Association of Dose Reduction of Abiraterone Acetate or Enzalutamide and PSA Progression in Veterans with Metastatic Castration Resistant Prostate Cancer

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Introduction and Objectives

- The androgen biosynthesis inhibitor abiraterone acetate (AA; indicated in combination with prednisone [AAP]), and the antiandrogen enzalutamide (ENZ) have been shown to reduce prostate-specific antigen (PSA), delay time to PSA progression, and prolong overall survival in men with metastatic castration-resistant prostate cancer (mCRPC)[1-4]
- Dose reduction or treatment interruption may be necessary in case of side effects, toxicity, or drug-drug interactions,[5,6] which may, in turn, lead to a rise in PSA levels
- This study aims to evaluate the association between the dose reduction of oral treatments used in the clinical management of mCRPC and PSA progression

Methods

Data Source

- Veterans Health Administration electronic health record database (VHA database) from April 2010 to December 2016

Study Design

- A retrospective longitudinal study design was used
- The relative dose intensity (RDI), calculated as the ratio of the dispensed dose to the standard dose recommended in the prescribing information, was used to evaluate dose reduction during the observation period and was updated monthly (**Figure 1**)
    - A dose reduction was defined as an RDI <80% post-index

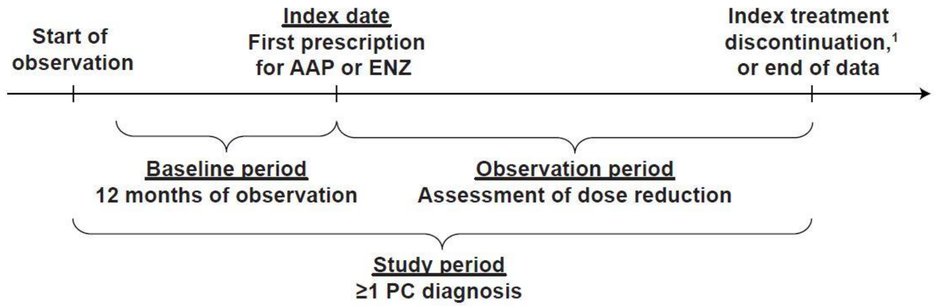
Study Outcome

- The primary outcome was time to PSA progression
    - PSA progression was defined as the first rise in PSA level of at least 2 ng/mL and at least 25% above the nadir. The nadir was defined as the lowest PSA measurement observed during the observation period (i.e., at least 0.2 ng/mL)

Statistical Analyses

- A multivariable Cox proportional hazards regression model was used to evaluate the association between PSA progression and RDI <80%, with the latter treated as a time-varying covariate and adjusting for baseline covariates
- The association was reported using adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) and p-values

Figure 1. Study Design Scheme



Note:
[1]Treatment discontinuation was defined as a gap in days of supply of >90 days

Table 1. Sample Selection

		Count of patients	
Inclusion criteria		**N**	**(%)**
Step 1	Male gender[1]	4,543,999	
Step 2	At least 1 prescription for AA or ENZ	10,164	(0.2%)
Step 2a	Concomitant use of prednisone[2] at the date of treatment initiation for patients initiated on AA	9,358	(92.1%)
Step 3	At least 12 months of observation prior to the index date (baseline period)	8,955	(95.7%)
Step 4	At least 18 years of age at of the date of treatment initiation	8,955	(100.0%)
Step 5	At least 1 diagnosis for prostate cancer (ICD-9-CM: 185.xx or ICD-10-CM: C61) during the study period	8,931	(99.7%)
Step 6	At least 2 PSA measurements within the first 3 months post-index	6,069	(68.0%)

Notes:
[1]There were 194,274 male patients with PC in the database.
[2]Concomitant use of prednisone was defined as a dispensing of prednisone on or within 7 days after AA initiation or any overlap of prednisone use with AA initiation.

