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Safety and outcomes of new generation hormone-therapy in elderly chemotherapy-naive metastatic castration-resistant prostate cancer patients in the real world

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ABSTRACT

Background: Abiraterone acetate and enzalutamide are standard treatments for chemotherapy-naive metastatic castration-resistant prostate cancer (CN-mCRPC). The purpose of this study was to evaluate the effectiveness and safety of these medications in elderly (≥ 75 years old) compared with young CN-mCRPC patients in a real-world clinical setting. Secondarily, we explored the survival prognostic value of different anatomo-clinical factors in elderly group.

Methods: In this retrospective observational multicentre study, we included 134 consecutive CN-mCRPC patients, 64 young and 70 elderly men, who had received AA or Enz.

Results: We did not find significant differences in treatment duration [16.6 months, (95% CI 9–24.2 months) vs. 16.8 months (95% CI: 6.3–27.2 months); p = 0.926] and overall survival [median not reached vs. 23.3 months (95% CI 10.2–36.3 months); p = 0.131] between the young and elderly groups. In elderly group, the only predictors of overall survival with AA or Enz were good ECOG performance status and high G8 score. Adverse events of grade ≥3 was similar in elderly group (12.9%) and in the young group (15.6%). Treatment was discontinued due to AEs in 6.3% of young group and 18.6% of elderly group.

Conclusions: Effectiveness and safety of treatment of CN-mRCPC with Abiraterone acetate and enzalutamide were similar in older and younger patients, although treatment discontinuation due to AEs was more frequent in the older age group. In addition to ECOG PS, assessment using specific geriatric scales as G8 screening tool could help to identify patients aged ≥75 who would most benefit from treatment with new-generation hormone therapy.

1. Introduction

In the context of population ageing, there is an increase in the prevalence of malignant tumours. Among these, prostate cancer is an important global health concern, because it is the most common malignancy and the second leading cause of cancer death in men in economically developed Western countries (Torre et al., 2012). Compared with younger patients (aged < 75 years), elderly men are more likely to present with advanced disease (Mukherji, Pezaro, Shamseddine, & De Bono, 2013). Analysis of the Surveillance,

Abbreviations: AA, abiraterone acetate; Enz, enzalutamide; CN-mCRPC, chemo-naïve metastatic castration resistant prostate cancer; mCRPC, metastatic castration resistant prostate cancer; CRPC, castration resistant prostate cancer; OS, overal survival; PCWG, prostate cancer working group; ADT, androgen deprivation therapy; ECOG PS, eastern cooperative oncology group performance status; AE, adverse event; PFS, biochemical progression free survival

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Epidemiology and End Results database showed that almost half (48%) of all metastatic prostate cancer cases and more than half of all prostate cancer deaths were in patients aged ≥ 75 years (Scosyrev, Messing, Mohile, Golijanin, & Wu, 2012). Although > 80% of patients with advanced PC initially have a favourable response to androgen deprivation therapy (ADT), disease progression to a lethal stage will eventually occur in most of these patients within a few years (Cornford et al., 2017). This is recognized as castration-resistant prostate cancer (CRPC), defined as progressive disease, despite the maintenance of a serum testosterone level within the castration range (Lam, Leppert, Vemulapalli, Shvarts, & Belldegrun, 2006). In this situation, it remains a considerable challenge to optimize therapy for elderly patients who are more likely to have medical comorbidities, physical frailty and serious toxic reactions to certain kinds of treatment (e.g., chemotherapeutics) (Droz et al., 2014; Mukherji et al., 2013).

In addition to docetaxel (Petrylak et al., 2004; Tannock et al., 2004), there are novel drugs, abiraterone acetate (AA, a potent androgen biosynthesis inhibitor) and enzalutamide (Enz, an androgen receptor inhibitor) which have become the basis of the most common therapeutic approach in chemotherapy-naive metastatic CRPC (CN-mCRPC) patients, due to associated improvements in overall survival (OS) and quality of life, as well as their moderate toxicity profile (Beer et al., 2014; Ryan et al., 2013, 2015). Nevertheless, there is still limited data available concerning the clinical outcomes with these two agents used for mCRPC patients in a routine clinical setting. In addition, outside post-hoc analysis of clinical trials (Graff et al., 2016; Smith et al., 2015), to our knowledge, no studies have been published to date that evaluate the effects of these medications on elderly CN-mCRPC patients in a real-world clinical setting.

