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ASSESSMENT OF ADDITION DOCETAXEL TO ANDROGEN DEPRIVATION THERAPY FOR PATIENTS WITH HORMONE-SENSITIVE METASTATIC PROSTATE CANCER : EXPERIENCE OF THE ONCOLOGY/HEMATOLOGY CENTER OF MED VI UNIVERSITY HOSPITAL CENTER, MARRAKECH

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ABSTRACT

Background: Prostate cancer (PCa) is a major health problem with more than three hundred thousand deaths worldwide. Androgen deprivation treatment (ADT) was the standard for first-line metastatic disease with survival ranging from 31 to 49 months. However, most patients developed ADT resistance with a median sensitivity duration estimated at 36 months. At an early stage, in patients with hormone-sensitive metastatic prostate cancer 3 randomized trials were performed, comparing 2 arms (ADT alone as standard to an experimental arm combining ADT with docetaxel), and have revealed survival outcomes that are not all statistically significant. The aim of this work is to assess the efficiency and the tolerance of the association ADT + docetaxel in the metastatic prostate cancer hormono-sensitive in 1st line.

Methods : This is a retrospective study conducted from March 2015 until December 2017 in the Oncology/Hematology Center of the Med VI University Hospital Center in Marrakech. All patients under supervision and treatment for metastatic prostate cancer evaluated after 3, 6,9 and 12 months with a high volume disease are part of our study. Patients were assigned to docetaxel at a dose of 75 mg per square meter of body-surface area given every 3 weeks for six cycles cycles without prednisolone combined to medical castration by goserelin 10.8 mg and zoledronic acid. The parameters studied were epidemiological data, response rate, psa rate, and tolerance.

Results : A total of 12 patients under supervision for metastatic prostate cancer were gathered in the Oncology / Hematology Center of the VI Med University Hospital Center in Marrakech. At the end of the 12-month evaluation period , 9 patients (75%) had a clinical benefit (partial response and clinical stability), , 2 patients had radiological progression. The proportion of patients who decreased their PSA level to less than 6 ng per milliliter at 12 months was 42%.

A complete clinical response with motor recovery was observed in a patient with spinal metastases and spinal cord compression D5-D7. No death has been recorded. The toxicities mostly encountered were neutropenia with 42% grade 3-4 neutropenia and 17% febrile neutropenia, 17% grade 3 allergy reactions ,25% grade 3 diarrhea and 8% grade3 peripheral neuropathy.

Conclusion : The results obtained in this small series are encouraging and have demonstrated the efficacy and tolerance of the ADT plus docetaxel combination. Our study suggests the importance of conducting further national studies for this type of patients given the prevalence of metastatic prostate cancer in Morocco.

KEYWORD

metastatic prostate cancer, hormone-sensitive, docetaxel and ADT, Efficacy, Toxicity.

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INTRODUCTION :

Prostate cancer (PCa) is a major health problem with more than three hundred thousand deaths worldwide [1]. In Morocco, it is the 2nd most common cancer after the lung with an incidence of 16% [2]. In less developed countries, metastatic disease is the most common presentation of prostate cancer. More than 70 years ago, Huggins and Hodges and Niehans proved the effectiveness of castration in symptomatic metastatic prostate cancer Androgen deprivation treatment (ADT) was the standard for first-line metastatic disease with survival ranging from 31 to 49 months, before the combination of new active treatments [3]. However, most patients developed ADT resistance with a median sensitivity duration estimated at 36 months [4]. In the castration resistance phase, chemotherapy with docetaxel plus prednisone resulted in an increase in median survival of approximately 2.5 months longer than mitoxantrone and prednisone [5]. At an early stage, in patients with hormone-sensitive metastatic prostate cancer 3 randomized trials were performed, comparing 2 arms (ADT alone as standard to an experimental arm combining ADT with docetaxel [6]. These trials are contradictory and have revealed survival outcomes that are not all statistically significant. . The aim of this work is to assess the efficiency and the tolerance of the association ADT + docetaxel in the metastatic prostate cancer hormono-sensitive in 1st line.

Patients and method:
This is a retrospective study conducted from March 2015 until December 2017 in the Oncology/Hematology Center of the Med VI University Hospital Center in Marrakech. Eligible patients had a pathological diagnosis of prostate cancer with ECOG performance-status score of 0, 1, or 2 , radiologic evidence of metastatic disease with a high volume disease (high volume defined by the existence of visceral metastases and / or 4 or more bone metastases with at least 1 at the pelvis or spine). , and who was assessed (clinically and radiologically) after 3, 6, 9 and 12 months. Patients were assigned to docetaxel at a dose of 75 mg per square meter of body-surface area given every 3 weeks for six cycles without prednisolone combined to medical castration by goserelin 10.8 mg and zoledronic acid. We used an androgenic anti for one month to avoid flare up syndrome.

The parameters studied were epidemiological data, response rate, psa rate, and tolerance.

Clinical evaluation was performed at three cycles. Tumor assessments, based on RECIST (version 1.1), were performed every 9 weeks.

Adverse events were monitored regularly and were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).

Statistical method
Descriptive data analysis was performed with the use of Excel 2010 software.

RESULTS:
A total of 12 patients under supervision for metastatic prostate cancer were gathered in the Oncology / Hematology Center of the VI Med University Hospital Center in Marrakech. The initial characteristics of the patients are shown in Table 1. The median age of our series is 69 years with extremes of age ranging from 65 to 81 years. The median follow-up was 26, 8 months.

