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The third line of treatment for metastatic prostate cancer patients: Option or strategy?

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Contents

Summary

New agents for metastatic castration-resistant prostate cancer (CRPC) developed in the past 3 years include cabaziataxel (Cbz), abiraterone acetate (AA) and enzalutamide (E). In this review, the results of clinical studies in which one of these drugs is included as the third line of treatment are discussed. Our review suggests that AA and E have limited activity, while Cbz seems to retain its efficacy. Prospective studies that further examine sequential treatments are warranted.

Keywords: Prostate cancer; Cabazitaxel; Abiraterone acetate; Enzalutamide; Sequential therapy

1. Introduction

In the past 3 years, different treatment options have become available for the management of castrate-resistant prostate cancer (CRPC) patients after docetaxel (D) progression [1–3]. These include: cabazitaxel (Cbz) [1] abiraterone acetate (AA) and [2] enzalutamide (E) [3] (Table 1). Furthermore, sipuleucel-T improved the survival of asymptomatic or mildly symptomatic men, most of whom had not received chemotherapy [4], and radium-223 improved survival in men with symptomatic CRPC and bone metastases [5].

Cabazitaxel is a novel taxane that inhibits microtubule depolymerization and cell division by binding tubulin, resulting in cell cycle arrest. In the phase III randomized Tropic trial, patients progressing during or after D achieved an overall survival (OS) of 15.1 months [1]. The median progression-free survival (PFS) was 2.8 months, while the median time to PSA progression was 6.4 months, with a PSA response rate in 39.2% of patients.

Abiraterone acetate is a selective inhibitor of cytochrome P450 and CYPC17 and inhibits the residual amount of

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Table 1
Median values of clinical outcome of new second line therapy.

	Overall survival (months)	PFS (months)	PSA progression (months)	PSA response rate (%)
Cabazitaxel	15.1	2.8	6.4	39.2
Abiraterone	14.8	5.6	10.2	29
Enzalutamide	18.4	8.3	8.3	54

androgenic steroid predominantly produced in the adrenal gland [2]**.** In a phase III, randomized COU-AA-301 trial, AA achieved an OS of 14.8 months, a time to PSA progression of 10.2 months, a PFS of 5.6 months and a PSA response rate of 29% in patients progressing during or after D. At a follow-up of 20.2 months, AA confirmed its efficacy [6].

Enzalutamide is an androgen-receptor signalling inhibitor that inhibits the nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment with no known agonistic effects [3]. In the AFFIRM phase III randomized trial, E significantly increased clinical outcomes compared to the placebo in men progressing during or after D. Enzalutamide achieved a median OS of 18.4 months, and a radiographic PFS and median time to PSA progression of 8.3 months.

In the absence of specific trials, as the third line of treatment, therapeutic options for metastatic CRPC patients may include all of these agents. Here, we review the first clinical studies in which CRPC patients received a third line of treatment with AA or Cbz or E.

2. Third line therapy with AA, E and Cbz for CRPC patients

On 30 Decemberr 2014, we searched the Pubmed MEDLINE database for trials containing the key words "abiraterone acetate", "enzalutamide", "cabazitaxel" and "prostate cancer sequential regimen". Twelve studies were chosen for review (Tables 2 and 3) [7–18]; all of the studies involved patients with metastatic CRPC who were treated with a third line of therapy that included AA, E or Cbz. Studies were excluded from the review if they not contain a third line of therapy and/or complete patients characteristics. The results of the 11 studies are summarized below and in Table 3.

2.1. Abiraterone acetate as the third line of treatment

Two retrospective studies have reported the activity of AA in patients previously treated with both D and E [7,8]. The first study involved 27 patients, while the second involved 38. Patient characteristics are similar for both studies. The median age (70 and 71, respectively), ECOG performance status of 0–1 (70% and 68% of patients, respectively), and visceral metastasis (30% and 26%, respectively) were very similar in both studies. Both of these studies report a decrease in the activity of AA compared to the expected activity. The decline of PSA > 50% response rates were 4% and 8%, respectively. The median time after AA administration to progression (monitored by increases in PSA levels or by objective or symptomatic criteria) were 3.6 months and 2.7 months, respectively, while the median OS was 11.6 months and 7.2 months, respectively. However, because of the

Table 2
Patients characteristics of studies with AA, Cbz and E as a third line of therapy.

Study author	Drug	Prior two lines	N. of patients	Median age (range)	% ECOG (0–1)	% Gleason score ≥ 8	% Patients with visceral metastasis	Median serum PSA (μg/l or ng/ml)
Noonan et al. (2013)	AA	D → E	27	70 (56–84)	70	43	30	NP
Loriot et al. (2013)	AA	D → E	38	71 (52–84)	68	37	26	232
Wissing et al. (2014)	AA	D → Cbz	63	65.6* (44–79)	84.1*	66.1*	NR	291*
Pezaro et al. (2014)	Cbz	D → AA/E	37** 4***	62** (NR) 51*** (NR)	83** 75***	50** 50***	35** 24***	717** 137***
Al Nakouzi et al. (2014)	Cbz	D → AA	79	69 (48–87)	59	NR	14	307
Sella et al. (2014)	Cbz	D → AA	24	65 (57–85)	NR	50	29.1	128.1
Wissing et al. (2014)	Cbz	D → AA	69	69.8* (52–88)	84.1*	55.7*	NR	130*
Schrader et al. (2013)	E	D → AA	35	70 (57–81)	NR	54.3	NR	NR
Bianchini et al. (2013)	E	D → AA	39	70 (54–85)	64.2	53.8	15.3	500
Thomsen et al. (2013)	E	D → AA	24	72 (57–82)	66.6	58.3	16.7°	578
Badrising et al. (2013)	E	D → AA	61	69 (64–74)	57	43	21	267
Schmid et al. (2014)	E	D → AA	35	72 (60–83)	77	40	17	NR
Brasso et al. (2014)	E	D → AA	137	71 (57–85)	70.8	61.4	NR	135

NR: Not reported.
* Value from the beginning of second line of therapy.
** Prior AA with or without E.
*** Prior E.
° Liver metastasis only.