The purpose of this study was to compare the effectiveness and safety between young (< 75 years of age) and elderly (≥ 75 years) men with CN-mCRPC treated with AA or Enz in a real-world clinical setting, and explore possible prognostic factors associated with OS in the elderly patient group.

2. Material and methods

We conducted a retrospective study of 134 consecutive patients with CN-mCRPC treated with AA or Enz in three Spanish centres between January 2013 and December 2016. The patients were divided into two groups by age: < 75 years old (n = 64) and ≥ 75 years old (n = 70). The diagnosis of mCRPC was defined as biochemical or radiological progression in accordance with the criteria of the Prostate Cancer Working Group (PCWG) (Scher et al., 2016) in patients with blood testosterone levels < 50 ng/dl. The choice of therapeutic agent after failure of ADT (androgen deprivation therapy) was at the discretion of the clinician. AA and Enz were initially administered at full dose in accordance with previously published dose regimens (Beer et al., 2014; Ryan et al., 2013). The treatment is given until i) progression according to the PCWG criteria, ii) clinical progression in patients that are not candidates for chemotherapy or iii) an intolerable adverse event (AE).

The clinical and histopathological data and previous treatments were obtained from personal health records. Before initiating treatment with AA or Enz, we assessed patients with the Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status (PS) (Oken et al., 1982), the Charlson comorbidity index (Goyal et al., 2014), the specific geriatric assessment using G8 screening tool (in patients ≥ 75 years old) (Bellera et al., 2012), and the Brief Pain Inventory-Short Form (Ryan et al., 2013); measured blood prostate-specific antigen (PSA) and other biochemical and haematological parameters; and performed a radiological examination based on computed tomography of the thorax, abdomen and pelvis and bone scintigraphy or a 11C-Choline positron emission tomography/computed tomography scan. Follow-up assessments were carried out every 4 to 8 weeks, with radiological examinations at the discretion of the clinician. Biochemical response was defined following the PCWG criteria (Scher et al., 2016) and AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE, 2019).

The statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 21.0 (IBM, Armonk, NY, USA). We carried out a descriptive analysis of the study variables and subsequently univariate analysis, applying the chi-square test for qualitative variables and Student's *t*-test (or the Mann-Whitney U test for non-normally distributed data) for quantitative variables. For the analysis of progression-free survival and OS, we used the Kaplan-Meier method and the log-rank test. Multivariate analysis of prognostic factors was carried out using stepwise Cox regression. In all cases, we performed calculations for a 95% confidence interval and assumed a beta error of 0.2 (power of 80%), and a p value < 0.05 was considered statistically significant. The competing risks analysis was performed using the computer program R.

Written informed consent to participate in the study was collected from all subjects. The ethics approval was unnecessary for retrospective observational study according to national regulations (Biomedical research law, BOE 4 July 2007), although a notification was sent to each Local Ethical Committee.

3. Results

3.1. Patient characteristics

A total of 64 men < 75 years of age and 70 men ≥ 75 years of age with CN-mCRPC received AA (94 patients) or Enz (40 patients). The distribution of the main clinical and histopathological parameters were similar in the two groups, except for a longer duration of response to ADT, a longer interval between the diagnosis of prostate cancer and treatment with mCRPC and a higher score in the Charlson comorbidity index in the older group (Table 1).

3.2. Response to AA and Enz

With a median follow-up of 13.3 months (1–48), 55.2% of patients continued with the treatment (56.4% of the under-75-year-old and 54.3% of those 75 or older). The maximum PSA decline from baseline levels is shown in Fig. 1. The biochemical progression free survival (bPFS) was 13 months (95% CI 8.4–17.5 months), with no significant differences between age groups (10 months, 95% CI 4.2–15.8 months, in the younger group vs 14 months, 95% CI 7.3–20.7 months, in the older group; $p = 0.901$) (Fig. 2). PSA levels fell by more than 50% with the treatment in around two-thirds (61.2%) of patients (64.1% of the younger group and 58.6% of the older group, $p = 0.635$). The mean treatment duration was 16.6 months (95% CI 10.5–22.3 months), with no significant differences between age groups (16.6 months, 95% CI 9–24.2 months, in the younger group vs 16.8 months, 95% CI: 6.3–27.2 months, in the older group; $p = 0.926$) (Fig. 3). Following disease progression, 50% of the under-75-year-old and 9.7% of those 75 or older were treated with docetaxel ($p = 0.006$). The median OS was 38.4 months (95% CI, 15–61.9 months) with no differences between the groups (median not reached in the under-75-year-old vs 23.3 months, 95% CI 10.2–36.3 months, in those 75 or older; $p = 0.131$) (Fig. 4).

