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CURRENT OPINION

Managing Metastatic Castration-Resistant Prostate Cancer in the Pre-chemotherapy Setting: A Changing Approach in the Era of New Targeted Agents

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Abstract In recent years, the therapeutic options for treating men with metastatic castration-resistant prostate cancer have increased substantially. The hormonal treatments abiraterone acetate and enzalutamide, the chemotherapeutics docetaxel and cabazitaxel, the radiopharmaceutical alpharadin and the immunotherapeutic Sipuleucel-T have entered the field. Additionally, corticosteroids, which are used extensively, have documented activity but no documented survival benefit. Physicians treating patients with metastatic prostate cancer immediately after castration resistance develops currently have at least four different options to choose from for the first treatment. These therapeutic choices and their several possible ways of sequential use have not yet been compared to each other head-to-head and may never be. Therefore, there is an unmet need to inform their use with prospective clinical data. Additionally, the new indications of docetaxel for hormone naïve prostate cancer is changing the landscape of prostate cancer treatment and questions the traditional classifications 'pre-chemotherapy' and 'post-chemotherapy'. In this work we attempt to address these challenges in the treatment of metastatic castration-resistant prostate cancer with the focus mainly on the non-cytotoxic agents. We try to integrate available clinical and preclinical information to suggest optimal ways of treatment.

Key Points

The use of docetaxel in the hormone-naïve setting will change the landscape of mCRPC treatment, changing the 'pre-chemotherapy' space.

Current evidence does not allow judgements on the superiority of any of the available agents.

Validated predictive biomarkers together with new targeted agents may render discussion of sequencing of current treatments obsolete in the near future.

1 Introduction: The Natural Course of the Disease

Prostate cancer (PCa) is a major morbidity factor worldwide, representing approximately 7 % of all deaths in males [1]. About 30 % of newly diagnosed patients develop metastatic disease and up to half of these will have metastatic disease at presentation [2]. Metastatic PCa is the lethal form of the disease and presents mainly with osteoblastic bone metastases and nodal disease and less often with liver and lung metastases. It is treated with surgical or chemical castration, [3] to which first generation antiandrogens can be added with limited benefit. Castration results in impressive responses but invariably leads to resistance despite anorchid levels of testosterone within a median time of 15–25 months [4]. This state is characterized as metastatic castration-resistant prostate cancer (mCRPC); mCRPC is a heterogeneous disease, as is evident from multiple large phase III trials [5, 6]. Some

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patients survive for several years and remain asymptomatic or mildly symptomatic for longer periods, while others succumb quickly to their disease. This clinical heterogeneity underlies a wide range of genomic aberrations [7].

Before modern treatments, the median survival of patients with mCRPC was between 12 and 20 months for symptomatic and asymptomatic patients, respectively [8, 9]. The only therapeutic options were secondary hormonal manipulations: diethylstilbestrol, ketoconazole, changing or withdrawing antiandrogens and monotherapy with corticosteroids, yet without any documented survival advantage [10].

After 2010 several new drugs appeared on the stage of mCRPC treatment, prolonging overall survival (OS) after castration resistance to approximately 3 years. Their optimal sequence and use has nevertheless not been established and there are several unanswered questions. In the current work we attempt to address these areas of controversy and to recommend optimal ways to use available treatments by integrating information from the available clinical and preclinical data.

