Detection of Early Progression with ^{18}F-DCFPyL PET/CT in Men with Metastatic Castration-Resistant Prostate Cancer Receiving Bipolar Androgen Therapy

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Bipolar androgen therapy (BAT) is an emerging treatment for metastatic castration-resistant prostate cancer (mCRPC). ^{18}F-DCFPyL is a small-molecule PET radiotracer targeting prostate-specific membrane antigen (PSMA). We analyzed the utility of ^{18}F-DCFPyL PET/CT in determining clinical response to BAT. **Methods:** Six men with mCRPC receiving BAT were imaged with ^{18}F-DCFPyL PET/CT at baseline and after 3 mo of treatment. Progression by PSMA-targeted PET/CT was defined as the appearance of any new ^{18}F-DCFPyL–avid lesion. **Results:** Three of 6 (50%) patients had progression on ^{18}F-DCFPyL PET/CT. All 3 had stable disease or better on contemporaneous conventional imaging. Radiographic progression on CT or bone scanning was observed within 3 mo of progression on ^{18}F-DCFPyL PET/CT. For the 3 patients who did not have progression on ^{18}F-DCFPyL PET/CT, radiographic progression was not observed for at least 6 mo. **Conclusion:** New radiotracer-avid lesions on ^{18}F-DCFPyL PET/CT in men with mCRPC undergoing BAT can indicate early progression.

Key Words: PSMA; testosterone; early progression

The imaging of prostate cancer in many parts of the world has recently been revolutionized by the introduction of small-molecule PET radiotracers that bind to prostate-specific membrane antigen (PSMA) (1). PSMA is a transmembrane glycoprotein that is expressed in most prostate cancers (2). Those agents, which include both ^{68}Ga-labeled (e.g., ^{68}Ga-PSMA-11 (3)) and ^{18}F-labeled (e.g., ^{18}F-DCFPyL (4)) compounds, have been shown to have high rates of detection of sites of prostate cancer in a variety of disease states (5).

There is an interplay between androgen signaling and PSMA expression in which blockade of the androgen-signaling pathway leads to upregulation of PSMA (6). Varying responses to androgen-axis–targeted therapies have been observed on serial PSMA-targeted PET studies (7), making it difficult to assess response to such therapies. To date, changes in serial PSMA-targeted PET have not been described in the context of bipolar androgen therapy (BAT).

BAT is being tested as a novel treatment for men with metastatic castration-resistant prostate cancer (mCRPC). Testosterone is administered to supraphysiologic circulating levels, which subsequently decrease over a 28-d cycle back to near-castrate levels (8). All men are maintained on androgen deprivation to suppress endogenous testosterone production from the testes. Several studies have demonstrated the efficacy of BAT as a treatment option for mCRPC patients (9–11). Measuring the clinical benefit of BAT using changes in prostate-specific antigen (PSA) is difficult because radiographic regression of disease has been observed, with stable or rising PSA values (10,11).

A novel imaging strategy to determine patients at high risk of progression on BAT is needed. In this pilot study, we examined changes in ^{18}F-DCFPyL PET imaging after treatment with BAT in men with mCRPC.

MATERIALS AND METHODS

^{18}F-DCFPyL PET/CT imaging was obtained as part of an Institutional Review Board–approved prospective substudy on 2 clinical trials for men initiating treatment with BAT (ClinicalTrials.gov identifiers NCT02286921 and NCT03554317). Written informed consent was obtained from all participants. All participants had mCRPC and prior treatment with at least 1 novel androgen receptor–targeted therapy. PET/CT images were acquired on either a Biograph mCT 128-slice scanner (Siemens Healthineers) or a Discovery RX 64-slice scanner (GE Healthcare) using 3D emission mode with CT-based attenuation correction. Scans were initiated 60 min after the intravenous infusion of 333 MBq (9 mCi) of ^{18}F-DCFPyL with a field of view from the mid thighs through the skull vertex. Images were reconstructed with standard ordered-subset expectation maximization.