Of the deceased patients, 27 were from PCa (20%) and 11 from other causes (8%). The overall probability of dying from prostate cancer at 1 and 2 years was 11.4% and 36.2% and dying from other causes 8.6% and 10.6% respectively (Fig. 5). The individualized analysis by age groups show that the overall probability of dying from prostate cáncer at 2 years was similar, 36.2% and 35.1% for < and ≥ 75 years old respectively ($p = 0.525$); while that of the mortality for other causes was higher in elderly group, 5.5% and 15.4% for < and ≥ 75 years old respectively ($p = 0.164$) (Fig. 6).

Table 1
Distribution of the main clinical and pathological characteristics, overall and in each age group (< and ≥ 75 years old). AA = abiraterone acetate; Enz = enzalutamide; ADT = androgen deprivation therapy; PSA: prostate-specific antigen; AF: alkaline phosphatase; LDH = lactate dehydrogenase.

Variable	< 75 years old (n = 64)	≥ 75 years old (n = 70)	All patients (n = 134)	P-value
Mean follow-up in months (range)	13.4 (2-26)	13.1 (1-48)	13.3 (1-48)	0.851
AA vs Enz (%)	43 (67.2) vs 21 (32.8)	51 (72.9) vs 19 (27.1)	94 (70.1) vs 40 (29.9)	0.598
Duration of response to ADT in months (range)	36 (4-132)	69.7 (5-246)	61.5 (4-246)	0.0001
Diagnosis-to-treatment interval in months (range)	63.3 (4-179)	96.9 (10-262)	80.6 (4-262)	0.001
ECOG (%)				0.096
0	50 (78.1)	46 (65.7)	96 (71.6)	
1	13 (20.3)	21 (30)	34 (25.4)	
2	1 (1.6)	3 (4.3)	4 (3)	
Symptomatic (%)[a]	9 (14.1)	14 (20)	23 (17.2)	0.361
Use of morphine derivatives (%)	3 (4.7)	10 (14.3)	13 (9.7)	0.054
Gleason score (%)				0.303
≤ 7	29 (45.3)	39 (55.7)	68 (50.7)	
≥ 8	35 (54.7)	31 (44.3)	66 (49.3)	
Bone metastasis (%)				0.835
No	11 (17.2)	13 (18.6)	24 (17.9)	
Yes	53 (82.8)	57 (81.4)	110 (82.1)	
Lymph node metastasis (%)				0.724
No	30 (46.9)	36 (51.4)	66 (49.3)	
Yes	34 (53.1)	34 (48.6)	68 (50.7)	
Visceral metastasis (%)				0.083
No	62 (96.9)	61 (87.1)	123 (91.8)	
Yes	2 (3.1)	9 (12.9)	11 (8.2)	
Mean baseline PSA level (range)	131.2 (3-1320)	102.1 (2-1234)	122.5 (2-1320)	0.485
Mean baseline haemoglobin level (range)	12.8 (7.9-16.3)	12.7 (8.4-15.3)	12.8 (7.9-16.3)	0.774
Mean baseline AF level (range)	328.7 (21-4175)	134.7 (16-929)	271.3 (16-4175)	0.074
Mean LDH level (range)	225.9 (32-603)	219.9 (123-603)	224.2 (32-603)	0.798
Charlson index (range)	6.8 (3.6-12.4)	8.5 (4.2-16)	7.7 (3.6-16)	0.0002
Comorbidities				
Diabetes (%)	18 (28.1)	14 (20)	32 (23.9)	0.171
Dyslipidaemia (%)	30 (46.9)	27 (38.6)	57 (42.5)	0.190
Hypertension (%)	32 (50)	41 (58.6)	73 (54.5)	0.234
Congestive heart failure (%)	7 (10.9)	8 (11.4)	15 (11.2)	0.928
Other heart diseases (%)	7 (10.9)	13 (18.6)	20 (19.9)	0.215
Cerebrovascular disease (%)	2 (3.1)	0	2 (1.5)	0.498
Liver failure (%)	1 (1.6)	2 (2.9)	3 (2.2)	0.613
Renal failure (%)	5 (7.8)	13 (18.6)	18 (13.4)	0.068

[a] score > 3 in Brief Pain Inventory–Short Form (BPI-SF).

