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METASTATIC HORMONE-SENSITIVE PROSTATE CANCER – OUTCOMES OF DOCETAXEL PLUS ANDROGEN-DEPRIVATION THERAPY AS FIRST-LINE TREATMENT IN A PORTUGUESE CENTER

PROJETO DE INVESTIGAÇÃO

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METASTATIC HORMONE-SENSITIVE PROSTATE CANCER – OUTCOMES OF DOCETAXEL PLUS ANDROGEN-DEPRIVATION THERAPY AS FIRST-LINE TREATMENT IN A PORTUGUESE CENTER

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ABBREVIATIONS

ADT – androgen-deprivation therapy

CTscan – computerized tomography scan

CI – confidence interval

DOC – docetaxel

IQR – interquartile range

mCRPC – metastatic castration-resistant prostate cancer

mHSPC – metastatic hormone-sensitive prostate cancer

mPC – metastatic prostate cancer

OS – overall survival

PETscan – positron emission tomography scan

PC – prostate cancer

PSA – prostate specific antigen

RCT – randomized controlled trial

ABSTRACT

Introduction: Prostate cancer (PC) is recognized as one of the most prevalent cancers among men, with important mortality rate associated. A minor part of the cases is diagnosed as metastatic disease and strong evidence shows the benefit of adding docetaxel (DOC) to androgen-deprivation therapy (ADT) in the treatment of hormone-sensitive disease with solid improvement in overall survival (OS). The aim of this study is to evaluate the effectiveness of this treatment in patients with metastatic hormone-sensitive prostate cancer (mHSPC) *ab initio* in a Portuguese center.

Materials and methods: This is a retrospective study enrolling 35 patients with mHSPC *ab initio* receiving DOC plus ADT as first-line treatment, between January 2018 and December 2020. Baseline and clinicopathologic features, as well as biochemical response, biochemical and radiological progression and OS were evaluated.

Results: In our cohort, most of the patients had high-volume disease (80%), with a median prostate specific antigen (PSA) at diagnosis of 172,2 ng/mL (interquartile range (IQR): 59,8-449,2). Almost 50% had a ISUP grade ≥4. Biochemical response was achieved in 71,9% of the patients, with a median PSA nadir of 1,32 ng/mL (IQR: 0,34-37,8). During a median follow-up of 28 months (IQR: 18-32), biochemical and radiological progression occurred in 50% and 55,9%, respectively. The median OS was 39 months (IQR: 22,13-55,87).

Conclusion: Contrasting to clinical trials, in our center the use of DOC plus ADT for mHSPC *ab initio* showed a slightly lower efficacy, as we hypothesize the difference between a real-world population and clinical trials populations being the main cause for that.

Keywords: Prostate cancer. Metastatic hormone-sensitive prostate cancer. Docetaxel. Progression-free survival. Overall survival.

INTRODUCTION

The first clinical case of prostate cancer (PC) was described by Dr. J. Adams in London 1853 as a rare disease.[1] More than a century later, PC is recognized as one of the most prevalent cancers among men, with important mortality rate associated. In 2020, according to the International Agency for Research on Cancer, PC was the second most frequent neoplasia and the fifth leading cause of cancer-death among men worldwide and the most frequent neoplasia and the third leading cause of cancer-death among men in Portugal.[2]

PC is mostly diagnosed asymptomatic – based on Prostate Specific Antigen (PSA) levels and prostate biopsy – and mainly as localized disease. However, a minor, but still important, part of the cases is diagnosed as metastatic disease – metastatic prostate cancer (mPC) *ab initio.*[3] In fact, in the last 20 years, the percentage of localized PC at diagnosis has been decreasing while the percentage of mPC *ab initio* has been increasing. The metastatic stage of the disease is responsible for most of the PC related deaths: 5-year survival for patients with localized disease tend to achieve 100%, on the contrary the ones with metastatic disease have a relative survival of 30.7%.[4]