All ^{18}F-DCFPyL PET/CT scans were interpreted by a single radiologist who was masked to the details of the patient's disease status while on BAT. Radiotracer uptake outside the normal biodistribution of ^{18}F-DCFPyL was categorized according to the PSMA Reporting and Data System, version 1.0, interpretive framework, and lesions that were category 3A/3B/4/5 were considered positive for prostate cancer (12). SUV_{max} was recorded for all lesions on baseline and follow-up scans (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). According to the study protocol, patients underwent ^{18}F-DCFPyL PET/CT imaging before starting BAT and

TABLE 1

TABLE 1
Best Biochemical, Radiographic, and ^{18}F-DCFPyL Response After 3 Months of BAT

Patient	PSA change	Tumor change	PSMA result
1	93%	Not evaluable	No progression
2	−98%	−44%	No progression
3	−93%	−23%	No progression
4	1%	−11%	Progression
5	−55%	−2%	Progression
6	−63%	−25%	Progression

again after 3 cycles. Clinicians were masked to the results of ^{18}F-DCFPyL PET/CT imaging, and those results were not used in clinical management.

Comparisons were made between the pretreatment and on-treatment PSMA-targeted PET/CT imaging to determine progression. PSMA progression was defined as having one or more new lesions deemed by the interpreting radiologist to be consistent with radiotracer-avid prostate cancer. Radiographic progression on conventional imaging was defined by RECIST, version 1.1 (soft-tissue lesions), and by Prostate Cancer Clinical Trials Working Group 3 guidelines (clinical and bone lesions), and objective response was defined using RECIST (13,14).

RESULTS

Six patients were enrolled. Five of the 6 (83.3%) began BAT on the same day as their baseline ^{18}F-DCFPyL PET scan, and the final patient started BAT the following day. The interval from initiation of therapy to follow-up PET was a median of 84 d (interquartile range, 83.25–87.75). At the time of the follow-up PET, repeat imaging was obtained with CT and bone scanning.

The best PSA and change in tumor response are listed for each patient in Table 1. Four of the 6 (66.7%) patients had a PSA_{50} (decrease in PSA level by 50% from baseline) response, and 1 patient achieved an objective response on conventional imaging. We assessed each patient for progression on PSMA-targeted imaging. Three of the 6 (50.0%) patients had progression on ^{18}F-DCFPyL PET/CT. A description of each ^{18}F-DCFPyL PET/CT lesion is provided in Supplemental Table 1. None of the patients had evidence of radiographic progression on conventional imaging at the time of the follow-up ^{18}F-DCFPyL PET/CT. Two patients, who achieved a PSA_{50} response with stable disease on CT and bone scanning, had new lesions seen on ^{18}F-DCFPyL PET. Neither patient with a PSA_{90} (decrease in PSA level by 90% from baseline) response had progression on ^{18}F-DCFPyL PET/CT. Maximum-intensity projections of the ^{18}F-DCFPyL PET/CT for patients before and during treatment are shown in Figure 1. Many radiotracer-avid lesions became less intense after BAT. For instance, patient 1 had a complete PSMA response to BAT (i.e., 100% reduction in SUV_{max} across all PSMA-avid lesions) in the clinical context of a rising PSA on therapy. Patients 4–6 had at least 1 new PSMA-avid lesion that developed on BAT. In all 3 cases of progression on PET/CT, most ^{18}F-DCFPyL–avid lesions became less intense.