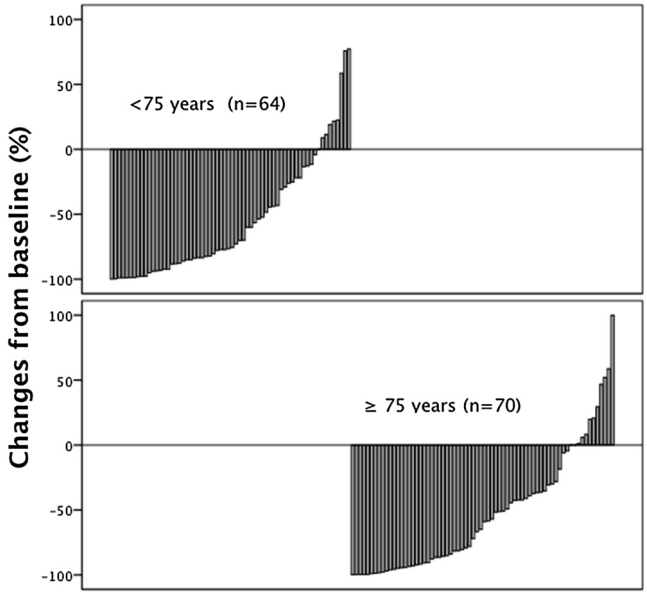

Fig. 1. Maximum percentage of PSA response during the treatment with abiraterona acetate and enzalutamide compared to baseline for each patient in both age groups (< and ≥ 75 years old).

3.3. Prognosis after treatment with AA or Enz in elderly patients

In the univariate analysis, the prognostic factors associated with a longer OS in elderly patients were good ECOG PS, G8 score > 14, and pre-treatment alkaline phosphatase levels < 2.5 UPN. In the multivariate analysis, however, only ECOG PS and G8 score were predictors of OS (Table 2).

Grouping patients using these factors, the median OS in the elderly patient group was median not reached for ECOG 0 and G8 > 14 points vs 38.4 months (95 CI 13.8-63.1.7) for ECOG 1 or 2 or G8 ≤ 14 points and 8.9 months (95% CI 6.9–11) for ECOG 1 or 2 and G8 ≤ 14 points ($p = 0.0003$).

3.4. Adverse events associated with AA or Enz treatment

The overall incidence of AEs was 46.3%. Grade 3 and 4 AEs were observed in 14.2% of patients, with no significant differences between groups based on age (15.6% in < 75-year-old vs 12.9% in ≥ 75-year-old, $p = 0.551$) (Table 3) or treatment (13.8% for AA v 15% for Enz; $p = 0.977$), except for asthenia of any type, which was more common with administration of Enz than administration of AA (15% vs 4.3%, $p = 0.04$), but age was not a risk factor (RR ≥ 75 years old: 0.373; 95% CI: 0.06–2.5).

We observed a dose reduction of 6.7%, with no significant differences between groups by age (8.6% ≥75-years-old vs 4.7% < 75-year-old; $p = 0.293$) or treatment (10% in patients treated with Enz vs 5.3% in patients treated with AA; $p = 0.261$). Treatment was temporarily discontinued due to AEs in 12.7% of patients, with no significant