As an hormone-dependent cancer in its initial stages, androgens play a key role in the development of normal and neoplastic prostatic cells.[5] Historically, the treatment of mPC relies on androgen-deprivation therapy (ADT). Initially, mPC is hormone-sensitive, but it known that with time it will progress to metastatic castration-resistant prostate cancer (mCRPC), the majority in 1-3 years.[6,7]

In the last two decades, strong evidence has emerged showing the benefit of associating taxane-based chemotherapy – Docetaxel (DOC) – to ADT in the treatment of metastasized disease with solid improvement in overall survival (OS) of these patients. DOC was initially approved as standard line for treating mCRPC and later for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) either after progression of localized disease or for *ab initio* diagnosis, being particularly beneficial in patients with high-volume metastatic disease.[8,9] More recently, other drugs have been studied and shown improvement in OS of patients with mHSPC, but DOC remains as a first-choice therapy for these patients.[10,11]

So, with this work, we aim to evaluate the clinical outcomes of patients with mHSPC *ab initio* treated with DOC plus ADT as first-line therapy in our institution.

MATERIALS and METHODS

This is retrospective study including all the patients with a diagnosis of mHSPC which received DOC plus ADT as first-line therapy from January 1, 2018, until December 31, 2020, (n=35) in urologic oncology department of *Centro Hospitalar e Universitário de Coimbra, Portugal*. The follow-up extended from January to December 2021. Patients were elected after an uro-oncology multidisciplinary team decision for treatment with DOC plus ADT, considering there was no contraindication for receiving chemotherapy.

Data was collected from electronic medical records database – *SClínico Hospitalar* – from December 1 to 30, 2021 and the database used was anonymized. A total of 35 patients fulfilling the criteria of mHSPC under first-line treatment DOC plus ADT were identified. From the 35 eligible cases, demographic and clinicopathological features were collected – age at diagnosis, Gleason score / ISUP grade (when available), pre-treatment PSA, metastasis location (bone, visceral or lymph nodes), volume of disease – high (visceral metastasis or ≥ 4 bone metastasis including ≥ 1 outside vertebral column or pelvis) or low (not high) – based on CHAARTED trial criteria.[12] Treatment features were also collected: number of cycles received, time to start DOC after diagnosis, PSA nadir value. Subsequent treatments after DOC plus ADT due to disease progression were also extracted. Biochemical response, biochemical and radiological progression and OS were evaluated.

The occurrence of biochemical response was defined as a reduction of $\underline{\geq}$ 50% of initial PSA level after 12 weeks of treatment. PSA progression was considered when three consecutives rises in PSA, at least one week apart, resulting in two 50% increases over the nadir were registered and PSA > 2ng/mL occurred. Radiological progression was defined as two or more new bone lesion or a new soft lesion scanned by bone scintigraphy, CT scan or G68 PSMA-PET. OS was defined as the time until death from any cause.

Statistical analysis was performed using IBM SPSS ® Statistics (version 28). Continuous variables were assessed for normality using the Shapiro-Wilk test and by visual analysis of their histograms. Since none had a normal distribution, they were described using medians and interquartile ranges (IQR). Categorical variables were described using absolute and relative frequencies. Time-dependent outcomes were modelled through Kaplan-Meier analysis, and groups were compared using the Log-Rank test when applicable. A significance cut-off value of 0.05 was used.

RESULTS

A total of 35 patients who initiated therapy with DOC plus ADT between January 2018 and December 2020 were included in the study. The baseline demographic and clinicopathological patients' characteristic are shown in table 1. Median age of the cohort was 69 years (IQR: 64-78).

All the patients were in an hormone-sensitive status and with metastasized disease *ab initio*. 85,7%, 65,7% and 25,7% had bone, lymph node and visceral metastasis, respectively. According to ISUP grade, no patients were ISUP 1 and only 2 patients (5,7%) had an ISUP 2; the majority had an ISUP associated with more aggressive disease: 3 (42,9%), 4 (25,7%) and 5 (22,9%). From the entire cohort, 80% had high-volume disease.

Concerning treatment, patients started DOC chemotherapy with a median 2 months (IQR: 1-5) from the diagnosis and were given a median of 6 cycles.