2 Corticosteroids: Two-faceted Drugs?

Corticosteroids are easily accessible drugs and their application in mCRPC dates back to the 1950s [11]. They are able to induce prostate-specific antigen (PSA) responses and symptomatic relief [5, 12, 13] and most mCRPC patients at some time point receive corticosteroids either as monotherapy or as an adjunct to other treatments. Dexamethasone monotherapy results in higher PSA response rates than prednisone (40 vs. 20 %) [12], and during abiraterone treatment PSA responses have been reported after substituting prednisone 5 mg twice daily (bid) with dexamethasone 0.5 mg once daily (od) [14]. Corticosteroids are hypothesized to act by suppressing the adrenocorticotropic hormone (ACTH) axis and reduce androgenic steroids that can then activate wildtype or mutated androgen receptor (mAR). The longer half-life of dexamethasone compared to prednisolone may suppress ACTH more efficiently and may explain this steroid switch response rate [12]. Furthermore, glucocorticoid receptor (GR) has been reported to transcribe genes otherwise regulated by AR [15] in androgen-deprived conditions and so contribute to castration resistance. Therefore, dexamethasone 0.5 mg od, corresponding to a lower equivalent glucocorticoid activity compared to prednisolone 5 mg bid, may result in reduced GR activation [12] which hypothetically could result in tumour regression. Mutant forms of AR may also be activated by prednisolone but not by dexamethasone [16]; in such cases a change of prednisone to dexamethasone may result in a withdrawal response [17]. Therefore, although corticosteroids are useful drugs in the treatment of CRPC, they should also be used with caution and discontinued if not clinically indicated as they have been reported to potentially drive PCa growth.

3 The Advent of a New Era: New Drugs for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

The first drug to show improved survival of mCRPC patients was docetaxel [18]. Sipuleucel-T [19] and cabazitaxel [20] were subsequently approved. Then abiraterone acetate and enzalutamide followed, proving that mCRPC remains dependent on ligand-dependent activation of the AR pathway [21]. This can occur with *AR* gene amplification [22], use by the tumour of androgenic steroids generated by the adrenals or the tumour itself [23, 24], *AR* mutations rendering AR sensitive to atypical ligands [25] or ligand-independent *AR* splice-variants [26]. Radium-223 [27] was the last drug to complete the current armamentarium for mCRPC treatment.

4 Abiraterone and Enzalutamide in mCRPC

Abiraterone is a CYP17 inhibitor, blocking the synthesis of androgens [28, 29] both extragonadally and in the tumour, and also acting as a potent AR inhibitor through its metabolites [30]. Enzalutamide binds AR at its ligand-binding domain and reduces AR translocation to the nucleus and its interaction with DNA [31]. Both drugs were tested initially in patients previously treated with docetaxel, ensuring patients' prior exposure to the then available standard treatment. Abiraterone combined with prednisone was tested against prednisone plus placebo in the COU-AA-301 trial [13] and enzalutamide against placebo in the AFFIRM trial [32], with 30 % of the patients in each arm receiving steroids at baseline [33]. Abiraterone showed a median OS (mOS) of 15.8 months compared to 11.2 months for placebo plus prednisone (hazard ratio (HR) 0.74; 95 % confidence interval (CI) 0.64–0.86) [34] and enzalutamide a mOS of 18.4 months versus 13.6 months for placebo (HR 0.63; 95 % CI 0.53–0.75). The slight differences in outcome in both the control and experimental arms of these trials may be interpreted as suggesting that one treatment is better than the other. However, this is not supported by the data. Certainly, a negative effect of prednisone on survival could be assumed based on the OS differences of the control arms, in line with the aforementioned preclinical data supporting the hypothesis that steroids can promote PCa growth. Further analysis is warranted to clarify this observation.

After COU-AA-301 and AFFIRM, abiraterone and enzalutamide were tested in chemotherapy-naïve patients. PREVAIL evaluated enzalutamide versus placebo in 1,717 minimally symptomatic patients and showed in a pre-planned interim analysis a significantly improved mOS of 32.4 versus 30.2 months with placebo (HR 0.71; 95 % CI 0.60–0.84) and a much more impressive difference in radiological progression favouring the experimental arm (HR 0.19; 95 % CI 0.15–0.23) [6]. In COU-AA-302, a phase III trial of abiraterone and prednisone versus prednisone alone in 1,088 asymptomatic or minimally symptomatic patients, abiraterone significantly improved mOS to 34.7 from 30.3 months with placebo (HR 0.81; 95 % CI 0.70–0.93) [35]. Both abiraterone and enzalutamide also showed improvement in a number of clinically meaningful secondary endpoints such as: time to initiation of chemotherapy, time to PSA progression, time to pain progression, time to first skeletal-related event, time to decline in performance status or time to decline in quality of life [36, 37]. Crucially, OS in both trials represented the effect of not only abiraterone or enzalutamide alone but also of post-trial treatments. Importantly, many patients initially on placebo were crossed over to active drug [6, 35]. Patients with poor prognostic factors [38] were excluded from both PREVAIL and COU-AA-302, and patients with an albumin of <30 g/L or 35 g/L, respectively, significant pain or an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of more than 1 were not enrolled. In COU-AA-302 visceral disease was also excluded.

