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ORIGINAL ARTICLE

Is there an anti-androgen withdrawal syndrome for enzalutamide?

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Abstract
Background The anti-androgen withdrawal syndrome (AAWS) can be seen in one-third of patients after discontinuation of first-generation non-steroidal anti-androgen therapy. With the introduction of new agents for anti-androgen therapy as well as alternate mechanisms of action, new therapeutic options before and after docetaxel chemotherapy have arisen (Ohlmann et al. in World J Urol 30(4):495–503, 2012). The question regarding the occurrence of an enzalutamide withdrawal syndrome (EWS) has not been evaluated yet. In this study, we assess prostate-specific antigen (PSA) response after discontinuation of enzalutamide.
Methods In total 31 patients with metastatic castration-resistant prostate cancer (mCRPC) underwent an enzalutamide withdrawal and were evaluated. Data were gathered from 6 centres in Germany. Patients with continuous oral administration of enzalutamide with rising serum PSA levels were evaluated, starting from enzalutamide withdrawal until subsequent therapy was initiated, follow-up ended or death of the patient occurred. Statistical evaluation was performed applying one-sided binomial testing using R-statistical software, version 3.0.1.
Results Mean withdrawal follow-up was 6.5 weeks (range 1–26.1 weeks). None of the 31 patients showed a PSA decline. Mean relative PSA rise over all patients was 73.9 % (range 0.5–440.7 %) with a median of 44.9 %.
Conclusions If existent, an AAWS is at least very rare for enzalutamide in patients with mCRPC after taxane-based chemotherapy and does not play a clinical role in this setting. This may be attributed to the different pharmacodynamics of enzalutamide. Longer duration of therapy or a longer withdrawal interval may reveal a rare EWS in the future.

Keywords Anti-androgen withdrawal syndrome · Enzalutamide · mCRPC · Prostate cancer

For the German Working Group on Castration Resistant Prostate Cancer (GWG-CRPC).

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Introduction

A confirmed prostate-specific antigen (PSA) decrease after complete cessation of anti-androgen (AA) medication was first described for flutamide. Without clear evidence for an improved overall survival, the effect was deemed usable as therapeutic option in patients with rising PSA under AA therapy [1, 2].

For patients with metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy, overall survival (OS) is limited, ranging from about 6 month to 2 years, mainly depending on the site and extend of metastases [3]. New substances, such as enzalutamide, are now readily available outside of clinical trials for the treatment of mCRPC in the post-docetaxel setting [4]. Other therapeutic options for this indication are cabazitaxel or the androgen biosysthesis-inhibitor abiraterone acetate [5]. The potential for enzalutamide (and also abiraterone acetate) with regard to an AAWS has been subjected to academic discussion [6–8], but it has not been empirically evaluated yet.

Enzalutamide, as a new non-steroidal AA, may hypothetically show a PSA decline after withdrawal. An explanation for the AAWS as well as a potential enzalutamide withdrawal syndrome (EWS) would be suspected to be associated with genetic alterations in the androgen receptor (AR), similar to its first-generation predecessors [9]. The pharmacodynamics of enzalutamide, however, and the clinical setting differ significantly from previous AA therapies [10], and thus, a clinical significant withdrawal effect still lacks sufficient evidence-based proof. The data on patients with discontinuation of enzalutamide are sparse. We therefore combined our data in a multi-centre study in order to address this interesting question regarding the very existence of an EWS for the first time.

