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ORIGINAL PAPER

Prostate-specific antigen response after Abiraterone treatment in mCRPC: PSA as a predictor of overall survival

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Summary ***Objectives: Abiraterone Acetate (AA) is an important agent in the treatment of advanced prostate cancer. It was primarily approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) after failure of androgen deprivation therapy. There is still no available strong data regarding the impact of early decline of prostate-specific antigen (PSA) in the overall survival. The aim of this study was to evaluate the clinical efficacy of an early prostate-specific antigen response as a predictor of overall survival (OS) in metastatic castration-resistant prostate cancer when treated with Abiraterone Acetate.***

Materials and methods: A dual center, retrospective, cohort study on patients diagnosed with mCRPC treated with abiraterone between 2013 and 2020 was performed. Primary endpoint was to demonstrate the efficacy of AA, with the analysis of PSA decline, and the correlation with overall survival.

Results: The cohort analysis consisted of 84 patients with a median age of 71 ± 9 years. A PSA response of > 30% and > 50% at 60 and 90 days was associated with improved OS. Multivariate analysis revealed that a 60 day PSA decline of > 30% was predictive of overall survival. Median OS of diagnosed mCRPC patients was 28 months. Docetaxel pre-treatment was not associated with longer OS. The median duration of drug exposure for patients submitted to AA was found to be 14 months.

Conclusions: Early PSA response rate can offer clinically meaningful information and can be considered a surrogate of longer OS. A > 30% or > 50% prostate-specific antigen decline at 60 and 90 days provided an important low-cost clinical tool to predict subsequent events in mCRPC patients treated with abiraterone.

KEY WORDS: Abiraterone; mCRPC; PSA; Overall survival; Progression free survival.

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INTRODUCTION

Prostate cancer is the second most commonly diagnosed malignancy in men around the world with an estimated 1.111.700 new cases and 307.500 deaths per year (1). Metastatic prostate cancer is characterized by a period during which suppression of serum testosterone with *androgen deprivation therapy* (ADT) is sufficient to control disease. Unfortunately, this period is followed by transition to castration resistance, during which progression occurs despite continued suppression of testosterone. This is referred to as *metastatic castration-resistant prostate cancer* (mCRPC) (2).

Treatment of mCRPC has evolved over the last decade, with results from large randomized clinical trials leading to the approval of several new agents showing an *overall survival* (OS) benefit in patients with mCRPC, both pre- and post-chemotherapy-based regimens (3, 4).

Abiraterone Acetate (AA) is an important agent in the treatment of advanced prostate cancer. It is a selective inhibitor of androgen biosynthesis which potentially and irreversibly blocks CYP17, a crucial enzyme in estrogen and testosterone synthesis. It was primarily approved for the treatment of metastatic castrate-resistant prostate cancer after failure of androgen deprivation therapy (5).

However, it is important to acknowledge that, although AA is effective in both pre- and post-chemotherapy setting, discrepancies exist regarding its effectiveness, with only a fraction of patients actually benefiting in the long term.

Prostate-specific antigen (PSA) is widely used to monitor prostate cancer and its decline after chemotherapy has been acknowledged as a valid surrogate for OS at 3 months (6). Although, the role of PSA response after new hormonal generation agents remains uncertain (7, 8). The aim of this study is to evaluate the efficacy and safety of AA in mCRPC patients, regarding early PSA response as a prognostic marker of OS.

MATERIALS AND METHODS

Patients with confirmed mCRPC treated with first line abiraterone between 2013 and 2020 at *Hospital Garcia de Orta* and *Centro Hospitalar Barreiro Montijo* were considered for analysis. PSA value at baseline, at four, eight, and twelve weeks were required for study inclusion.

Exclusion criteria included absence of baseline values. Demographics and baseline characteristics such as prior docetaxel exposure were recorded, as well as routine lab studies including PSA, *neutrophil to lymphocyte* ratio (NL ratio), and *hemoglobin* (Hgb) at start of treatment, when available (Table 1).

