Original Study

Impact of Enzalutamide Administration on Primary Prostate Cancer Volume: A Metabolic Evaluation by Choline Positron Emission Tomography in Castration-Resistant Prostate Cancer Patients

Orazio Caffo,[1] Francesca Maines,[1] Davide Donner,[2] Antonello Veccia,[1] Franca Chierichetti,[2] Enzo Galligioni[1]

Abstract

Enzalutamide is an efficacious drug in the treatment of castration-resistant prostate cancer. Its metabolic effects were assessed by ^{18}F-fluorocholine-positron emission tomography/computerized tomography. In 12 patients, the enzalutamide administration produced a significant volume reduction of the primary tumor. Our results could suggest the potential efficacy of enzalutamide therapy for localized prostate cancer.

Background: Enzalutamide is active in advanced castration-resistant prostate cancer (CRPC) patients, in whom it has shown to be able to increase survival. We report the enzalutamide effect on primary prostate tumors, assessed by changes of metabolic tumor activity detected by ^{18}F-fluorocholine-positron emission tomography/computerized tomography (^{18}F-FCH PET/CT). **Patients and Methods:** We treated 31 patients with pretreated metastatic CRPC in an enzalutamide named-patient program. All patients were initially evaluated and then followed up by means of repeated ^{18}F-FCH PET/CT examinations. We identified most radiotracer-avid lesions, which were defined as specific regions of interest (ROIs): for each ROI we defined the maximum radiotracer standardized uptake value (SUV_{max}) and the threshold-based volume of interest (VOI) with a cutoff SUV value ≥ 2.5. In the 12 patients who did not receive a radical treatment for localized disease, the prostate was also considered an ROI. **Results:** The baseline prostate median SUV_{max} of 7.25 showed reductions of 25% ($P = .012$) and 43% ($P = .009$) after 3 and 7 months of enzalutamide treatment, respectively. The baseline median prostate VOI of 12.73 cm^3 showed a reduction of 73% ($P = .002$) at 3 months and a reduction of 90% ($P = .005$) at 7 months. **Conclusion:** In addition to the metabolic changes of metastatic lesions observed with enzalutamide in CRPC patients, our data have shown significant volume reductions of the primary tumors according to ^{18}F-FCH PET/CT evaluation. These results could suggest the potential of enzalutamide therapy for localized prostate cancer.

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Introduction

Androgen receptor (AR)-mediated signaling is critical to the growth and survival of prostate cancer cells not only during the hormone-sensitive phase of the disease but also when a condition of castration resistance is developed. In fact castration-resistant prostate cancer (CRPC) is characterized by AR overexpression, amplification, and mutations that enhance the cells sensitivity to even minimal levels of androgens.[1]

For this reason, drugs interfering with AR machinery could be active in CRPC. Enzalutamide, a novel, second-generation AR antagonist, acts by blocking the AR axis at 3 different levels: it binds ARs, prevents their nuclear translocation, and inhibits coactivator recruitment of the ligand receptor complex.[2] This drug has demonstrated its efficacy in treating CRPC by increasing survival in patients who had received docetaxel-based first-line chemotherapy.[3] Because of its potent ability to block the AR axis, it could be

[1]Department of Medical Oncology
[2]Department of Nuclear Medicine
Santa Chiara Hospital, Trento, Italy

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Address for correspondence: Orazio Caffo, MD, Medical Oncology Department, Santa Chiara Hospital, Largo Medaglie d'Oro 38100, Trento, Italy
E-mail contact: orazio.caffo@apss.tn.it

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postulated that enzalutamide is active in controlling primary prostate cancer, although, to date, no data are available concerning this possibility or the ability of enzalutamide in tumor downsizing. This article presents a prospective evaluation of enzalutamide's effect on primary prostate tumors by changes of metabolic tumor activity detected by ^{18}F-fluorocholine-positron emission tomography/computerized tomography (^{18}F-FCH PET/CT).

Patients and Methods

Enzalutamide is, to date, not available for daily clinical practice in Italy, but it is expected to be approved by Italian regulatory authorities in the near future. However, it was previously available in our country by means of expanded access or named-patient programs supervised by local ethics committees to allow CRPC patients to receive the drug after docetaxel failure.

Our hospital conducted an enzalutamide named-patient program, that started in November 2012 and continued until March 2013. All enrolled patients (n = 31) had progressive metastatic CRPC after having received first-line docetaxel-based chemotherapy.

