy after abiraterone treatment was investigated and compared to the TROPIC trial of cabazitaxel in abiraterone-naïve patients as an historical control group [2,16,17]. These studies suggested retained efficacy of cabazitaxel after prior abiraterone, as the observed PSA response rates were similar when compared to the TROPIC trial. However, to date, the efficacy of cabazitaxel has never been directly compared between patients with and without prior abiraterone or enzalutamide, which limits clinical conclusions.

In the current study, we aimed to investigate the influence of prior novel AR-targeted therapy (ART) on the efficacy of cabazitaxel. For this purpose, we used data from a randomised phase II trial to directly compare clinical outcome and response to cabazitaxel in men with and without prior ART.

2. Patients and methods

2.1. Study population and data collection

CABARESC (Dutch Trial Registry number: NTR 2991, EudraCT number: 2011-003346-40) is an ongoing randomised, open-label, multicentre, phase II trial that was designed to investigate the effects of budesonide on cabazitaxel induced diarrhoea. The primary endpoint of the original study was the incidence of grade 2–4 diarrhoea. In order to detect a reduction of 15% in grade 2–4 diarrhoea a total sample size of 250 patients was planned for this study. Eligible men were randomised to either cabazitaxel (25 mg/m^2) and prednisone (10 mg daily) plus oral budesonide (9 mg daily during 44 days), or standard cabazitaxel 25 mg/m^2 plus rednisone (10 mg daily). It has been shown previously