We next explored the relationship between ^{18}F-DCFPyL PET/CT findings and radiographic progression on conventional imaging. In the 3 patients who did not have progression on ^{18}F-DCFPyL PET/CT, radiographic progression on BAT was not observed until 6–9 mo after the second PET/CT scan (Fig. 2). In contrast, all patients with progression on PET/CT had evidence of progression on conventional imaging by 3 mo. In all instances of early progression, the sites of progression on CT or bone scanning correlated with the PSMA-targeted PET findings.
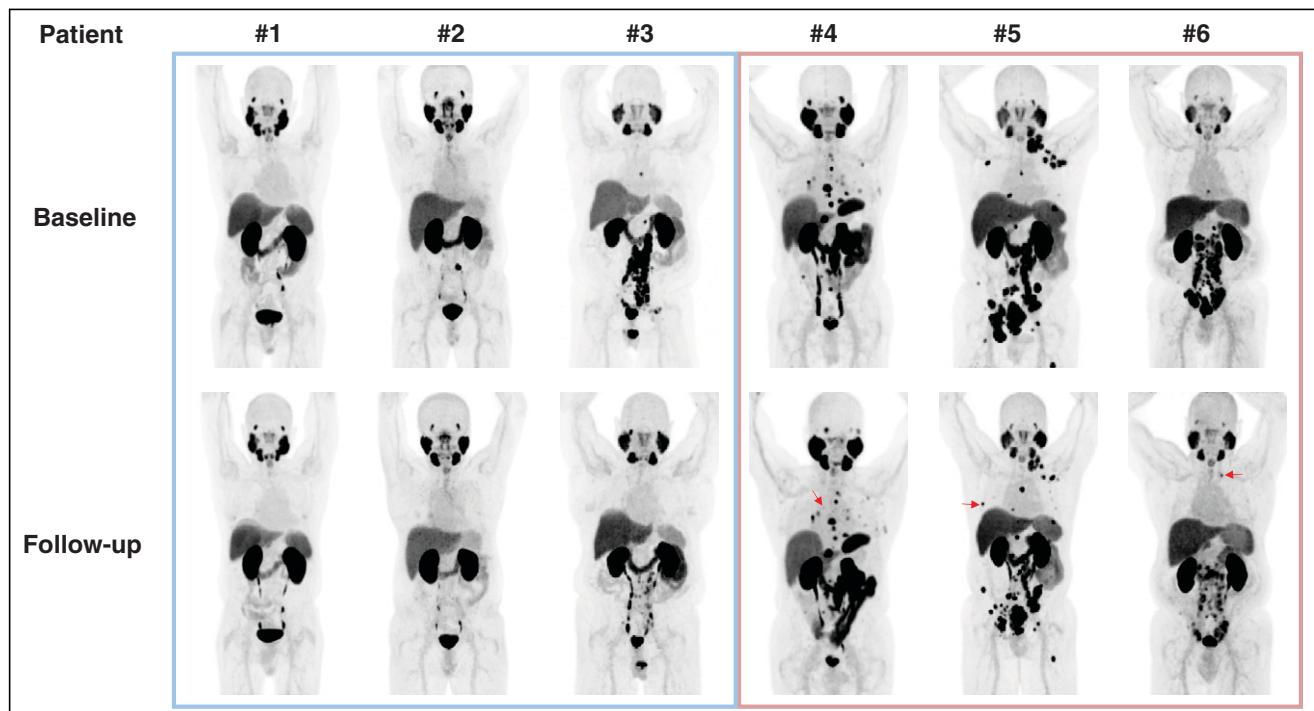
FIGURE 1. Changes in ^{18}F-DCFPyL PET/CT imaging after 3 mo of BAT. Baseline and follow-up maximum-intensity-projection whole-body images are shown for each patient included in study. For patients 4–6, representative new lesions or sites of progression are demarcated with arrows. Additional new lesions may be hidden by normal uptake or other sites of disease.
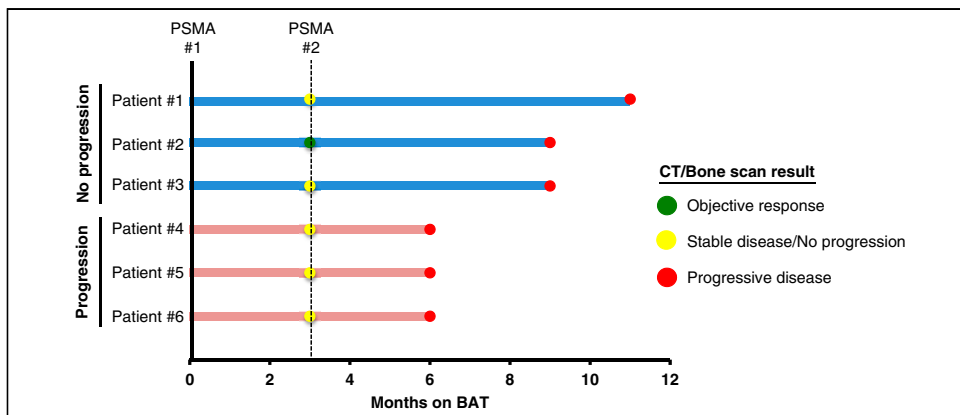
FIGURE 2. Swimmer plot showing radiographic response/progression on BAT. All patients were followed until radiographic progression. ^{18}F-DCFPyL PET/CT imaging was performed before start of BAT and after 3 mo of treatment. Patients 1–3 had no progression noted with ^{18}F-DCFPyL. Patients 4–6 had new ^{18}F-DCFPyL–avid lesions. These data suggest that disease progression on PSMA-targeted PET imaging precedes detection on conventional imaging.

