Brain Metabolic Correlates of the Off-Target Effects of Enzalutamide on the Central Nervous System of Patients with Advanced Prostate Cancer

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The management of prostate cancer increasingly relies on androgen axis–targeted therapies, such as enzalutamide, which is now administered progressively earlier and for longer durations (*1*). Enzalutamide increases the risk of fatigue, falls, dizziness, headache, and mild cognitive impairment (*2,3*). These off-target effects seem to be associated with enzalutamide's pharmacodynamics and ability to penetrate the blood–brain barrier. [^{18}F]FDG PET can capture synaptic function or dysfunction in neurocognitive disorders.

We compared brain metabolism in a cohort of metastatic castration-resistant prostate cancer patients, some treated with enzalutamide and others not, all undergoing [^{18}F]FDG PET. The institutional review board approved this retrospective study (Ethics Committee, Liguria, approval 590/2020), and the requirement to obtain informed consent was waived. Patients had preserved daily living activities and no history of neuropsychiatric diseases. Whole-brain voxelwise group analysis (SPM12 software) was used to identify relative hypometabolism compared with 48 age-matched controls (familywise error–corrected $P < 0.05$; nuisance variables: age, previous androgen deprivation therapy duration, previous abiraterone or taxane-based chemotherapy).

Of 68 patients, 39 had previously received enzalutamide. Aside from the duration of previous androgen deprivation therapy, the clinical characteristics of the 2 subgroups were balanced (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). Enzalutamide treatment was associated with hypometabolism in the left dorsolateral-prefrontal and front-insular cortex ($P < 0.005$; Fig. 1), whereas enzalutamide-naïve patients did not show significant regions of hypometabolism. The topography of these findings corresponds to cortical correlates of fatigue and memory/executive dysfunction (*2,3*). These findings align with the only imaging study with arterial spin-labeling MRI showing reduced blood flow in the prefrontal cortex in patients receiving enzalutamide (*4*). Our finding linking prefrontal cortex metabolism to enzalutamide suggests further investigation of [^{18}F]FDG PET for symptom objectification or biomarker validation.

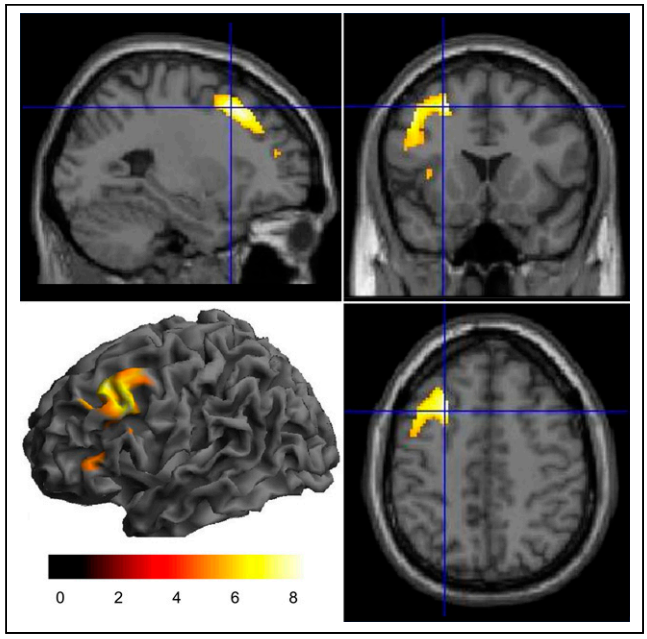

FIGURE 1. Hypometabolism in patients treated with enzalutamide compared with controls. Color bar indicates *z* scores for significant voxels. Left in the image is left in the patient.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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