Are these treatments also suitable for chemo-naïve patients who have these poor prognostic factors? The data from the post-chemotherapy trials COU-AA-301 and AFFIRM provide some hints. They recruited patients with an ECOG PS of ≤2, visceral disease and significant pain, while patients with an albumin of <30 g/L and a haemoglobin of <9 g/L were excluded. In the subgroup analysis of AFFIRM the HR for death was in favour of enzalutamide in all subgroups although not statistically significant in the small subgroups that had an ECOG PS of 2, or two or more previous chemotherapy regimens [32]. The same holds true for COU-AA-301 and patients with an ECOG PS of 2. This, however, probably relates to insufficient statistical power [34]. Therefore enzalutamide and abiraterone should be considered in chemo-naïve patients with poor PS even more since they are better tolerated than chemotherapy. In both AFFIRM and COU-AA-301, patients with significant pain also derived a clear benefit and had a significantly reduced HR (0.71; 95 % CI 0.54–0.94 and 0.78 95 % CI 0.63–0.96, respectively) [32, 34].

Regarding patients with visceral disease, both in PREVAIL and in AFFIRM the HRs were favourable (HR 0.82; 95 % CI 0.55–1.23 and HR 0.78; 95 % CI 0.56–1.09, respectively) but did not reach statistical significance [6, 32], with the lack of statistical power being the most probable reason for this as only 214 and 278 patients, respectively, had liver or lung disease. In COU-AA-301 trial the beneficial effect of abiraterone in the subset with visceral disease (352 patients out of 1195) reached statistical significance at the first interim analysis [13] (HR 0.70; 95 % CI 0.52–0.94) but not at the final analysis [34], and was confirmed in a separate post hoc analysis [39]. Therefore, use of abiraterone or enzalutamide for the treatment of patients with visceral disease in the pre-chemotherapy setting is supported by the data overall.

5 Enzalutamide and Abiraterone versus Docetaxel as First Option After Castration

Physicians have tended to treat patients with poor prognostic parameters with chemotherapy, considering it as more 'active' based on the fact that these patients were excluded from the pre-chemotherapy trials of enzalutamide and abiraterone. Nevertheless, looking into the docetaxel versus mitoxantrone trial TAX-327, it becomes evident that docetaxel is not an ideal option in this subset either: The survival curves of both arms were overlapping in the first 6 months, indicating that patients with a life expectancy of <6 months did not derive significant benefit. Patients with pain, a Karnofsky performance status ≤80 % or visceral disease, however, still had a favourable HR compared to the mitoxantrone arm [40].

In addition, there is a prevalent concept that docetaxel being a cytotoxic drug can act 'faster' compared to hormonal treatments. Time to palliation of symptoms can be used to compare speed of effect onset. In TAX-327 patients with pain had a median time to pain response of 27 days [41], whereas it was 5.6 months in COU-AA-301 [37]. The true meaning of such post hoc comparisons is uncertain. Further studies are needed to elucidate how to best sequence these drugs.

Emerging data from the CHAARTED trial in patients with non-castrate metastatic prostate cancer (nCMPC) comparing docetaxel together with androgen deprivation therapy (ADT) versus ADT alone and the STAMPEDE trial comparing standard of care versus standard of care plus docetaxel in hormone-sensitive locally advanced and metastatic PCa suggest that patients treated early with docetaxel derive significant survival benefit [42, 43]. A smaller trial, GETUG-AFU 15, however, did not show any OS survival benefit from adding docetaxel to castration in this population [44]. In CHAARTED the mOS for the experimental arm was 57.6 months versus 44 months for the control arm, with a HR of 0.61 (95 % CI 0.47–0.80) and an absolute gain of 13.6 months of mOS. In STAMPEDE the mOS for the ADT plus docetaxel arm was