DISCUSSION

BAT and PSMA-targeted imaging both remain under clinical investigation for patients with prostate cancer. When testosterone binds to androgen receptor, it induces PSA expression, meaning there is an urgent need for the development of a biomarker that can identify early disease progression because rising PSA is unreliable.

We performed a pilot imaging study assessing the effect of BAT on ^{18}F-DCFPyL PET/CT imaging. After initiation of treatment, most sites of radiotracer uptake had a decrease in SUV_{max} at the 3-mo time point. There are several possible explanations for this finding. One is that BAT induced regression of disease across multiple sites, as is consistent with the lack of radiographic progression after 3 mo of therapy. However, given the degree of change in SUV_{max}, one would expect to see more objective responses at that time point. A second explanation is that BAT inhibits the expression of PSMA protein. Prior studies have shown that androgen receptor inhibition increases PSMA expression and may cause a flare on PSMA-targeted PET (6,15). It is plausible that reengagement of androgen receptor via exogenous testosterone may downregulate PSMA expression while maintaining tumor viability. This artifact would result in a false-negative scan result. Alternatively, BAT may downregulate PSMA protein as an early event in apoptosis. It has been shown that PSMA may direct cellular growth through phosphatidylinositol-3′-kinase/protein kinase B signaling (16). Thus, decreasing PSMA expression may result in tumor regression. True radiographic progression did not occur for 9–12 mo after the ^{18}F-DCFPyL PET scan, which would support the possibility that these findings indicate an early clinical response. Arguing against transcriptional inhibition of PMSA expression are the findings of new or worsening ^{18}F-DCFPyL–avid lesions. That phenomenon was observed only in patients who experienced radiographic progression at their next restaging scan.

The utility of ^{18}F-DCFPyL PET/CT imaging may be in identifying those patients at highest risk of progressing on BAT. Patients who demonstrate new ^{18}F-DCFPyL–avid lesions all had early radiographic progression.

This study was limited by the small number of patients and the use of only 2 imaging time points. In addition, the fact that all scans were read by a single radiologist (although masked) could bias the results of the study. A larger prospective study is under way to confirm these findings (NCT04424654).

CONCLUSION

Treatment with BAT induced radiographic changes on ^{18}F-DCFPyL PET/CT imaging. New radiotracer-avid lesions on ^{18}F-DCFPyL PET/CT in men with mCRPC undergoing BAT can indicate early progression.

DISCLOSURE

KEY POINTS

QUESTION: Early progression on BAT is difficult to detect given the effect of testosterone on PSA expression and the limitations of conventional imaging.

PERTINENT FINDINGS: New radiotracer-avid lesions on ^{18}F-DCFPyL PET/CT imaging were observed in mCRPC patients on BAT who experienced early progression on conventional radiography.

IMPLICATIONS FOR PATIENT CARE: PSMA-targeted PET/CT may identify mCRPC patients at risk of early progression on BAT.

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