Patients and methods

We systematically reviewed patient's records with mCRPC for cases of PSA progression under AA therapy with enzalutamide. Data from 6 urological centres in Germany (Aachen, Frankfurt, Hannover, Homburg, Munich, Tuebingen) were available for retrospective analysis. Ethics board approval for retrospective data review and analysis of the German Working Group on Castration Resistant Prostate Cancer (GWG-CRPC) database was obtained. All patients having received oral treatment with enzalutamide in combination with androgen deprivation therapy (ADT) during the time period 2012–2013 were reviewed. Out of 52 patients with enzalutamide therapy, a total of 31 patients with histologically confirmed cancer of the prostate were evaluable for an EWS. Patients were excluded if still under active therapy with enzalutamide or if an alternative treatment was initiated within 1 week of cessation of enzalutamide. Data collection included primary therapy, Gleason score, T-stage, age, initial local therapy, prior androgen deprivation and AA therapy, chemotherapy, duration of prior enzalutamide administration, baseline serum PSA level at the beginning of enzalutamide withdrawal and PSA level at the end of enzalutamide withdrawal. Treatment failure of complete androgen blockade (CAB) was defined as PSA raise $\geq$25 % from baseline PSA or three consecutive rises under CAB [11]. Patients had heterogeneous cytotoxic, AA and androgen deprivation treatment prior to initiation of enzalutamide. In all, 20 and 3 patients had previous therapy with bicalutamide and flutamide. A total of 23 patients had been subjected to abiraterone acetate. Further hormonal therapy prior to enzalutamide included ketoconazole and estramustine phosphate. Cytotoxic therapy with docetaxel or cabazitaxel was documented in 96.8 and 19.4 % of cases. Combined therapy with docetaxel plus custirsen was reported in 2 (6.5 %), and salvage chemotherapy with docetaxel plus carboplatin [12] was administered in 4 (12.9 %) of patients. Prior therapy and patient characteristics are depicted in Table 1. Luteinising-hormone-releasing hormone (LHRH) therapy was continued in all patients during therapy with enzalutamide and during enzalutamide withdrawal. The one-sided binomial test was applied to calculate the probability for our results for varying assumptions of an EWS. An EWS was defined as a 50 % decrease in baseline PSA level. A one-sided t test was applied to assess PSA change according to length of enzalutamide withdrawal. All tests were interpreted given $\alpha = 0.05$. Statistical evaluation was performed using R-statistical software, version 3.0.1.

Results

In total, 31 patients were evaluable for the study. Median initial Gleason score was 8 (range 6–10). Mean PSA level at initiation of enzalutamide withdrawal was 478.4 ng/mL (range 11.8–2645 ng/mL). Mean duration of withdrawal was 45.5 days (range 7–183 days). Mean PSA level at the end of enzalutamide withdrawal was 769.5 ng/mL (range 15.6–4,440 ng/mL). None of the 31 patients had a PSA decline. The mean relative PSA rise over all patients was 73.9 % (range 0.5–440.7 %) with a median of 44.9 %. PSA change was higher for patients after longer enzalutamide withdrawal. When dichotomized at the median withdrawal interval, relative PSA mean above and below the median was (108.4 and 37.1 %, respectively, ($p = 0.0224$)). All PSA measurements with corresponding withdrawal duration are depicted in Fig. 1. Assuming the existence of an AAWS for enzalutamide, the probability of missing an EWS in 31 patients was calculated: In a one-sided binomial test, the probability for obtaining 31 negative results with a true occurrence rate for an EWS of 10, 20 and 30 % were $p = 0.0382$, $p = 0.001$ and $p < 0.0001$, respectively.

Table 1 Patient characteristics

Patient characteristics	*n* (days)	Range
Patients	31	100 %
Age (median, range)	70	48–86
TNM stage		
T-stage 1c	1	3.2 %
T-stage 2a	1	3.2 %
T-stage 2b	0	0 %
T-stage 2c	4	12.9 %
T-stage 3a	4	12.9 %
T-stage 3b	9	29 %
T-stage 4	4	12.9 %
T-stage NA	8	25.8 %
Gleason score		
≤6	2	6.5 %
=7	6	19.4 %
≥8	22	71 %
NA	1	3.2 %
Primary therapy		
No primary local therapy	10	32.3 %
Radical prostatectomy	15	48.4 %
External beam radiation	5	16.1 %
Brachytherapy	1	3.2 %
Hormonal therapy		
Bicalutamide	20	64.5 %
Flutamide	3	9.7 %
Orchiectomy	1	3.2 %
LHRH Analogue	30	96.8 %
Orteronel	2	6.5 %
Ketoconazole	6	19.4 %
Estramustine	3	9.7 %
Abiraterone acetate	23	74.2 %
Chemotherapy		
Docetaxel	30	96.8 %
Docetaxel + Carboplatin	4	12.9 %
Cabazitaxel	6	19.4 %
Docetaxel + Custirsen	2	6.5 %
Enzalutamide therapy		
Duration (mean [d], range)	115.1	22–294
Withdrawal (mean [d], range)	45.5	7–294