The primary investigation of interest was PSA decline as a

Table 1.
PSA decline > 50% at 60 days; Log Rank 5.6, p = 0.018.

Baseline characteristics	N	Median
Total patients	84	
Age (years)	84	71 +/- 9 years
PSA at diagnosis	84	57.73 ng/dL [IR 136]
Gleason score (median)	84	7 [IR 2]
Neutrophil/Lymphocytes ratio	84	2.3 [IR 1.28]
Patients without prior docetaxel	64	
Patients with prior docetaxel	20	
Abiraterone duration (months)	84	14
Time until progression of disease with abiraterone (months)	84	12
PSA response (%)	84	67.9%
Hematologic toxicity with abiraterone	2	

predictor of overall PSA response and survival. PSA was procured at four, eight, and twelve weeks. PSA response was defined as > 30% decrease from the PSA at the start of treatment. PSA responses > 50% decrease from the PSA at the start of treatment were also analyzed. Kaplan-Meier analyses were used to estimate overall survival differences between groups at each time point. Associations between PSA response and survival were evaluated via univariate Cox regression analysis for ≥ 30% and ≥ 50% response at four, eight, and twelve weeks and with multivariate Cox regression models regarding these parameters.
Data analysis was completed via IBM SPSS software.
84 male patients diagnosed with mCRPC that experienced treatment failure with one or more lines of treatment (hormonal manipulation or chemotherapy) were selected and abiraterone acetate (1.000 mg daily) along with prednisone (5 mg twice daily) was administered.

Results

In this dual institution retrospective study, a total of 112 mCRPC patients were considered. After strict analysis, only 84 patients with a median age of 71 ± 9 years were included for statistical review. 67,9% showed a good response in PSA reduction. A PSA response of > 30% and > 50% at 60 days was associated with improved OS (Log Rank 13.7, p < 0.001, Log Rank 5,6, p = 0.018) as compared to subjects without such a decline (Figure 1 and Figure 2). There was also a strong correlation of PSA response of > 30% and > 50% at 90 days (Log Rank 6.7, p = 0.009 and Log Rank 3.7, p = 0.043) which was associated with improved OS (Figure 3 and Figure 4).
Multivariate analysis revealed that 60-day PSA decline of > 30% was predictive of overall survival (HR 0.995, 95% CI 0.13-0.57, p = 0.001). ROC curve showed that PSA value at 60 days is a highly specific tool to determine overall survival with a cut-off value of > 30% (AUC 0.754, p = 0.001) and it could be used as a clinical tool to determine patients that most benefit from treatment with abiraterone (Figure 5).
Median OS of diagnosed mCRPC patients was 28 months. Docetaxel pre-treatment in this study was not associated with longer OS (Log Rank: 0.024, p = 0.878) (Figure 6).

Figure 1.
PSA decline > 30% at 60 days Log Rank 13.7, p < 0.001.

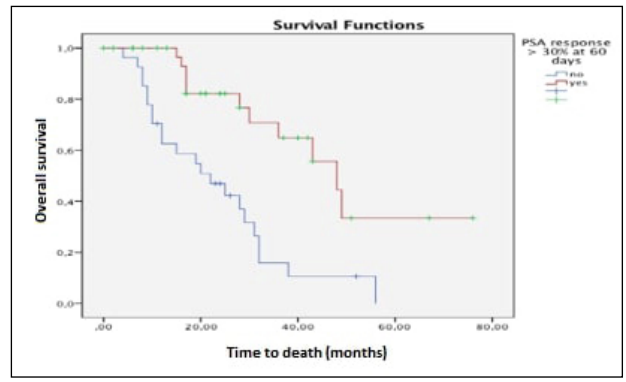


Figure 2.
PSA decline > 50% at 60 days.