Table 1 – *Baseline and clinicopathological characteristics for all patients (N = 35)*

Age at diagnosis (years)	
Median	69
IQR	64 – 78
Pre-treatment PSA level (ng/mL)	
Median	172,2
IQR	59,8 – 449.2
ISUP grade, no. (%)	
1	- (0)
2	2 (5,7)
3	15 (42,9)
4	9 (25,7)
5	8 (22,9)
NA	1 (2,9)
Sites of disease (%)	
Bone	85,7
Visceral	25,7
Lymph Node	65,7
Volume of disease, no. (%)	
Low	6 (17,14)
High	28 (80)
NA	1 (2,85)

***Table 1** (continued) – Baseline and clinicopathological characteristics for all patients (N = 35)*

Number cycles of docetaxel	
Median	6
IQR	6 – 10
Time until start Docetaxel after diagnosis (months)	
Median	2
IQR	1 – 5
PSA nadir (ng/mL)	
Median	1,32
IQR	0,34 – 37,8

ADT = androgen deprivation therapy; IQR = interquartile range; NA = not available; mo = months.

[a] High volume of disease was defined by the presence of visceral metastases or four or more lesions with at least one beyond the vertebral bodies and pelvis.[12]

Overall Survival

During a median follow-up of 23 months (IQR: 18-32), 14 deaths occurred (40% of patients), in which 9 patients had a PC-related death, with a median OS of 39 months (95% CI: 22,13-55,87). Figure 1 shows the OS curve of the cohort.

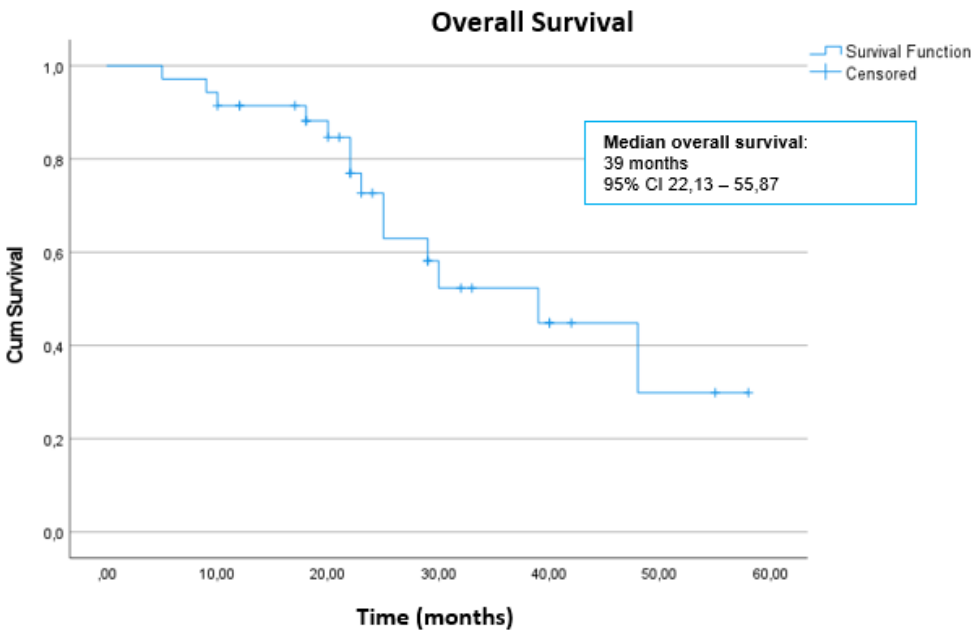

***Figure 1** – Kaplan-Meier curve for overall survival*

A subgroup analysis revealed no statistically significant difference in the OS of patients with low-volume disease (39 months) and high-volume disease (30 months) (p=0,488), which is presented in figure 2.