Pathology and previous treatment prior to enzalutamide therapy (NA = pathological data not available)

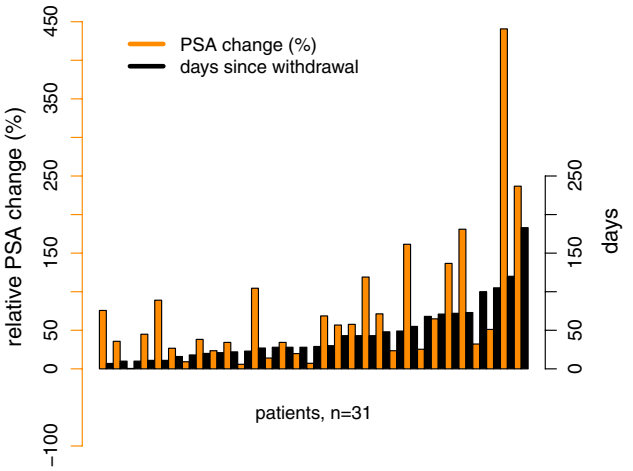

Fig. 1 Relative PSA response to withdrawal of enzalutamide for 31 patients. All patients showed a rise in serum PSA after discontinuation of enzalutamide (*orange*). The black bars indicate the corresponding days after discontinuation of enzalutamide

Discussion

The AAWS has been shown for a variety of substances including estradiol, flutamide, bicalutamide, nilutamide and even hydrocortisone [1, 9, 13–19]. There is growing evidence that prostate cancer cells subjected to treatment with second-generation AAs, invariably acquire resistance to the AA in a similar way. Several AR activating point mutations have been described so far. For first-generation AA mutations, W741C, T877S and H874Y were identified for bicalutamide, flutamide and nilutamide, respectively [20–22]. Furthermore, for estradiol and cyproterone acetate, point mutation E872Q was identified as AR activating alteration [23]. It is therefore only reasonable to assume a similar effect for the AA enzalutamide. However, to date there is no valid clinical proof for the existence of an EWS. Recent research identified genetic alterations of the AR that are similar to those of the previously mentioned first-generation AAs. The missense mutation F876L in the ligand binding domain of the AR in cell lines of CRPC confers agonist activity in vitro and in vivo. Interestingly, the F876L mutant is detectable in plasma DNA from patients treated with ARN-509 [24], a novel AA, in the treatment of castration-resistant prostate cancer similar to enzalutamide [25]. Functional studies by Korpal et al. [26] confirmed that F876L confers an AR switch that drives phenotypic resistance. These preclinical findings together with data from first-generation AA would suggest a possible withdrawal effect for enzalutamide on a similar molecular basis.

On the other hand, enzalutamide was introduced not to act solely on the AR. The emphasize during the introduction of the new substance, formally known as MDV3100, lays on its multiple molecular modes of blocking the AR signalling pathway: enzalutamide has not only a higher affinity to the AR compared to first-generation AA, it also inhibits the trans-location of the homodimerized androgen receptor ligand to the cell nucleus and blocks the activation of androgen-responsive genes [10]. It is therefore not clear whether an activating point mutation of the AR alone can result in an EWS.