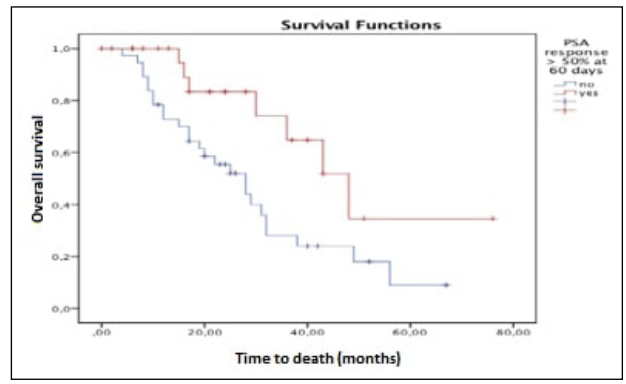


Figure 3.
PSA decline > 30% at 90 days. Log Rank 6.7 p = 0.009.

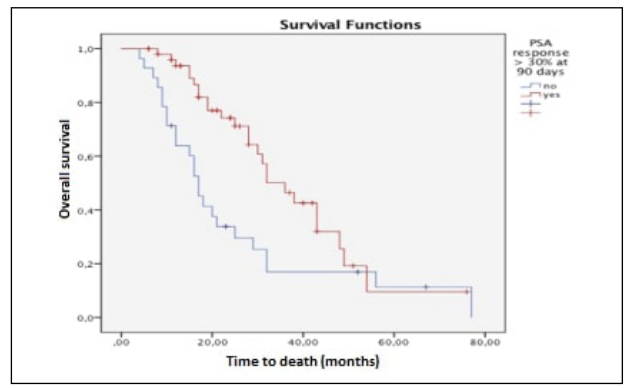


Figure 4.
PSA decline > 50% at 90 days. Log Rank 63.7 p = 0.043.

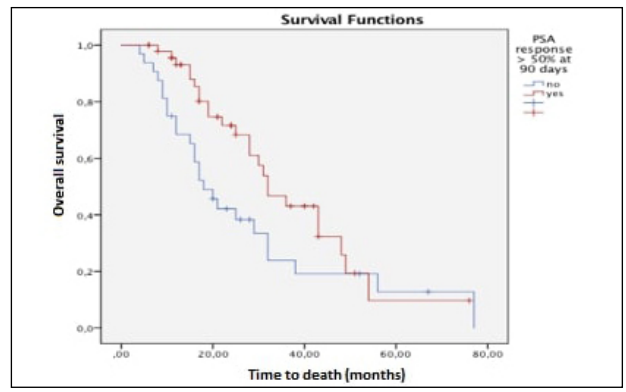


Figure 5.
ROC curve.

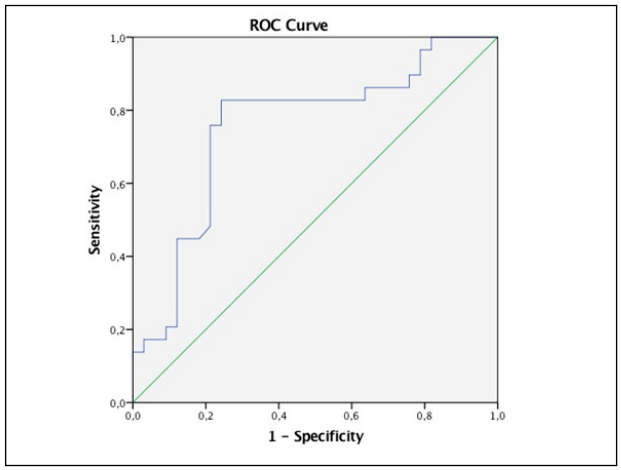
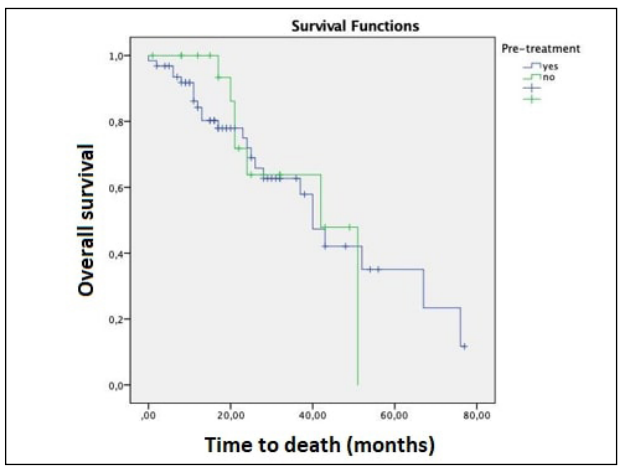