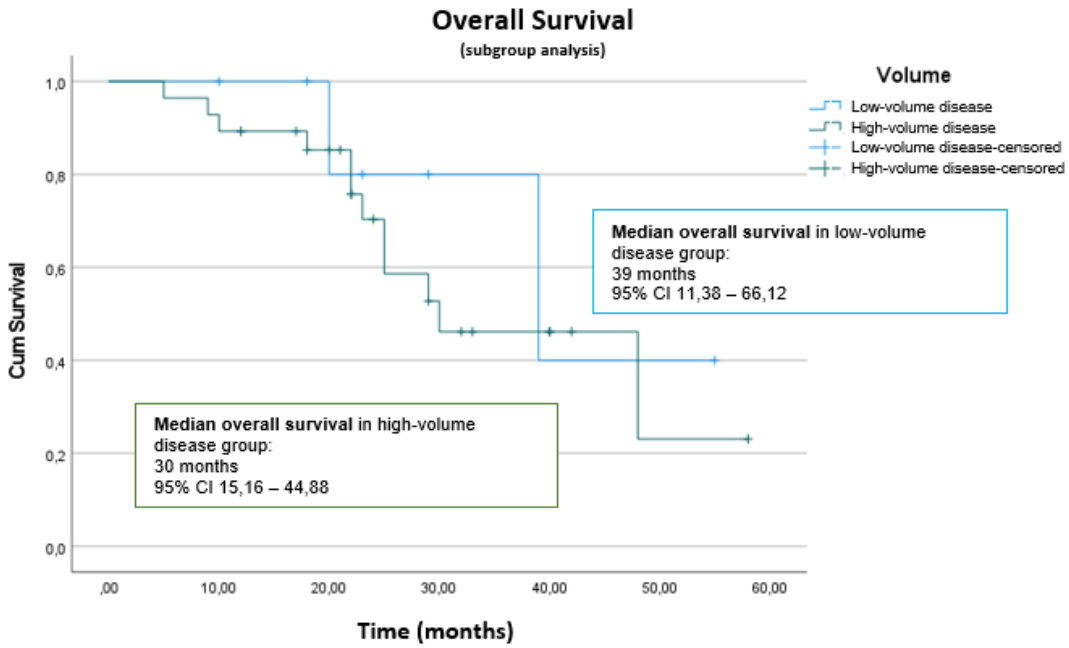

Figure 2 *– Kaplan-Meier curve for overall survival in subgroups: low-volume disease group versus high-volume disease group*

Biochemical Response

The median PSA level at diagnosis was 172,2 ng/mL (IQR: 59,8-449,2) and biochemical response – decrease in serum PSA levels of at least 50% in 12 weeks – was observed in 71,9% of the cohort, with a median PSA nadir of 1,32 ng/mL (IQR: 0,34-37,8).

Biochemical Progression

PSA progression occurred in 60% of the patients (21 out of 35) and the median time to biochemical progression was 12 months (95% confidence interval (CI): 8,06-15,95). The biochemical progression-free survival curve is shown in figure 3.