In order to adequately asses the probability of an EWS, we have to and can only put our data into perspective with clinical data gathered from AAs other than enzalutamide: Schellhammer et al. presented the first prospective trial on AAWS with two non-steroidal AAs. All patients were on continuous treatment with the LHRH agonist goserelin- or leuprolide acetate for androgen deprivation plus either flutamide or bicalutamide for at least 140 days prior to withdrawal of the AA. During the trial, 50 % (4 out of 8 for flutamide) and 29 % (4 out of 14 for bicalutamide) showed an AAWS with a PSA decline of ≥50 % and a response duration between 9 and 37 month. Another study, the Southwest Oncology Group Trial (SWOG 9426), included 210 patients. All patients were under combined hormone ablative therapy with either orchiectomy or a LHRH agonist together with an AA on a regular basis. Progression-free survival (PFS) was prolonged to over 1 year due to AAWS in 19 % of the patients. The AAs used in the SWOG trial were non-steroidal AAs exclusively. Response rates for flutamide, bicalutamide and nilutamide were 24, 13 and 25 %, respectively. The overall response rate (defined by a PSA decline of ≤50 % after discontinuation of AA therapy) in this study was 21 %, with a median freedom from biochemical progression of 3 month [14]. A selection of previous studies on AAWS is depicted in Table 2. Experience from these previous works shows response rates of >20 % in general, bearing in mind that previous studies determined a confirmed PSA response differently, varying between "any response" and "response >50 %" of baseline PSA. We therefore carefully chose an assumed occurence rate of at least 20 % for "any decline" in PSA after withdrawal of enzalutamide as basis for statistical comparison.

Not only occurrence rates of the AAWS for various AAs vary, but also time to AAWS after cessation of therapy. Discontinuation of flutamide and bicalutamide as described by Schellhammer et al. resulted in an AAWS with very different kinetics between the two substances. While PSA almost immediately dropped within 4–8 days in patients previously treated with flutamide, a decline in PSA levels after the withdrawal of bicalutamide was not seen before 4–8 weeks. The authors attributed these changes to the different half-lives of the two AAs [17]. When comparing our data with the expected time frame of flutamide, all of our cohort would be expected to hypothetically be able to show a PSA response in the sense of an EWS. When looking at the subset of patients exceeding the 4–8 weeks time frame of bicalutamide, we were still able to identify 11 patients exceeding 4 weeks and 8 patients exceeding 8 weeks withdrawal. The odds for missing an existing EWS under these restrictions are still very low: Given a theoretical probability of 20 % for an EWS with data from bicalutamide and flutamide as point of reference and applying a one-sided binomial tests, the type I error with all patients included would be as low as $p < 0.001$ (0.95 CI 0–0.0921). Our p value would increase to $p = 0.0144$ (0.95 CI 0–0.1459) if we excluded patients that fall short of the 4 week time frame. However, taking into account the metabolism of enzalutamide, the expected time frame for an expected withdrawal syndrome might be even longer: Enzalutamide is hepatically metabolized to the active metabolite *N*-desmethyl enzalutamide by the enzymes CYP2C8 and CYP3A4. Interestingly the activity of *N*-desmethyl enzalutamide is similar to enzalutamide itself. While the mean half-life (t) of enzalutamide after a single oral dose is 5.8 days, the half-life of its equally active metabolite is approximately another 7.8–8.6 days. Bicalutamide on the other hand undergoes metabolism by means of glucuronidation and oxidation to an inactive metabolite [27, 28]. An EWS may therefore be expected after a considerably longer withdrawal than 8 weeks. These differences in metabolism add to the difficulties in comparing our data with first-generation AA.

Table 2 Selection of previous studies on anti-androgen withdrawal [1, 13–15, 17, 31, 35, 36]

Study	Anti-androgen	Patients	AAWS [%]
Scher and Kelly [1]	Flutamide	35	29
Dupont et al. [15]	Flutamide	40	75
Small et al. [18]	Flutamide	82	15
Figg et al. [13]	Flutamide	33	21
Herrada et al. [35]	Flutamide	39	28
Schellhammer et al. [17]	Flutamide	8	50
	Bicalutamide	14	29
Sartor et al. [14]	Flutamide	210*	21*
	Bicalutamide		
	Nilutamide		
Matsumoto et al. [31]	Flutamide	121*	28.9*
	Bicalutamide		

