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# Complete Response To Enzalutamide In A Patient With Metastatic Hormone-Sensitive Prostate Cancer : What About Therapeutic De-Escalation?

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***Abstract*** **- Androgen receptor pathway inhibitors (ARPIs) with or without docetaxel have revolutionised the treatment of metastatic castrate-sensitive prostate cancer.**

**Case presentation: A 78-year-old patient with low-volume de no vo metastatic prostate cancer was started on enzalutamide at a dose of 160 mg per day along with triptoreline every three months. Within 6 months, the patient achieved a complete prostate-specific antigen response. Follow-up 18F-fluorocholine positron emission tomography showed no area of pathological metabolic activity. Treatment was well tolerated over 36 months.**

***Conclusion:*** **Complete response to ARPI is an emerging situation that deserves further consideration.**

***Index Terms:*** **enzalutamide, metastatic, castrate-sensitive, prostate cancer, complete response**

## I. INTRODUCTION:

Prostate cancer is a global health problem and is the third most common cause of cancer death in men (1). The use of early detection strategies in favour of conventional screening appears to be influencing the epidemiological profile of this disease, with a consequent increase in hormone-sensitive metastatic forms (2).

Metastatic prostate cancer is a heterogeneous disease. For many years, the treatment of metastatic prostate cancer was based on androgen deprivation therapy (ADT) alone, either by surgical or medical castration (3).However, the emergence of new therapies has broadened the therapeutic armamentarium and improved patient survival. Nowadays, deprivation What to do in the event of a complete response after intensified therapy is still unclear.

must be part of a strategy of therapeutic intensification, including chemotherapy, new hormonal agents (NHA) or even triplet therapy in selected patients. Intensification also includes local treatment of the prostate and/or metastases.

We report the case of a Moroccan patient with newly diagnosed metastatic castrate-sensitive prostate cancer (mCSPC) who achieved a complete morphological response after ADT combined with NHA.

## II. CASE REPORT

A 78-year-old man with no significant medical history presented to our hospital with pelvic pain associated with acute urinary retention for which transurethral resection of the prostate was performed. Histological examination revealed a poorly differentiated prostatic adenocarcinoma, Gleason 8 (4+4). The baseline PSA level was 57.66 ng/ml. An extended work-up was indicated. A bone scintigraphy revealed an osteocondensing lesion of the left ischio-pubic ramus (Figure 1). A thoracic-abdominopelvic computed tomography scan showed no visceral lesions. 18 F-fluorocholine positron emission tomography (FCH-PET) showed pathological hypermetabolism in the prostate, left external iliac lymph node and left ischio-pubic ramus (Figure 2a,b-c).

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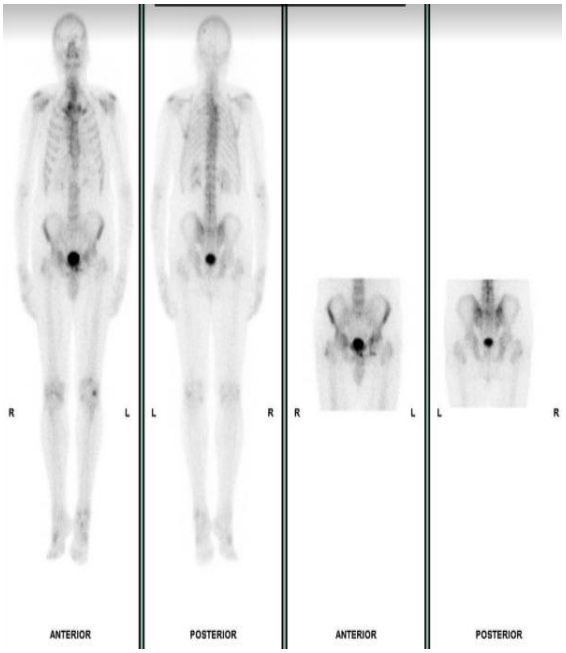


Figure 1: Bone scintigraphy showing an osteocondensing lesion of the left ischio-pubic ramus.

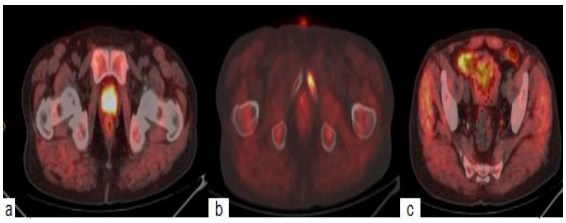


Figure 2: FCH-PET showing pathological hypermetabolism in the prostate (a), left ischio-pubic ramus (b) and left external iliac lymph node (c).

The decision made at the multidisciplinary consultation was to start the patient on LHRH agonist ADT: Triptorelin 11.25 mg every three months, in addition to enzalutamide as NHA 160 mg daily, with regular assessment of disease progression and good tolerability.

After three months of treatment, the patient reported a clear clinical benefit with resolution of pain and resumption of normal daily activities. The PSA level decreased to 0.57 ng/ml at 3 months and 0.1 ng/ml at 6 months.

Morphologically, FCH-PET showed a complete metabolic response with disappearance of target lesions in bone and lymph nodes.

Given the good tolerability of the treatment and the good clinical, biological and morphological evolution, it was decided to continue with the same treatment.

The patient subsequently received prostate radiotherapy. The complete response has been maintained after 27 months of treatment.

## III. DISCUSSION

mCSPC is a highly heterogeneous entity. Treatment selection should take into account prognostic factors often used to stratify patients in clinical trials, such as the number and location of bone metastases, the presence of visceral metastases, the synchronous or metachronous nature of metastases, and the Gleason score of the primary tumour (4). Patients are thus classified according to tumour volume or risk of progression. However, these definitions appear to be quite consistent, with the majority of "high volume" patients corresponding to "high risk" patients (5).