The enzalutamide was administered at a standard dose of 160 mg once a day, and the patients continued luteinizing-hormone releasing hormone (LHRH) agonist treatment that they had been administered before the start of the drug. During the enzalutamide treatment, the patients were assessed monthly to check their hematologic parameters and prostate-specific antigen (PSA) levels. They also were followed up by means of repeated ^{18}F-FCH PET/CT examinations using a protocol shared with the Nuclear Medicine Department: ^{18}F-FCH PET/CT imaging was performed at the baseline, after the first 3 treatment months, and thereafter every 4 months. ^{18}F-FCH PET/CT was performed by a Biograph Sensation 64 (Siemens SPA, Milan, Italy) equipped with a 64-slice CT and a dedicated tomograph. Patients were injected with the radiotracer ^{18}F-fluorocholine 1 hour before the acquisition of images and they were in fasting condition. ^{18}F-FCH PET/CT images were viewed and interpreted by a single nuclear medicine physician.

The treatment continued until disease progression, which was defined on the basis of the Prostate Cancer Working Group 2 (PCWG2) criteria.[4] In cases of biochemical progression only during the first 3 treatment months, evidence of instrumental progression was required to stop the therapy. Because the patients were followed up using ^{18}F-FCH PET/CT imaging, instrumental response was evaluated on the basis of the European Organisation for Research and Treatment of Cancer (EORTC) criteria.[5]

The EORTC criteria are based on a semiquantitative analysis that assesses radiotracer uptake values by means of lesion-specific regions of interest (ROIs) drawn on the baseline study (before treatment) and then applied on subsequent scans. The lesions chosen were the most radiotracer-avid, and maximum standardized uptake value (SUV_{max}) was established. Moreover, we recorded the threshold-based volume of interest (VOI) with a cutoff SUV value $\geq$ 2.5. In cases of patients who did not receive a radical treatment (surgery or radiotherapy) for localized disease, the prostate was also submitted as an ROI for evaluation: prostate SUV_{max} and VOI were recorded at each time point assessment.

The changes of SUV_{max} and VOI were compared with the baseline values by Wilcoxon matched pairs signed rank sum test.

The data were statistically analyzed using SPSS version 12 (IBM, Armonk, New York).

The present paper focused on metabolic changes in prostate ROI, while the changes observed in metastatic ROIs will be reported in a separate paper.

Results

A consecutive series of 31 patients received enzalutamide: 16 patients who had received a radical treatment for prostate cancer (10 prostatectomy and 6 external radiotherapy) were excluded from the analysis; in 3 more patients who had bladder catheter at the baseline ^{18}F-FCH PET/CT assessment, prostate ROI was not evaluable, so they were also excluded from the present analysis. The remaining 12 patients were reevaluated at the first assessment point and were considered evaluable for the purpose of the present study; their characteristics are shown in Table 1. Data from the 3-month ^{18}F-FCH PET/CT imaging are available for all evaluable patients, whereas data from the 7-month ^{18}F-FCH PET/CT imaging are available for 10 patients (2 patients had progressed by the previous assessment and stopped the treatment).

Metabolic outcomes of the prostate ROI analysis are shown in Table 2. At baseline, the prostate median SUV_{max} was 7.25 (range, 4.13-14.17). After 3 months of enzalutamide treatment, the median SUV_{max} decreased to 5.44 (range, 2.25-9.94), for a reduction of 25% (P = .012). After 7 months of enzalutamide treatment, the median SUV_{max} was 4.13 (range, 2.80-8.63), for a reduction of 43% (P = .009). There was a not complete concordance between the metabolic changes at the prostate ROI and the remaining ROIs corresponding to the metastatic sites, whereas biochemical response reflected the SUV_{max} changes in most of the cases (Table 2).

The baseline median prostate VOI was 12.73 cm^3 (range, 1.22-684.44 cm^3). At 3 months, it decreased to 3.44 cm^3 (range, 0.01-56.73 cm^3), for a reduction of 73% (P = .002); after 7 months, the median prostate VOI remained 1.27 cm^3 (range 0.01-12.50 cm^3), for a reduction of 90% (P = .005). The prostate VOI significantly decreased irrespectively of either the metabolic response observed in the metastatic ROIs or biochemical response (Table 2).

Assessing the best SUV_{max} changes in extraprostatic ROIs in all 28 evaluable patients (with or without primary prostate cancer), overall the best metabolic response was partial response in 9 patients (all showing a PSA reduction $\geq$ 50%), stable disease in 9 patients (8

Table 1 Baseline Patient Characteristics (at Enzalutamide Start)

Number of patients	12
Median age, years (range)	77 (59-86)
Median time from diagnosis, mo (range)	62.5 (16-157)
Median number of previous hormonal lines (range)	3 (1-4)
Median number of previous chemotherapy lines (range)	1 (1-2)
Median baseline PSA level, ng/mL (range)	73.04 (21.62-4837)
Disease extension, number of patients (%)	
Bone metastases	11 (92)
Nodal metastases	10 (83)
Visceral metastases	1 (8)