Original Study

Incidence and Characterization of Antiandrogen Withdrawal Syndrome After Discontinuation of Treatment With Enzalutamide in Castration-resistant Prostate Cancer

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Abstract

Antiandrogen withdrawal syndrome (AAWS) is a well-reported phenomenon with first-generation antiandrogens. AAWS is a less well-defined phenomenon with the antiandrogen enzalutamide. The present retrospective evaluation of men with progression during enzalutamide therapy failed to demonstrate a clinically significant incidence of enzalutamide withdrawal. These findings argue against the need to account for AAWS with enzalutamide in clinical trial designs.

Background: Antiandrogen withdrawal syndrome (AAWS), manifested as a prostate-specific antigen (PSA) decline after discontinuation of a first-generation antiandrogen has been well characterized. The objective of the present study was to assess the incidence of AAWS with enzalutamide in men with metastatic castration-resistant prostate cancer. **Patients and Methods:** Patients from a single-institution cohort with metastatic castration-resistant prostate cancer who had discontinued enzalutamide after PSA or radiographic progression were included. AAWS after enzalutamide was defined as any PSA decline after discontinuation of enzalutamide. The baseline patient, disease, and treatment characteristics were compared between patients with and without AAWS after enzalutamide. Statistical analysis of the baseline characteristics included descriptive statistics using the Wilcoxon rank sum test and the Fisher exact test. The median duration of enzalutamide therapy was compared using the log-rank test, and the progression-free survival of the patients with AAWS was evaluated using the Kaplan-Meier method. **Results:** Of 47 eligible patients, 5 experienced AAWS after enzalutamide discontinuation. The PSA response in these 5 patients was 84%, 32%, 17%, 15%, and 15%. The median AAWS response time until subsequent PSA progression was 3.3 months. No patient, disease, or treatment characteristics differed among the patients with and without AAWS after enzalutamide discontinuation. **Conclusion:** To the best of our knowledge, this is the largest reported cohort documenting the incidence and characterization of AAWS after enzalutamide to date. The AAWS frequency after enzalutamide was low and of short duration. No patient- or disease-related characteristics were associated with AAWS with enzalutamide. The occurrence of AAWS after enzalutamide was not clinically meaningful. Thus, accounting for this phenomenon in clinical practice or trial designs could be unnecessary.

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Introduction

Antiandrogen withdrawal syndrome (AAWS) in prostate cancer was first described by Scher and Kelly[1] in 1993 with the nonsteroidal antiandrogen (AA) flutamide. Shortly thereafter, this phenomenon was demonstrated in other nonsteroidal AAs, including bicalutamide and nilutamide.[2,3] An estimated 11% to

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33% of patients receiving AA therapy will experience AAWS, with a median duration of response of 3 months.[4] In ≤ 19% of patients experiencing AAWS, this response will exceed 12 months.[5,6] The most predictive clinical parameter associated with AAWS has been the duration of AA therapy.[5] Despite a demonstrable improvement in progression-free survival, no overall survival benefit associated with AAWS has been documented.[7] The occurrence of AAWS has the potential to confound the interpretation of objective responses with subsequent therapies, because prostate-specific antigen (PSA) responses can manifest weeks after discontinuation of medication.[1] Thus, most trials of men with castration-resistant prostate cancer (CRPC) have mandated a washout period for the first-generation AAs. One hypothesized explanation for the occurrence of AAWS is the development of mutations in the androgen receptor (AR) that confer agonist activity to the once antagonist AA.[8] Subsequent discontinuation of the AR antagonist disrupts the ongoing paradoxical agonistic activity, resulting in PSA and, occasionally, objective responses.[9]

Enzalutamide is a second-generation AA approved for the treatment of men with metastatic CRPC (mCRPC). It has 4 times the potency of first-generation AAs for the AR.[8] The incidence of AAWS has not yet been well characterized or established in the context of enzalutamide. Despite this, current clinical trials have continued to mandate a washout period for enzalutamide, delaying subsequent therapies for these men with progressive CRPC. In the present retrospective analysis, we investigated the incidence and clinical characteristics of AAWS in the context of enzalutamide in men with mCRPC.