Patient numbers under observation and response rates for various AAs show a percentage of confirmed PSA almost exclusively above 20 % (AAWS = anti-androgen withdrawal syndrome, * combined patients and response rates)

Our observations take place at the late stage of mCRPC. Therefore, the prior administration of enzalutamide does not reach as long treatment durations as can be seen for AA therapy before chemotherapy: our mean treatment duration prior to withdrawal of enzalutamide was 115.1 days (range 22–294 days). The model of prostate cancer progression is known to be a function of time. This means that continuous administration of the AA results in the selection of prostate cancer cell sub-populations that are able to survive under androgen ablative therapy, thus leading to treatment failure but also to cancer cell lines possibly susceptible to an AAWS [29]. Even though an AAWS can be seen even after short administration of the AA, several studies

confirmed the role of AA treatment duration as predictor of higher response rates: for patients treated with flutamide for example, it had been shown that the duration of the AA usage was linked to the development of AR mutations in prostate cancer [30]. The mean duration of AA therapy prior to withdrawal was 25 month in the SWOG 9426 trial. The odds ratio was 1.00 for patients ≤9 month AA treatment and increased up to an odds ratio of 5.51 for patients with prior AA therapy of more than 32 month [14]. In a recent retrospective study of 121 patients treated with either flutamide or bicalutamide, the rate of AAWS was only 13.6 % for patients with previous AA therapy of less than 18 month, while patients with longer AA therapy responded with an AAWS in 43.5 % of cases [31]. In the series of Small et al., longer duration of AA therapy was identified as predictor of an AAWS. However, two patients with AAWS had a previous AA therapy with flutamide of ≤3 month. These data clearly identify length of AA therapy as important for an AAWS. According to the above-mentioned data, our mean duration of prior enzalutamide therapy of 115.1 days does not exclude an EWS, and it may, however, limit its occurrence.

Another factor that might hinder EWS in late-stage prostate cancer is the development of tumour growth independent of the AR. It has been shown earlier that steroid hormone receptors, including the AR, can be activated without ligand binding by means of so-called outlaw or bypass pathways. An example of ligand-independent activation of the AR signalling pathway is the over expression of HER-2/neu tyrosine kinase that can activate prostate cancer growth in the absence of androgens and is suspected to promote AR signalling independent of the AR ligand binding domain [32]. Other examples of AR-independent cancer growth in prostate cancer are the Akt signalling cascade [33], or the expression of Bcl-2 a critical anti-apoptotic protein in prostate cancer [34]. Our patient cohort comprises a subset of patients that has already experienced chemotherapy as well as varying modes of androgen deprivation. Withdrawal of the AA will unlikely result in an AAWS if progression is not only castration resistant but increasingly independent of the AR.

These molecular considerations together with the previously mentioned aspects of drug kinetics and treatment duration should be taken into account when assessing EWS in patients with late-stage prostate cancer, and they conclude the limitations of this observational study.

Conclusion

The possibility of a rare EWS cannot be rejected for reasons imminent to patient cohort and sequence of therapy in this study. Our first data on the subject support the conclusion that, if existent, an EWS probably occurs in less than 10 % of cases and does therefore not play a clinical role in the treatment of patients with mCRPC in the post-chemotherapy setting. It will be interesting to see whether enzalutamide will change its place in the treatment algorithm of prostate cancer and whether administration at an earlier stage opens the possibility of an enzalutamide withdrawal as therapeutic option in the future.

Conflict of interest All authors are involved in the treatment of prostate cancer with the substance enzalutamide and other hormonal and non-hormonal substances. All authors were directly or indirectly involved in the administration of enzalutamide in the AFFIRM Trial and/or the MDV3100 expanded access program. The manuscript was not motivated nor funded by any external sources/companies, and the authors have no conflicts of interest to declare.

Ethical standard Ethics board approval was obtained for this retrospective observational study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Data were anonymized prior to analysis or protocoled data transfer. No additional data were created nor used aside from retrospective evaluation of our database.

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