77 months compared to 67 for the control arm (HR 0.76; 95 % CI 0.63–0.91). The reported benefits in absolute OS were impressive, surpassing any previous experience in mCRPC, but the HRs were not much different from what was previously described for AFFIRM (0.63), PREVAIL (0.70), COU-AA-301 (0.74), COU-AA-302 (0.52) and TAX-327 (0.76). It therefore seems reasonable to suggest that the reason for this big difference in absolute OS is that the improved HR for death is acting over a longer period of time, from castration to even beyond discontinuation of docetaxel, resulting in an increased cumulative absolute survival benefit. It remains to be seen whether the use of abiraterone and/or enzalutamide for hormone-sensitive metastatic disease can generate this degree of benefit.

Extrapolating this hypothesis, it could be assumed that initiating treatment with docetaxel immediately after castration resistance arises and reserving abiraterone or enzalutamide for later use might result in longer OS rather than following the opposite approach. Nevertheless, a retrospective series reporting on 198 patients, compared OS from the time point of first treatment initiation after the development of castration resistance to death in patients who received after castration resistance abiraterone first and then docetaxel versus patients who received first docetaxel and subsequently abiraterone. This study reported a trend in favour of abiraterone being administered first but this did not reach statistical significance [45]. Another retrospective study exploring the same question in 58 patients also could not find a difference [46]. These studies are limited by their retrospective nature, but indicate that the above-described hypothesis might not be correct. A retrospective trial is needed to provide robust evidence.

6 Sequencing Enzalutamide and Abiraterone

It was thought initially that using abiraterone and enzalutamide sequentially might offer benefit as they act at different sites in the AR pathway. Several retrospective studies show only limited activity of enzalutamide post abiraterone with >50 % PSA responses ranging between 12 and 28 % and mPFS of approximately 3–4 months (Table 1). Nevertheless, patients who do experience a PSA response also have improved OS [47]. Abiraterone post enzalutamide was investigated in fewer studies with response rates varying between 10 and 18 % and a short time to progression [71, 72]. In view of this limited activity, sequential treatment should not be considered as a standard option in mCRPC, as delaying another active treatment might prove detrimental, especially in rapidly progressing patients. Recent work has also suggested that patients with CTCs expressing the AR splice variant AR-v7, a ligand-independent splice variant lacking the ligand binding domain, are unlikely to respond to subsequent treatment with abiraterone or enzalutamide; patients with CTCs not expressing AR-v7 had a PSA response rate of 50 % with enzalutamide and 68 % with abiraterone [48]. This finding certainly needs to be verified in larger studies, but use of such predictive biomarkers to identify responders will enable informed sequential treatment with abiraterone or enzalutamide and provide for some patients extra months of life of good quality. Trials regarding sequential use and combinations of abiraterone and enzalutamide are ongoing (NCT02125357, NCT02116582 and NCT02268175), but if ligand-independent AR splice variants are confirmed to be a major factor for resistance to these drugs, we should not anticipate major improvements of OS in unselected patients with sequential or combined strategies.

7 Toxicity and Choice of Drug

Enzalutamide and abiraterone appear largely equivalent in activity but their different toxicity profiles may guide the physician's choice. Abiraterone is infrequently associated with hyperaldosteronism due to an excess of mineralocorticoids. This is usually mitigated by suppressing the ACTH axis by coadministration of corticosteroids or through the use of mineralocorticoid receptor antagonists like eplerenone. Spironolactone should be avoided since this can activate wildtype AR signalling [49]. Patients receiving abiraterone can therefore be exposed to the side effects of protracted corticosteroid use such as osteoporosis, glaucoma, diabetes, insulin tolerance or Cushing's syndrome [50–52]. Enzalutamide is associated with fatigue, headache, diarrhoea, musculoskeletal pain and cognitive impairment, and has been described to cause convulsions as a dose-limiting toxicity in phase I trials and in <1 % of patients in phase III trials [32, 53]. Isolated cases of posterior reversible encephalopathy have also been described in association with enzalutamide [54]. Based on the side-effect profile, patients with uncontrolled hypertension, diabetes or contraindications to steroids should be discouraged from using abiraterone. On the other hand enzalutamide should be avoided in patients with conditions predisposing to seizures or central nervous system disorders.