Patients and Methods

Men with mCRPC treated at a National Cancer Institute–designated comprehensive cancer center from October 2013 to October 2016 with enzalutamide and with subsequent progression were included in the present analysis. The eligibility criteria included biopsy-proven prostatic adenocarcinoma, metastatic disease found on imaging studies, and previous PSA progression, in accordance with the Prostate Cancer Working Group 2 criteria,[10] during continuous androgen deprivation therapy with a documented castrate level of serum testosterone at progression. Previous treatment with chemotherapy was permitted.

AAWS was defined as any decrement in the PSA level after discontinuation of enzalutamide. The baseline patient, disease, and treatment characteristics were collected (Table 1).

Statistical analysis of the baseline characteristics included descriptive statistics using the Wilcoxon rank sum test and the Fisher exact test. The median duration of enzalutamide therapy was compared using the log-rank test, and progression-free survival of those experiencing AAWS was evaluated using the Kaplan-Meier method (Figure 1).

Results

A total of 47 patients met the inclusion criteria (median age, 59 years; range, 46-95 years). The median Gleason score at diagnosis was 8 (range, 6-10), and the median PSA and alkaline phosphatase level before starting enzalutamide was 101.3 ng/mL (range, 0.1-973.4 ng/mL) and 251 U/L (range, 35-1231 U/L), respectively. Of the 47 patients, only 18 (~38%) had previous exposure to docetaxel chemotherapy and no other treatment in the CRPC setting. Only 5 of the 47 eligible patients (~11%) experienced any degree of AAWS after discontinuation of enzalutamide, and only 1 patient had a decline in the PSA level of ≥ 50%. For the 5 patients with AAWS, the PSA decline was 84%, 32%, 17%, 15%, and 15%. The median AAWS response duration was 3.3 months (specifically, 2.76, 1.35, 3.29, 3.65, and 4.47 months). The baseline disease and patient characteristics, duration of enzalutamide therapy, and use of previous chemotherapy were similar in those with and without AAWS after treatment with enzalutamide (Table 1).

Table 1 Patient, Disease, and Treatment Characteristics

Characteristic	AAWS		*P* Value
	No (n = 42)	Yes (n = 5)	
Age (y)	69	63	.48[a]
Gleason score	7	8	.25[a]
PSA before ENZA (ng/mL)	59.4	23.3	.50[a]
ALPH before ENZA (U/L)	122	103	.43[a]
PFS during ENZA (mo)	NA	8.4	NA
Previous chemotherapy	16/42 (38)	2/5 (40)	1.00[b]
RT with ENZA (mo)	8.4	6.0	.87[c]
AAWS duration (mo)	NA	3.3	NA

Data presented as median or n (%).
Abbreviations: AAWS = antiandrogen withdrawal syndrome; ALPH = alkaline phosphatase; ENZA = enzalutamide; NA = not applicable; PFS = progression-free survival; PSA = prostate-specific antigen; RT = response time.
[a]Wilcoxon rank sum test.
[b]Fisher's exact test.
[c]Log-rank test.

Discussion

In general, an AA withdrawal phenomenon was seen infrequently with enzalutamide. Despite using a liberal definition of any PSA response, we identified only 11% of patients in our cohort with any degree of AAWS. Also, only 1 patient (~2%) would have met the traditional definition of AAWS (≥50% decline in PSA). In contrast, AAWS with a PSA decline of ≥ 50% with nonsteroidal AAs has been reported in ≤ 30% of patients.[7]

Enzalutamide was specifically designed using structural activity relationship methods to provide AR antagonism without concurrent potential for AR agonism.[11-13] However, a subsequent investigation into the mechanisms of drug resistance to second-generation AAs by Joseph et al[14] in 2013 demonstrated the F876L missense mutation in the ligand-binding domain of the AR confers agonist activity of enzalutamide in both in vitro and in vivo models of CRPC. Unlike first-generation AAs, this agonist activity was independent of intracellular AR concentrations. Another group, studying reporter-based mutagenesis screens to identify AR mutations that might confer resistance to enzalutamide, also demonstrated that the AR F876L mutation resulted in subsequent agonist activity to enzalutamide.[15] As expected, the introduction of AR F876L in enzalutamide-sensitive cells led to inhibition of enzalutamide activity. Although compelling, somatic events in the AR leading to agonism in the presence of enzalutamide, such as F876L, are rare events.[14,16,17] It is possible that the patients experiencing AAWS in our study expressed F876L; however, no molecular testing was