One of the intensification pathways in mCSPC has been the introduction of chemotherapy at the start of castration, suggesting a potential efficacy of chemotherapy on a smaller tumour volume with fewer resistant tumour clones. 3 randomised trials (GETUG-AFU 15, CHAARTED and STAMPEDE) and their meta-analysis have therefore established the combination of ADT and docetaxel as the standard treatment for synchronous mCSPC (6), with an improvement in overall survival and morphological progression-free survival at the expense of an early and transient deterioration in quality of life. This benefit appears to be limited to high tumour burden, defined in the CHAARTED trial (7) as the presence of visceral metastases or the presence of 4 or more bone metastases, at least one of which is extravertebral or pelvic.

The efficacy of abiraterone, an androgen synthesis inhibitor, was evaluated in LATITUDE, a phase III, double-blind study in patients with high-risk de novo metastatic prostate cancer. High risk was defined by at least 2 of the following 3 criteria: a Gleason score ≥8, the presence of at least 3 lesions on bone scan and the presence of measurable visceral lesion(s). Increased ADT with abiraterone resulted in a 38% reduction in the risk of death and a 53% reduction in the risk of progression. There was also a significant improvement in all secondary endpoints assessed: time to PSA progression, progression of painful symptoms, time to new skeletal event, initiation of chemotherapy or other specific treatment (8). In addition to these benefits, there is an improvement in quality of life compared to ADT alone. Exploratory analyses support the use of abiraterone in combination with ADT regardless of the risk of disease progression (9).

After docetaxel and abiraterone acetate, enzalutamide, a potent androgen receptor axis targeted therapy (ARPI), positioned itself as a third option for patients with mCSPC following the results of the ENZAMET trial (10), a randomised phase III trial comparing ADT in 1125 patients with either enzalutamide or a first-generation androgen receptor inhibitor. The primary objective of the study was met with a gain in OS with a 33% reduction in the risk of death. This benefit was seen across all disease volumes. It was confirmed in another study (ARCHES) with a significant 61% reduction in the risk of radiographic progression and in the risk of death in patients on dual therapy (11).

TITAN is a phase III study that investigated the addition of apalutamide in patients with mCSPC. After a median follow-up of 44 months, the overall survival benefit was confirmed. The safety profile was satisfactory. Its long-term results confirm the place of the new ARPI in the initial treatment of mCSPC, regardless of the patient subgroup (12).

Regarding the place of a combination of docetaxel plus NHA versus NHA alone. PEACE-1(13) and ARASENS(14) suggest that the triplet appears to be more effective than the combination of ADT plus docetaxel. The addition of an NHA (abiraterone acetate in one case, darolutamide in the other) to ADT combined with docetaxel chemotherapy confers a significant overall survival benefit compared with ADT plus docetaxel. Tolerance is as expected with any agent. Toxicity was greater with the combination of chemotherapy and NHA. The question of the real benefit of docetaxel in this triplet approach has not been evaluated. However, it seems important to define the patients who are most likely to benefit from this intensification of therapy.

Loco-regional treatment can also be escalated. The STAMPEDE trial supports the clinical interest of prostate irradiation in cases of de novo metastatic prostate cancer with low tumour volume as defined by conventional imaging (15). Common sense would also dictate that irradiation should include both the prostate and metastases in a maximal stereotactic approach to control the disease. Furthermore, data from randomised trials do not allow a clear conclusion to be drawn about the efficacy of local treatment of metastases, even in the context of metachronous metastases (16-17).

The choice of systemic treatment in our patient seems to be justified by the favorable tolerance profile of NHA but also and above all by the significant improvement in radiological progression-free survival and overall survival of therapeutic intensification with enzalutamide attested by two randomized studies. This benefit is obtained regardless of the risk and tumor volume. After 6 months of treatment, he had a complete metabolic response with an undetectable PSA. The response to treatment, easily assessed by PSA, is optimized by therapeutic intensification protocols. In the CHAARTED study, there were significantly more patients with a PSA nadir $\leq$ 0.2 ng/ml in the arm that received docetaxel (32% vs 19% at 6 months, 27% vs 16% at 12 months). Enzalutamide significantly increases the rate of undetectable PSA in the ARCHES study (68.1% vs 17.7%).

PSA nadir <0.2 ng/ml has been validated as a prognostic factor in mCSPC. In the ARASENS trial, undetectable PSA at 24 months was predictive of a good prognosis. In TITAN, deeper and earlier ultra-low PSA decline ($\leq$0.02 ng/ml) with apalutamide was associated with improved outcomes, including long-term survival and radiographic progression-free survival. In PEACE-1, radiographic progression-free survival and overall survival were also significantly better in patients with a PSA $\leq$ 0.2 ng/ml at 8 months. Morphological objective response data were only reported with enzalutamide in ARCHES, with a significant benefit in favour of the ADT + enzalutamide arm (83.1 vs. 63.7%), and complete responses were achieved with enzalutamide in castrate-refractory prostate cancer (complete response in the order of 20% in PREVAIL).

The management of a complete metabolic response is not well codified. The design of the original trials was to continue treatment until progression or intolerance. Discontinuation of NHA in the case of a complete response can be discussed if the decision is shared with the patient and validated in a multidisciplinary consultation. The median duration of treatment before discontinuation remains to be determined.

## IV. CONCLUSION

The treatment of mCSPC has been revolutionised by the advent of NHA, and a complete response can have both a positive physical and psychological impact on patients. The approach to be adopted in these cases needs to be evaluated in dedicated clinical trials.

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