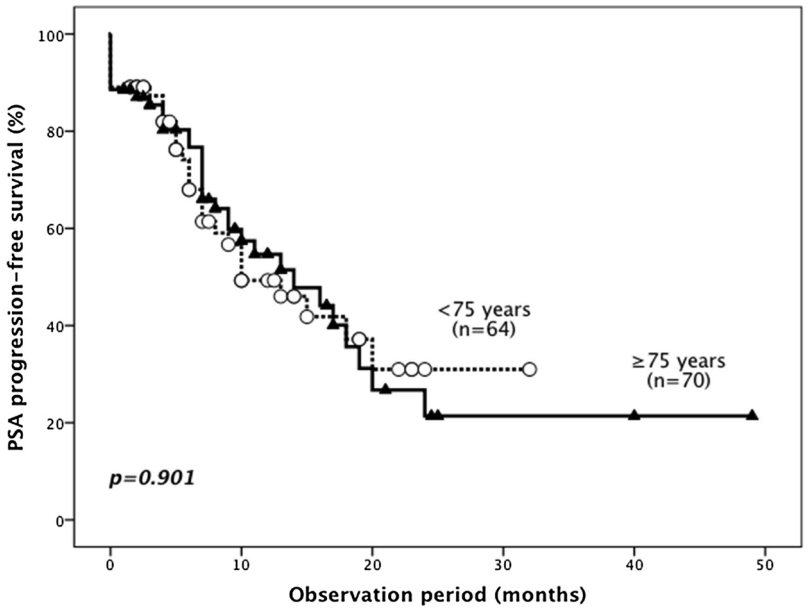

Fig. 2. Biochemical progression-free survival for mCRPC treated with abiraterona and enzalutamide in both age groups (< and ≥ 75 years old).

differences between age groups (6.3% in < 75-year-old vs 18.6% ≥ 75-year-old; $p = 0.06$), but treatment discontinuation was more frequent in the Enz group (25% vs 11.9% in the AA group; $p = 0.012$). Treatment was stopped due to AEs in 6% of patients, with no differences between the younger and older groups (3.1% vs 8.6%, respectively, $p = 0168$), or by type of treatment (10% with Enz vs 4.3% with AA; $p = 0.185$).

4. Discussion

In the literature, there is evidence indicating that AA and Enz significantly increase both progression free survival (PFS) and OS with an acceptable profile of AEs in patients with CN-mCRPC (Beer et al., 2014, 2017; Ryan et al., 2013, 2015). In randomised controlled trials (RCTs), the median treatment duration was found to be 13.8 months and the OS 34.7 months with AA (Ryan et al., 2013, 2015), and corresponding figures were 20 and 35.3 months, respectively, with Enz (Beer et al., 2014, 2017). These results are in agreement with other series (Miyake, Hara, Terakawa, Ozono, & Fujisawa, 2017; Terada et al., 2016) and our findings are very similar, with treatment duration of 16.6 months and an OS of 38.4 months. In contrast, most studies in the real world have obtained poorer results, with treatment durations of 5.3–12 months (Poon et al., 2016; Salem et al., 2017; Thortzen, Thim, Røder, & Brasso, 2016) and OS of 16.6–18.1 months (Poon et al., 2016; Thortzen et al., 2016). These differences are probably due to the small number of patients (Thortzen et al., 2016; Poon et al., 2016), the high percentage of symptomatic patients (Salem et al., 2017), with ECOG PS ≥ 2 (Salem et al., 2017), or the small percentage of patients who received subsequent treatment with docetaxel (Poon et al., 2016) in these studies.

With regards to the effectiveness of AA and Enz in older patients, we are only able to compare our results with the post-hoc analysis of the two RCTs. Notably, however, despite at least half of patients with metastatic prostate cancer being over 75 years old (Malangone-Monaco et al., 2016; Mukherji et al., 2013; Rocha et al., 2017), this age group

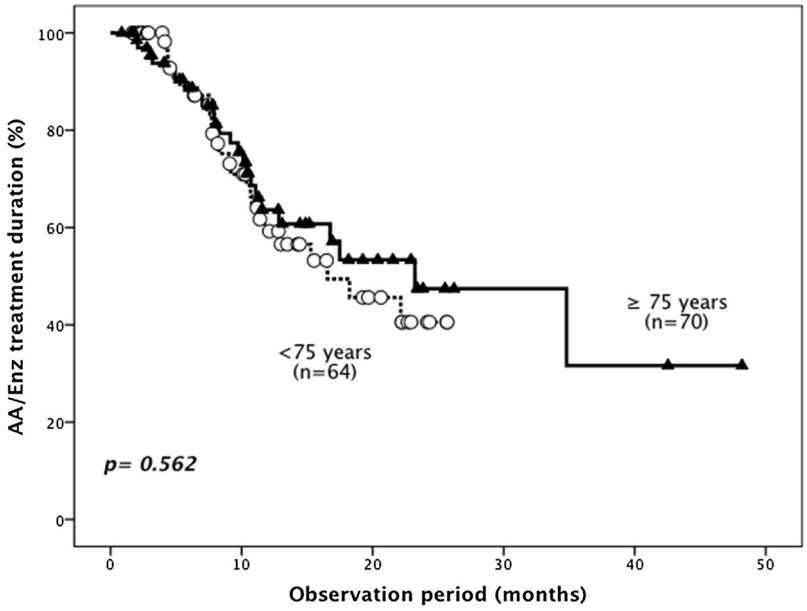

Fig. 3. Abiraterona acetate and enzalutamide treatment duration for mCRPC in both age groups (< and ≥ 75 years old).