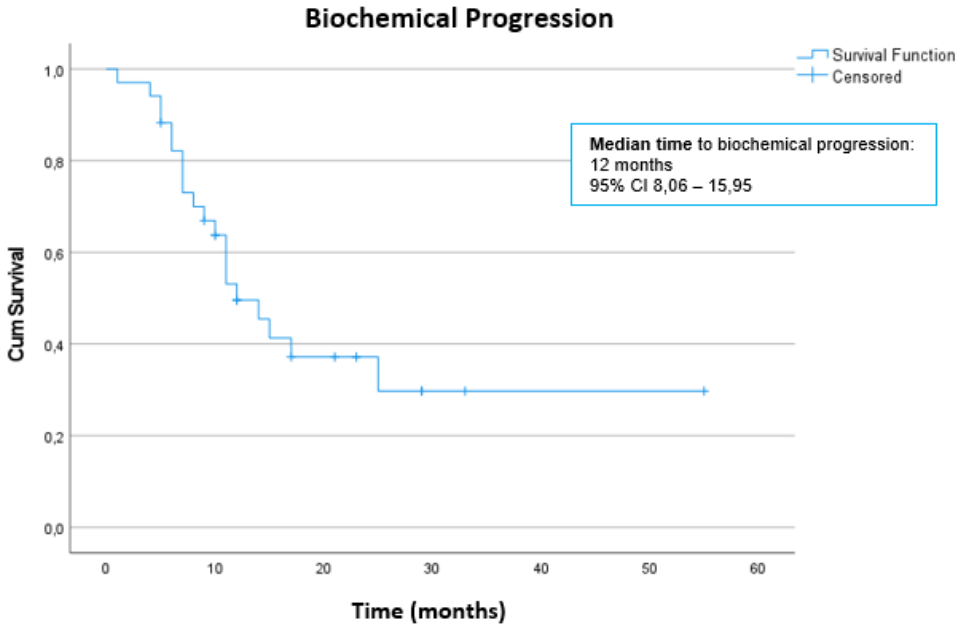

Figure 3 *– Kaplan-Meier curve for biochemical progression-free survival rate*

Radiological Progression

55,9% of patients had radiologic progression (19 out of 34). Figure 4 shows the radiological progression-free survival curve. The median time to radiological progression was 24 months (95% CI: 16,33-21,67). As expected, biochemical progression foregoes radiologic progression of the disease.

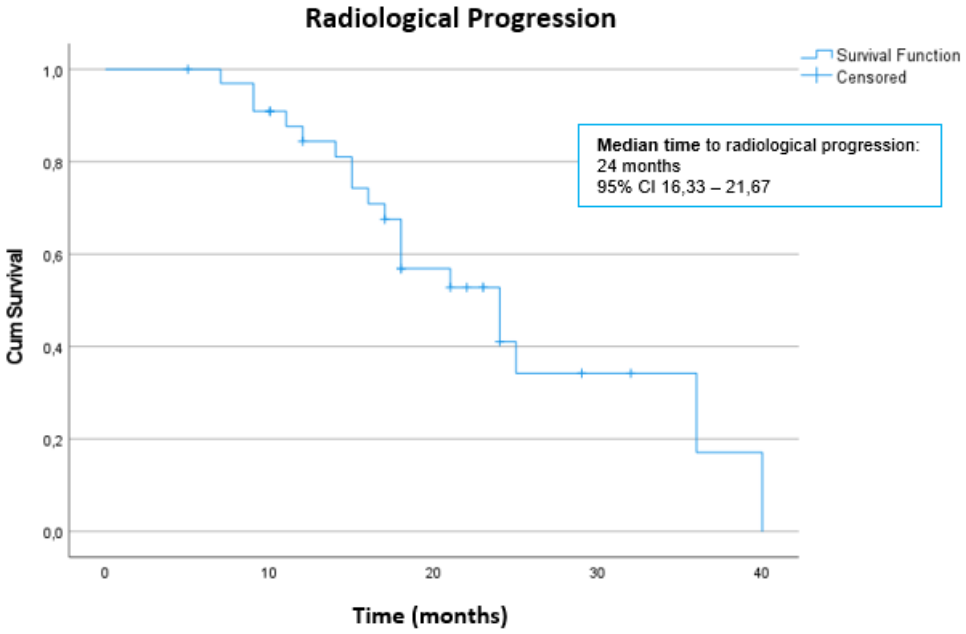

Figure 4 – Kaplan-Meier curve for radiological progression-free survival rate

Subsequent treatment after progression

At the time of the analysis, 19 patients received subsequent treatment due to disease progression after DOC plus ADT. The majority had either a re-challenge of DOC (31,6%), or received one of the novel hormonal agents, enzalutamide (26,3%) and abiraterone (26,3%). One patient received subsequent treatment with cisplatinum/etoposide and to another was given cabazitaxel. These treatments potentially affected the OS.

DISCUSSION

DOC was firstly approved for the treatment of mCRPC and only more than a decade later was authorised for mHSPC patients,[13,14] supported by three large phase III trials and one meta-analysis to consider it as a standard option in mHSPC.[12,15-17]

Data from randomized controlled trials (RCT) does not necessarily provide suitable information to judge the impact of a new treatment in a population considering that RCT mainly response the question of efficacy and clinicals need to know the effectiveness. The difference between RCT populations and real-world populations could result in contrasting results and lower efficacy. So, the main goal the present this study was to determine the effectiveness of using DOC pus ADT in a Portuguese cohort with mHSPC.