8 Other Treatment Options: Alpharadin and Sipuleucel-T

Two other treatment options have gained regulatory approval: Radium-223 and Sipuleucel-T. $^{223}RaCl_2$ is a calcium mimetic selectively deposited in bone stroma,

Table 1 Studies evaluating sequential treatment with enzalutamide and abiraterone

	n	Prior docetaxel	Endpoint	Response rate (%)	mPFS
Enzalutamide post abiraterone					
Schrader et al. [64]	35	Yes	>50 % PSA decline	29	NA
Bianchini et al. [65]	39	Yes	≥30 % decline in PSA confirmed after ≥4 weeks	41	2.8 mo (PSA, radiological or clinical)
			≥50 % decline in PSA confirmed after ≥4 weeks	13	
Thomsen et al. [66]	24	Yes	>30 % PSA decline	46	NA
Badrising et al. [67]	61	Yes	≥30 % decline in PSA confirmed after ≥4 weeks	46	12 wks (radiological)
			≥50 % decline in PSA confirmed after ≥4 weeks	21	
Azad et al. [68]	68	Yes	≥50 % decline in PSA confirmed after ≥3 weeks	22	4.6 mo (radiological or clinical)
	47	No	≥50 % decline in PSA confirmed after ≥3 weeks	25	6.6 mo (radiological or clinical)
Suzman et al. [69]	30	No	≥50 % decline in PSA	34	4.7 mo (radiolological or clinical)
Brasso et al. [47]	137	Yes	Unconfirmed >30 % PSA decline	38	3.1 mo (radiological)
			Unconfirmed >50 % PSA decline	18	
Cheng et al. [70]	79	No	≥30 % PSA decline	28	4.0 mo (PSA only)
			≥50 % PSA decline	18	
	165	Yes	≥30 % PSA decline	24	2.8 mo (PSA only)
			≥50 % PSA decline	17	
Schmid et al. [73]	35	Yes	≥50 % PSA decline	10	3.1 mo (radiological)
Abiraterone post enzalutamide					
Noonan et al. [71]	30	Yes	≥30 % PSA decline	10	15.4 wks (PSA, radiological or clinical)
Loriot et al. [72]	38	Yes	≥50 % decline in PSA confirmed after ≥4 weeks	8	2.7 mo (PSA, radiological or clinical)
			≥30 % PSA decline	18	

PSA prostate-specific antigen, *NA* not available, *mo* months

where it emits α particles. These induce DNA double-strand breaks [55, 56] but have a short penetration range (<100 μm; 2–10 cell diameters) and cause minimal effects in the surrounding bone marrow [55, 57]. ALSYMPCA compared six injections of $^{223}RACl_2$ every 4 weeks to placebo in 922 symptomatic patients with mCRPC without visceral metastases, who may not have had prior docetaxel but had at least two bone metastases on bone scan; nodal disease had to be no larger than 3 cm in short axis [58]. The study showed a significantly improved mOS of 14 versus 11.2 months in the placebo arm [27]. Skeletal-related events (SREs) were lower and time to first SRE was significantly delayed in the $^{223}RACl_2$ arm. The toxicity profile of $^{223}RACl_2$ was favourable, with low rates of grade 3 and 4 neutropenia, thrombocytopenia and diarrhoea.

Because ^{223}Ra is acting over a short distance it might have more impact when employed at an earlier stage when the disease is less likely to have extraosseous metastatic sites or to have developed soft tissue emanating from the bone lesions; indeed, trials testing this in asymptomatic patients are already recruiting (NCT02043678), but from the subset analysis of ALSYMPCA the opposite seems to hold: Patients with less than six metastatic sites in the bones seem to derive less benefit [27].

Sipuleucel-T consists of peripheral blood mononuclear cells obtained through leukapheresis from each patient and cultured in vitro for 2–3 days with a fusion protein of prostatic acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor, supposed to be inducing an immune response to PAP-expressing PCa cells once the cells

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