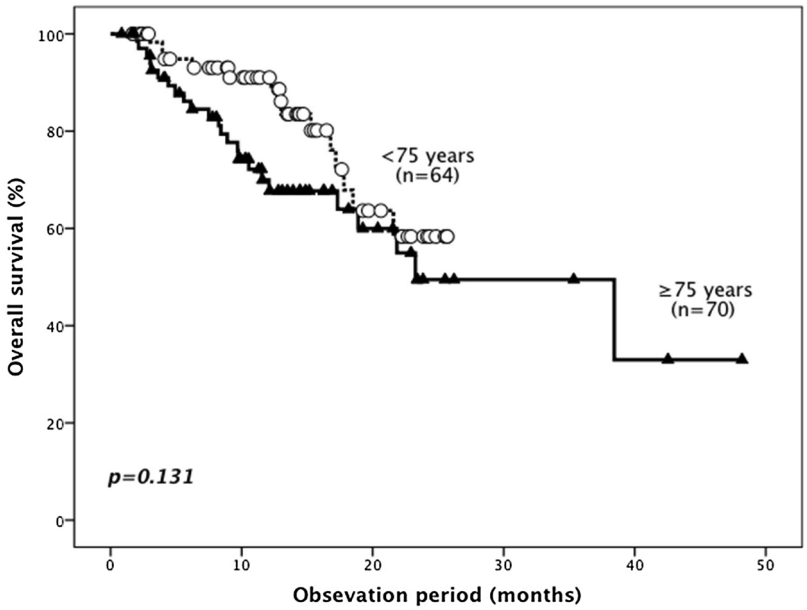

Fig. 4. Overall survival for mCRPC treated with abiraterona acetate and enzalutamide in both age groups (< and ≥ 75 years old).

only represented 37% and 35.5% of the study populations, respectively, in the AA (Beer et al., 2014) and Enz (Graff et al., 2016) RCTs. This is attributable to the strict selection criteria of RCTs excluding a significant percentage of elderly patients, generally due to comorbidities associated with their age (Talarico, Chen, & Pazdur, 2004). In our series, over half of patients (52%) were ≥ 75 years of age with similar baseline characteristics to the younger patients (< 75 years of age), except that they obtained higher scores in the Charlson comorbidity index, had longer durations of response to ADT and longer intervals between diagnosis of prostate cancer and treatment with AA or Enz. In the sub-analysis of the Enz RCT (Graff et al., 2016), the time from diagnosis to treatment was much longer in the subgroup of elderly patients (88.3 vs 53.4 months), although the authors did not explain whether this was due to a delay in the treatment or longer duration of response to ADT, as in our study. Like in our series, in both RCTs (Graff et al., 2016; Smith et al., 2015), the percentage of patients with ECOG 1 was higher in the group of older patients (45% vs 24.7% for Enz and 37.8% vs 16.6% for AA), although we also included patients with ECOG 2. This fact, together with the inclusion of symptomatic patients (20%), excluded in the RCTs, and higher pre-treatment PSA levels (131.2 ng/ml in our series, compared to 73.3 ng/ml and 48.4 ng/ml for the RCTs with Enz and AA, respectively) may explain why the OS in patients ≥ 75 years of age was lower in our study than in the AA (Smith et al., 2015) and Enz (Graff et al., 2016) RCTs (23.3 vs 28.6 and 32.4 months, respectively). Nevertheless, results were similar for bPFS (14 months in our study vs 13.7 months with Enz) (Graff et al., 2016) and for treatment duration (16.6 months in our study vs 11.8 months with AA and 16.6 months with Enz) (Graff et al., 2016; Smith et al., 2015).