The GETUG-AFU-15 trial enrolled 385 patients to evaluate the benefit of adding DOC to ADT in mHSPC patients. It surprisingly shown the combination did not significantly increase OS: 58,9 months in DOC/ADT group vs. 54,2 months in ADT group.[15] This result was later explained by the impact of metastatic burden in a long-term survival analysis.[18] In CHAARTED trial, 790 patients were randomized for ADT plus DOC or ADT only and reported a median follow-up of 28.9 months. It showed a median OS 13,6 months longer favouring ADT plus DOC therapy.[12] These findings were also corroborated by the results of the STAMPEDE trial, which included 1086 mHSPC patients and compared the same two groups – ADT/DOC vs. ADT: during a median follow-up of 78.2 months the combination therapy had a clear evidence of improved survival rate.[16]

Considering this, we can conclude that adding DOC to ADT is beneficial in mHSPC patients and further systematic reviews and meta-analysis of CHAARTED, GETUG-AFU-15 and STAMPEDE trials indicated that DOC plus ADT should be considered standard of care for men with mHSPC who are starting treatment for the first time.[17]

This study's cohort is slightly older, has higher PSA at diagnosis and a greater percentage of patients with high-volume disease than populations from studies that approved DOC.[12,15,16] This may be explained by the usual tendency of clinical trials using fitter patients. However, in this cohort a lower median ISUP score is registered compared to the mentioned RCT.

The OS, a main endpoint in our study, was 39 months, lower than it was achieved in the previously cited RCT: 58,9, 57,6 and 59,1 months in GETUG-AFU-15, CHAARTED and STAMPEDE, respectively.[12,15,16] Firstly, it can be explained by the differences in populations' characteristics, as this cohort had clinical features which can predict worse prognosis; second, we had a considerably high mortality rate (40%). Besides, we only evaluated patients with

mPC *ab initio* but not patients who had disease progression after local treatment. Concerning the volume disease sub-analysis, our findings agree with STAMPEDE trial results, in which no difference in OS was found between low-volume and high-volume disease.[16]

Regarding biochemical response, our cohort achieved a response of 71,9%. It is hard to compare with RCT results because each study uses different definitions for biochemical response. Comparing to GETUG-AFU-15 study we got a lower response but using stricter criteria.[15] When analysing CHAARTED results, we achieved an higher response rate but with larger criteria.[12]

Other important and clinically relevant endpoints are biochemical and radiological progression, which could be considered as predictors of OS and prognosis factors in mHSPC and mCRPC.[19,20] In our study, the median time to biochemical progression was 12 months (95% CI: 8,06-15,95) and the median time to radiological progression was 24 months (95% CI: 16,33-21,67). As the OS, these results were also inferior to the main RCT evaluating DOC in mHSPC.[12,15] We predict the same real-world population bias as causing these differences.

This study has some limitations. First, the sample size is limited and it potentially affects the outcomes. Second being a retrospective study, it is dependent on the quality of the data records. Moreover, the threshold and image modality used to evaluate radiological progression was not specified and it could introduce some bias in this parameter. Finally, the median follow-up period is relatively short.

The main strength of this study is that it evaluates a real-world population with high-volume disease in most of the cases (80%), allowing us to understand what the real impact of RCT results in daily practice is.

CONCLUSION

The effect of DOC plus ADT as the first-line treatment to mHSPC patients has shown great outcomes in RCT. However, there is a lack of information about the effect of this treatment in clinical practice. This work's main value lies in studying the effectiveness in our center. In our cohort the benefit of DOC plus ADT was also shown, although it appears to be less evident than what is reported in RCT and to our knowledge it is likely related to differences in population characteristics. We hypothesize the use of fitter patients in RCT as the main difference to this real-world result.

Studies like this are needed mainly to confront RCT results with what we can really achieve in the daily practice. Further reports on this theme, with wider samples sizes, might provide a better understanding of the outcome of DOC plus ADT therapy in clinical practice.

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