At the end of the 12-month evaluation period , 9 patients (75%) had a clinical benefit (partial response and clinical stability), 2 patients had radiological progression. A complete clinical response with motor recovery was observed in a patient with spinal metastases and spinal cord compression D5-D7 . No death has been recorded The proportion of patients who decreased their PSA level to less than 6 ng per milliliter at 12 months was 42%.

The main reported toxicities were neutropenia with 42% grade 3-4 neutropenia and 17% febrile neutropenia, 25% grade 3 diarrhea, 17% grade 3 allergy reactions, and 8% grade3 peripheral neuropathy. A dose reduction of doses to 50 mg per square meter of body-surface area given was required in three patients.

DISCUSSION:
The survival of metastatic prostate cancer has been significantly improved thanks to the many therapeutic advances made. This study was designed to evaluate the efficacy and safety of the ADT plus docetaxel combination in hormone-sensitive metastatic prostate cancer.

In our study, the median age was 69 years. These results are similar to those found by CHAARTED and GETUG AF -15 [7,8].

Three large phase III trials (GETUG AF-15, CHAARTED and STAMPEDE), tested this combination with not all positive results in overall survival [7]. Chaarted and Stampede achieved median overall survival respectively of 57.6 months (HR = 0.61, 95% CI: 0.47-0.80, p <0.001) and 81 months (HR = 0.78, 95% CI: 0.66-0.93, p = 0.006). in favor of the ADT + docetaxel arm [9]. In the GETUG AF-15 study the overall median survival was 58.9 months (95% CI: 50.8-69.1) in the ADT plus docetaxel group and 54.2 months in the ADT alone group (HR = 1.01, 95% CI: 0.75-1.36) , which means that the main objective of this trial has not been achieved [7].

However, there are differences between the populations included in the 3 trials. 98% of the patients included in GETUG-AFU 15 were ECOG 0, versus only 69% in CHAARTED and 72% in the control group of Stampede. Regarding the proportion of patients with metastases at the time of diagnosis, she was the same in GETUG-AFU 15 and CHAARTED but the proportion of the disease at high volume was higher important in CHAARTED. There was no information on the volume of metastases in the Stampede Trial. The Gleason score was higher in CHAARTED and STAMPEDE.

A meta-analysis of these three trials was conducted and confirmed a 9% absolute improvement in overall survival at 4 years with the combination of docetaxel and ADT in hormone-sensitive metastatic prostate cancer [10] .

Several other no phase 3 studies have tried to evaluate the combination docetaxel plus ADT. Botrel et al. which included 3 studies with a total of 2262 subjects. The median follow-up was 29-83.9 months. All studies used as a protocol docetaxel 75 mg / m2 every 3 weeks (6-9 treatments on average). They demonstrated that the combination of docetaxel and ADT was superior to ADT alone in overall survival (HR 0.64, 95% CI 0.55, 0.75, p <0.0001, NNT = 3), biochemical-free survival (HR 0.63, 95% CI 0.57, 0.69, p <0.0001, NNT = 2) and clinical progression-free survival (HR 0.73, 95% CI) % 0.64, 0.84, p <0.0001, NNT = 2) [11].

As looks at the toxicity, the toxicities found in the literature are especially those common to docetaxel: neutropenia, anemia, thrombocytopenia, peripheral sensory neuropathy, peripheral motor neuropathy, febrile neutropenia, gastrointestinal reactions (fatigue, diarrhea, nausea and vomiting), alopecia and cutaneous reactions. In the CHAARTED study, Grade 3 -5 adverse events were 29% in the ADT + docetaxel arm and 52% in STAMPEDE [12]. In our study, the proportion of Grade 3-4 adverse events was 51%.

CONCLUSION:
The results obtained in this small series are encouraging and have demonstrated the efficacy and tolerance of the ADT plus docetaxel combination. Our study suggests the importance of conducting further national studies for this type of patients given the prevalence of metastatic prostate cancer in Morocco.

Conflicts of interest
The authors do not declare any conflicts of interest

What is already know on this topic
- Metastatic prostate cancer is a poor prognosis disease
- Androgen deprivation treatment combined with docetaxel is the standard in hormono-sensitive in 1st line
- The non-negligible side effects of combination, responsible for the reduction of the dose

What this study adds
- The efficiency and the tolerance of the combination androgen deprivation treatment with docetaxel
- The experience of treatment of an African center.

- The incidence of metastatic prostate cancer in Morocco.

Table 1: Base line Characteristics of the patients

Base line Characteristics of the patients	
Age (yr) **Median (yr)**	69 65-81
ECOG performance status **1** **2**	 2 10
PSA level at start of ADT- ng / ml **Median (ng / ml)** **Range (ng/ ml)**	 64 6-182
Extent of disease (%) **Bone metastases** **Visceral disease**	 100 12

Table 2: Patients distribution according their evaluation after 12 months of supervision

Evaluation after 12 months	Patients (Nos)	Proportion (%)
clinical benefit (clinical and radiological stability)	9	75
Complete clinical response	1	8.33
Progression	2	16.66
PSA level <0.2 ng/ml at 12 mo	5	41.66
Death	0	0

Table 3: Adverse events of grade3 or higher

Adverse Events	Grade3	Grade4 No of patients (%)	Grade5
Neutropenia	3 (25)	2(16.66)	0
Febrile neutropenia	0	2(16.66)	0
Allergic reaction	2(16.66)	0	0
Diarrhea	3 (25)	0	0
Neurpathie sensory	1(8.33)	0	0

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