To our knowledge, predictors of OS in patients ≥75 years of age with CN-mCPRC have not previous been investigated. The International Society of Geriatric Oncology Prostate Cancer Clinical Trials Working Group recommend systematic assessment using specific geriatric scales (Droz et al., 2017). In our study, the combined use of G8 screening tool geriatric scale and ECOG PS have helped us to distinguish the group of older patients with a similar OS to younger patients who received AA or Enz pre-chemotherapy (32.4 vs 35.3 months, respectively) (Graff et al.,

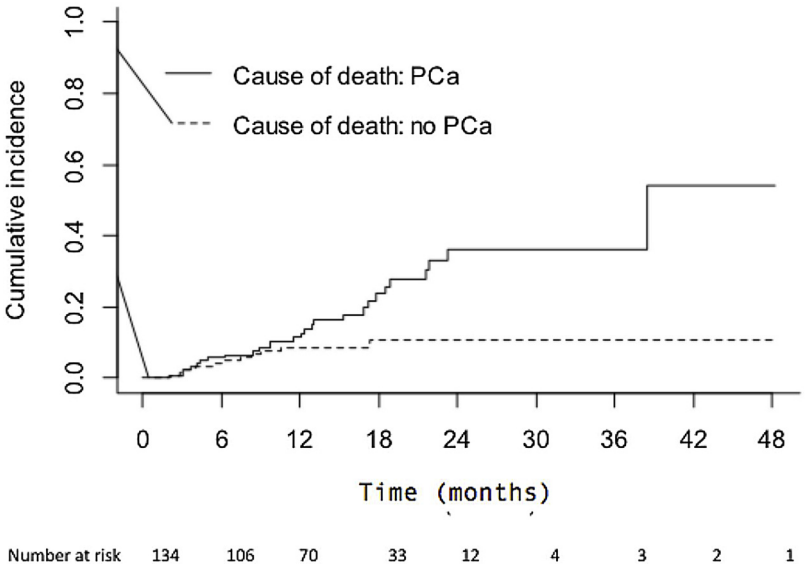

Fig. 5. Cumulative incidence curve of mortality competitive events. Global series (n = 134). Mortality attributable to PCa (prostate cancer) and other causes.

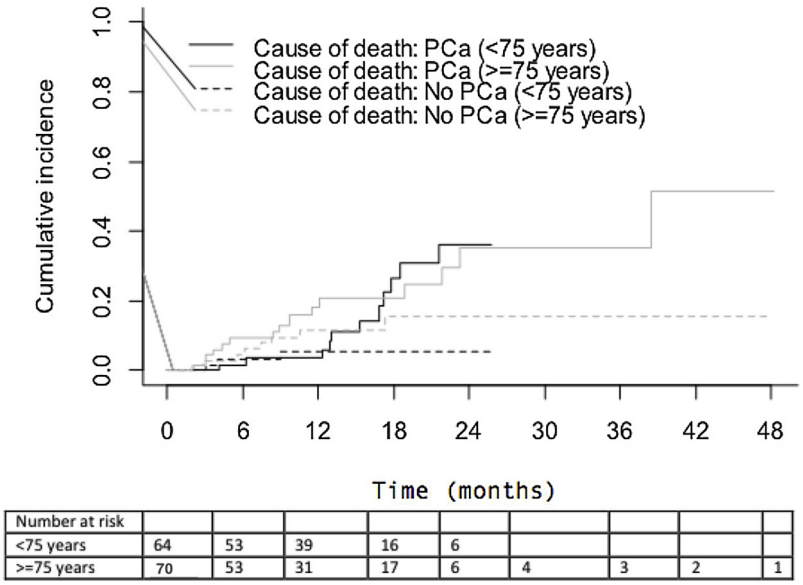

Fig. 6. Cumulative incidence curve of mortality attributable to PCa (prostate cancer) and other causes ($n = 134$) stratified by age $<$ and $\geq$ 75 years old. Gray test (mortality attributable to PCa), $p = 0.525$. Gray test (mortality attributable to other causes), $p = 0.164$.

Table 2
Cox regression analyses for overall survival in elderly patients ($\geq$ 75 years old). HR: hazard ratio; CI: confidence interval; ADT = androgen deprivation therapy; PSA: prostate-specific antigen; UPN = upper limit of normal; NA = not applicable.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
ECOG (0 vs. 1 vs. 2)	4.06 (1.81-11.68)	0.001	2.5 (1.24-5.04)	0.01
G8 score (>14 vs. ≤ 14)	3.7 (1.03-13.25)	0.032	3.13 (1.13-8.66)	0.028
Charlson index (<7 vs. ≥ 7)	2.33 (0.66-8.24)	0.187	NA	NA
Gleason score (≤ 7 vs >7)	1.16 (0.41-3.26)	0.773	NA	NA
Duration of ADT (<2 vs. ≥ 2 years)	0.44 (0.093-2.06)	0.295	NA	NA
Symptoms (negative vs. positive)	1.61 (0.49-5.34)	0.434	NA	NA
Visceral metastases (negative vs. positive)	0.16 (0.02-1.77)	0.136	NA	NA
Bone metastases (negative vs. positive)	1.67 (0.11-26.26)	0.946	NA	NA
PSA (<60 vs. ≥ 60 ng/ml)	1.02 (0.31-3.42)	0.971	NA	NA
Haemoglobin (<12 vs. ≥ 12 g/dl)	1.14 (0.41-3.16)	0.806	NA	NA
Alkaline Phosphatase (<2.5 vs. ≥ 2.5 UPN)	6.42 (1.31-31.6)	0.022	2.48 (0.98-6.28)	0.055
AA vs Enz	0.29 (0.05-1.61)	0.158	NA	NA