Figure 6.
Docetaxel pre-treatment. Log Rank 0.024, p = 0.878.



The median duration of drug exposure for CRPC who received AA was found to be 14 [IR 16] months. Regarding adverse events, two patients revealed hematologic toxicity, which didn't lead to treatment discontinuation.

Discussion

There is a growing number of therapeutic options capable of extending survival in mCRPC patients. Despite that, there is a lack for biomarkers that can simultaneously guide treatment decisions and predict which patients will benefit the most from these treatments. AA and enzalutamide have shown clinical efficacy in multicenter phase III RCT's (9), although evidence is not clear regarding which drug results in a better clinical and biochemical response. Some evidence suggests there is a better biochemical response in favor of enzalutamide versus abiraterone, particularly in those patients submitted to previous taxane therapy (10). However, in patients achieving biochemical response, this advantage is not consistent what suggests that there is a need for prognostic biochemical markers to predict which patients will benefit the most from each novel hormonal agent. Thus, the development of new surrogate markers for clinical outcomes is becoming increasingly important with the emergence of multiple lines of treatment with better survival benefit for mCRPC patients.

PSA remains a questionable surrogate for survival in late-stage prostate cancer. *Prostate Cancer Clinical Trials Working Group* (PCWG) 2 states that the clinical significance of a post-therapy PSA decline remains controversial and advises against its early use. In fact, an increase in serum PSA, or 'flare', may occur in some patients before they experience a subsequent and sometimes significant PSA decline. This is why PCWG2 recommends securing a sufficiently large drug exposure window and avoid relying on serum PSA decline as a surrogate for clinical benefit. Perhaps even more importantly, the group advises not to interpret a rise in serum PSA as progression and early withdrawing a therapy from which the patient may benefit (11).

Nonetheless, drugs targeting *androgen receptor* (AR) signaling, such as AA, may have a different association to an early PSA decrease, since PSA is a pharmacodynamic biomarker of androgen receptor signaling in absence of aberrations on the PSA promoter or key regulators of PSA production and secretion. The results of this study are consistent with *Rescigno et al.* study (12) in which a PSA response > 30% was a predictor of OS at four weeks. Additionally, these results reported a PSA response > 30% and > 50% as statistically significant for OS at 60 and 90 days which suggests that early decline of this biomarker could be used as a clinical tool to monitor treatment response and as a prognostic marker for these patients.

Furthermore, it demonstrates the potential role of early PSA decline as a cost-effective tool to monitor mCRPC patients and identify which patients will benefit the most from this therapy.

Some limitations of this study should be noted regarding it's retrospective nature and a relatively small sample size.

Conclusions

Abiraterone acetate is a drug of choice for CRPC and also for those who had previously received one or two chemotherapy regimens. This data suggests that clinicians could utilize early PSA response as a predictor of subsequent events after AA therapy. It supports a meaningful and stronger clinical benefit of early PSA response as a prognostic factor. The results of this study showed that AA significantly lowered the PSA values and prolonged overall survival in metastatic castration resistant prostate cancer patients who had progressed after first-line or second-line treatment.

Early PSA response rate can provide clinically meaningful information and can be considered a surrogate of longer OS. A > 30% or > 50% prostate-specific antigen decline at 60 and 90 days provide an important clinical tool to predict subsequent events in mCRPC patients treated with abiraterone and, according to our study, they should be used in clinical practice to determine which patients will have a better clinical response and as a prognostic marker.

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