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Age Adjusted Charlson Comorbidity Index Strongly Influences Survival, Irrespective of Performance Status and Age, in Patients With Advanced Prostatic Cancer Treated With Enzalutamide

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Abstract. *Background/Aim: Enzalutamide is prescribed for advanced prostatic cancer patients, regardless of physical comorbidity. We hypothesized that comorbidity negatively affects survival regardless of age, performance status and prostate-specific antigen (PSA) response. Patients and Methods: All patients (n=106) treated at the ADRZ Medical Center with enzalutamide in the period 2015-2018 and who had undergone at least one PSA response evaluation were included in a multivariate analysis to test which variables independently affected Time to PSA progression (TPSAP) and/or overall survival (OS). Results: A poorer performance status appeared to relate to a two times increased risk of dying (HR=2.032, 95%CI=1.078-3.830). An older age did not appear to influence OS, whereas an ACCI of more than 9 points appeared to relate to a more than three times increased risk of dying (HR=3.538, 95%CI=1.466-8.538). Conclusion: Survival appeared to be strongly affected by comorbidity, irrespective of age and performance status in patients treated with enzalutamide.*

Patients with castration-resistant advanced prostatic cancer treated with the androgen receptor (AR) targeted agent enzalutamide have shown clinical benefit in both the pre- and post-docetaxel treatment setting (1, 2). The efficacy of enzalutamide depends on the integrity of the AR-binding ligand domain within the tumor cells. Testing of circulating tumor cells (messenger RNA) or cell-free DNA for AR-splice variants with poorer or absent binding capacity could be a convenient way for selecting patients for AR-targeted therapy, including treatment with enzalutamide (3-6). However, the failure to obtain test results in a considerable part of patients still hampers the introduction of such testing into daily clinical practice. Currently, the percentage PSA decline in the first months of AR-targeted therapy appears to be a more practical biomarker of clinical benefit (7-12).

Advanced prostatic cancer, a disease of the older male, is often accompanied by benign comorbidity, which usually does not preclude enzalutamide treatment due to its limited toxicity profile. Subgroup analyses of the PREVAIL study (enzalutamide pre-docetaxel) and the AFFIRM study have shown that elderly patients (75 years or older) showed equal benefit from enzalutamide treatment compared to their younger counterparts (13, 14). We hypothesized, that comorbidity influences survival in this patient group, irrespective of age, performance status and treatment response. The Charlson Comorbidity Index is a prognostic classification that was initially developed for patients who may have a number of comorbid conditions, and this index has been validated in many clinical settings (15-19). During its validation, age was found to be a significant contributing factor to overall survival, and this was subsequently incorporated into the Charlson comorbidity score to create a single index that accounted for both age and any medical comorbidities present; this became the Age-adjusted Charlson Comorbidity Index (ACCI).

Patients and Methods

All patients who had been treated with enzalutamide in the period 2015-2018 and who had undergone at least one PSA response evaluation were included in the analysis. As our institution has a 100% preference for treatment with enzalutamide (abiraterone is not prescribed) the dataset could be regarded as an unselected population.

A Cox regression analysis was performed in order to test whether either of the following variables is independently related to the time to PSA progression (TPSAP) and/or overall survival (OS): Gleason Score (6, 7 *vs.* 8-10), temporal mode of metastasis (synchronous *vs.* metachronous), location of metastases (bone only *vs.* miscellaneous), age (≤74 years *vs.* >74 years), performance status (0-1 *vs.* 2), ACCI

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Table I. *Characteristics of 106 consecutive patients treated with enzalutamide in the ADRZ Medical Center for advanced prostatic cancer within the period 2015-2018.*

Gleason score	6-7 (n=39)	8-10 (n=41)	Not determined (n=26)
Temporal mode of metastasis	Metachronous (n=66)	Synchronous (n=40)	
Location of metastases	Bone Only (n=46)	Miscellaneous (n=60)	
Age at start of enzalutamide treatment	<75 years (n=55)	≥75 years (n=51)	
Performance status	0-1 (n=66)	2 (n=40)	
Age-adjusted CCI	≤9 points (n=57)	>9 points (n=49)	
Timing of enzalutamide treatment	Pre-docetaxel (n=80)	Post-docetaxel (n=26)	
PSA response	Yes (n=88)	No (n=18)	
Maximum % PSA decline	No decline (n=18)	≤70% (n=36)	>70% (n=52)

CCI: Charlson Comorbidity Index.

(≤9 points *vs.* >9 points); https://www.mdcalc.com/charlson-comorbidity-index-cci), temporal mode of enzalutamide treatment-(pre-docetaxel *vs.* post-docetaxel) and maximum % PSA decline (no decline *vs.* ≤70% decline *vs.* >70% decline).

With regards to overall survival no discrimination between all-cause mortality and cancer related mortality was performed. For the statistical procedures IBM SPSS software was used. The patient and treatment related data were retrieved and stored by the first author according to the General Data Protection Regulation. As the analysis did not encompass any intervention, critical appraisal of the study protocol was not deemed compulsory by the local Medical Ethical Committee.