2016; Smith et al., 2015) from those with a much lower OS than that reported by Rocha et al. (2017), their OS not even reaching that of younger patients who receive AA or Enz after chemotherapy (15.8 and 18.4 months, respectively) (De Bono et al., 2011; Scher et al., 2012).

In our series, the rate of grade 3 and 4 AEs (14.2%) was much lower than that ones observed in the RCTs (54% for AA and 45.7% for Enz) (Beer et al., 2017; Ryan et al., 2015), although similar to that ones in other "real-world" treatment series (7.5–15.5%) (Miyake et al., 2017; Poon et al., 2016), and was slightly higher in the older age group, for which the rate was similar to what published in the RCTs (Graff et al., 2016; Smith et al., 2015). The rates of dose reduction and treatment discontinuation due to AEs in our series were similar to those in the RCTs, although much lower than the 18% found in the study of Terada et al. (2016), in which all patients received Enz, more than half (56.2%) after chemotherapy. The rate of treatment discontinuation reported by Poon et al. (5.2%) in a series of 110 patients treated with AA pre-chemotherapy (Poon et al., 2016) was, however, lower than that in our study, although exposure time was also shorter (6.8 vs. 16.6 months in our study respectively). Although it was more common for doses to be reduced or the treatment discontinued or stopped due to AEs in the older age group, as in the RCTs (Graff et al., 2016; Smith et al., 2015) and another "real world" series (Miyake et al., 2017), the differences in our study were not statistically significant.

As in all not randomized and retrospective studies, the mains limitations of this study are the selection bias (the choice of AA or Enz was at the discretion of the clinician) and the potential information bias, mainly associated with the underreporting of AEs. Further, bPFS and treatment duration may have been influenced by the follow-up interval, which was decided by clinicians. The combined analysis of the response to AA and Enz may have overlooked differences in the results, due to their mechanisms of action.

5. Conclusions

In our study, the effectiveness and safety of treatment of CN-mRCPC with AA and Enz were similar in older and younger patients, although doses reduction, treatment discontinuation or stopping due to AEs were more frequent in the older age group. In addition to ECOG PS, assessment using specific geriatric scales as G8 screening tool could help to identify patients aged $\geq$75 who would most benefit from treatment with new-generation hormone therapy.

Conflict of interest statement

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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Table 3
Distribution of the most frequent adverse events associated with treatment with abiraterona acetate and enzalutamide in both age groups (< and ≥ 75 years old).

	< 75 years old (n = 64)		≥75 years old (n = 70)		p-value	
Adverse event	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Any	34 (53.1)	10 (15.6)	28 (40)	9 (12.9)	0.177	0.551
Asthenia	6 (9.4)	0 (0)	4 (5.7)	2 (2.9)	0.634	0.408
Neurological symptoms	5 (7.8)	3 (4.7)	1 (1.4)	1 (1.4)	0.064	0.268
High cholesterol	4 (6.3)	1 (1.6)	1 (1.4)	0 (0)	0.103	0.478
Liver symptoms	3 (4.7)	2(3.1)	3(4.3)	0 (0)	0.911	0.503
Fluid retention	3 (4.7)	1 (1.6)	8 (11.4)	1 (1.4)	0.148	0.260
Hypertension	3 (4.7)	1 (1.6)	1 (1.4)	0 (0)	0.260	0.223
Hot flushes	2 (3.1)	0 (0)	1 (1.4)	0 (0)	0.505	–
Heart symptoms	1 (1.6)	0 (0)	2 (2.9)	1 (1.4)	0.609	0.253
Gastrointestinal symptoms	1 (1.6)	1 (1.6)	3 (4.3)	2 (2.9)	0.343	0.609

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