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Results

Baseline Characteristics

- The mean±SD duration of the observation period was 12.3±8.5 months
- A majority (65.0%) of patients received the index medication between 2013 and 2015

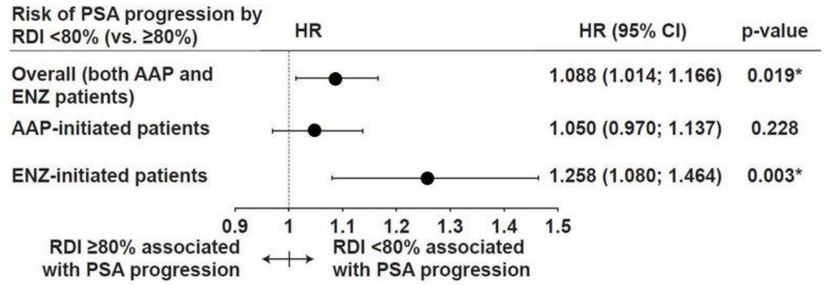
Association Between Dose Reduction and PSA Progression

- During follow-up, PSA progression occurred in 62.7% of patients
- Overall, at least one occurrence of RDI <80% was present in 64.4%of patients, including 63.6% and 67.2% of AAP- and ENZ-initiated patients, respectively
- The Cox model showed that an RDI <80% was associated with an 8.8% higher likelihood of having PSA progression (HR [95%CI]=1.088 [1.014; 1.166], p=0.019; **Figure 2**)
    - Using a threshold of 85% for RDI, similar and directionally identical results were also found, indicating the stability of this trend

Limitations

- Results may be impacted by confounding due to unmeasured factors; in particular, clinically confirmed data on disease stage and metastasis were limited
- Reasons for dose reduction were not available in this study. It was not possible to ascertain whether observed outcomes were clinically intended to be dose reduction as opposed to treatment interruption or discontinuation

Figure 2. Association between PSA progression and the occurrence of at least one RDI <80%



*Indicates p<0.05.

Note:

[1]Cox proportional hazards model included PSA progression as the dependent variable and RDI <80% as a time-varying independent variable, along with index year, age, race, BMI category, region, QCI, baseline PSA, baseline testosterone, baseline concomitant therapies

Table 1. Patient Demographic and Clinical Characteristics

	All Patients N=6,069	AAP Patients N=4,694	ENZ Patients N=1,375
Age (years), mean ± SD [median]	76.4 ± 9.5 [77.2]	74.4 ± 9.2 [73.9]	75.4 ± 9.1 [74.5]
Race, N (%)			
White	4,218 (69.5)	3,279 (69.9)	939 (68.3)
Black	1,533 (25.3)	1,165 (24.8)	368 (26.8)
Asian	26 (0.4)	23 (0.5)	3 (0.2)
Native American	35 (0.6)	25 (0.5)	10 (0.7)
Other	30 (0.5)	24 (0.5)	6 (0.4)
Unknown	227 (3.7)	178 (3.8)	49 (3.6)
Region, N (%)			
Northeast	822 (13.5)	635 (13.5)	187 (13.6)
Midwest	1,506 (24.8))	1,195 (25.5)	311 (22.6)
South	2,151 (35.4)	1,626 (34.6)	525 (38.2)
West	1,188 (19.6)	940 (20.0)	248 (18.0)
Other	79 (1.3)	60 (1.3)	19 (1.4)
Unknown	323 (5.3)	238 (5.1)	85 (6.2)
Body Mass Index (BMI)[1] (kg/m^2), mean ± SD [median]	29.1 ± 5.8 [28.4]	29.0 ± 5.7 [28.3]	29.4 ± 6.2 [28.7]
<30 kg/m2, N (%)	3,091 (50.9)	2,428 (51.7)	663 (48.2)
30 to <35 kg/m2, N (%)	1,208 (19.9)	924 (19.7)	284 (20.7)
≥35 kg/m2, N (%)	677 (11.2)	499 (10.6)	178 (13.0)
Unknown	1,093 (18.0)	843 (18.0)	250 (18.2)
Quan-Charlson Comorbidity Index[2,3] mean ± SD [median]	5.6 ± 2.5 [6.0]	5.5 ± 2.5 [6.0]	5.7 ± 2.7 [6.0]

Notes:

[1]Among patients with a BMI measurement. [2]Among patients with baseline Quan-Charlson comorbidities. [3]Quan H, Sundararajan V, Halfon P, Fong A, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130–1139.

Conclusion

- In this study of Veteran men with mCRPC treated with AAP or ENZ, dose reduction occurred in a majority of patients and was associated with a statistically significant increased risk of PSA progression
    - For patients treated with ENZ, this increased risk of PSA progression remained statistically significant

References

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