Results

The analysis encompassed 106 patients with a median age of 74 years, whose characteristics are depicted in Table I. Eighty eight out of 106 patients achieved a PSA response. Thirty-six patients achieved a PSA decline of 70% or less and 52 patients achieved a PSA decline of more than 70%. At the time of analysis 55 out of 88 responders displayed PSA progression. Table II shows the main results of the logistic regression analysis regarding the variables, which independently related to TPSAP. A steep PSA (>70%) decline appeared to independently relate to a longer TPSAP (median TPSAP 19 *vs.* 7 months), whereas enzalutamide appeared to be more effective, when given before chemotherapy (median TPSAP 10 *vs.* 7 months). At the time of analysis 47 out of 106 patients had died. Table III shows the main results of the variables, which independently related to OS. Enzalutamide given prior to chemotherapy and a steep PSA decline appeared to relate to an improved OS. Patients with a performance status of 2 appeared to have a two times increased risk of dying compared to patients with a performance status of 0 or 1. An older age did not appear to influence OS, whereas a poor ACCI appeared to relate to a more than three times increased risk of dying. Table IV shows the relation between ACCI, performance status and age. A higher ACCI was encountered more often in older patients and patients with a poorer performance status.

Discussion

As expected, the results of our analysis underline the efficacy of enzalutamide treatment and the significant role of % PSA decline as a biomarker of PFS and OS benefit.

It is broadly recognized that the benefit of cancer treatment can be affected by the patients' clinical condition. In prospective randomized trials, researchers usually make sure that the control and comparator arms are well-balanced for age and performance status. Our analysis underlined the significance of performance status as a poor prognosticator of OS, but age in itself did not appear to play a predictive role. A poor ACCI however appeared to relate to a more than three times increased risk of dying,

Our patient cohort could be regarded as a real-life picture of the PREVAIL/AFFIRM trial setting. Our results suggest that balancing treatment arms for age and performance status does not exclude an imbalance in comorbidity, which could bias OS-data.

Due to the small sample size (the study is to be repeated with a larger multicenter cohort) and the relatively low number of events, our results should be regarded as hypothesis-generating instead of a robust answer to the question. But they correspond well with a study by Lund *et al.*, who retrieved 8114 patients with a first-time discharge

Table II. *Variables related with time to PSA progression (TPSAP) in 106 patients with advanced prostatic cancer, who had been treated with enzalutamide in the ADRZ Medical Center within the time period 2015-2018 (Cox Regression Analysis).*

Variable	TPSAP (months)	Hazard risk of progression	95%CI	*p*-Value
Temporal mode of metastasis				
Synchronous	7	0.734	0.485-1.7777	0.199
Metachronous	10			
Enzalutamide timing				
Pre-docetaxel	10	2.140	1.278-3.586	0.004
Post-docetaxel	7			
Maximum % PSA decline				
≤70%	7	1.460	1.292-1.649	0.000
>70%	19			

CI: Confidence interval.

Table III. *Variables related with overall survival (OS) in 106 patients with advanced prostatic cancer, who had been treated with enzalutamide in the ADRZ Medical Center within the time period 2015-2018 (Cox Regression Analysis).*

Variable	Median OS (months)	Hazard risk of death	95%CI	*p*-Value
Enzalutamide timing				
Pre-docetaxel	24	2.093	0.982-4.462	0.056
Post-docetaxel	21			
Age				
≥75 years	21	0.811	0.372-1.770	0.599
<75 years	Not reached			
Performance status				
0-1	Not reached	2.032	1.078-3.830	0.028
2	13			
Age-adjusted CCI				
≤9 points	Not reached	3.538	1.466-8.538	0.005
>9 points	14			
Maximum % PSA decline				
No response	8	1.141	1.031-1.262	0.010
>70%	Not reached			
≤70%	21			

CI: Confidence interval; CCI: Charlson Comorbidity Index.

Table IV. *Relation between age-adjusted Charlson comorbidity index, age and performance status in 106 patients with advanced prostatic cancer, who had been treated with enzalutamide in the ADRZ Medical Center within the time period 2015-2018.*

Age-adjusted CCI	Age	Performance status
≤9 points	<75 years (n=46)	0-1 (n=45)
	≥75 years (n=11)	2 (n=12)
>9 points	<75 years (n=9)	0-1 (n=21)
	≥75 years (n=40)	2 (n=28)

diagnosis of prostate cancer in the period 1995-2006 from the Danish cancer registry (20). Intriguingly, the adjusted mortality rate ratio for comorbidity rose from 3.11 in the 1995-1997 period to 5.08 in the 2004-2006 period, which could reflect a tendency to expand the volume of prostate cancer screening towards the less fit patients.

In conclusion, enzalutamide displays strong antitumor activity in the pre-chemo and post-chemo treatment setting, regardless of age. The ultimate survival, is however, negatively affected by comorbidity. Adding the ACCI to the baseline procedures of prospective randomized cancer trials (for the elderly) may further clarify disparities between treatment and comparator groups.

Conflicts of Interest

Authors have no conflicts of interest to disclose regarding this study.

Authors' Contributions

All Authors contributed to the writing of the manuscript, had full access to the data and analyses, and vouch for the accuracy and completeness of the report.

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