Enzalutamide and sleep apnea: an emerging central nervous system side-effect?

Enzalutamide is a recently developed drug, improving overall survival in men with metastatic castration-resistant prostate cancer [1]. Different central nervous system (CNS) adverse events such as seizures, cognitive impairments, and attention disorders associated with asthenia have been described with enzalutamide [1, 2]. Sleep apnea (SA) has never been associated. SA is defined as an increase on the Apnea–Hypopnea index (AHI), recorded by polysomnography and it is frequently observed with symptoms such as excessive daytime sleepiness or cognitive impairment [3, 4]. SA was diagnosed 6 weeks after beginning enzalutamide in a 58-year-old man. He had no risk factors for SA (including a body mass index = 25.4), neither seizures, nor concomitant treatment modifications. Symptoms were excessive daytime sleepiness and diurnal apnea confirmed by the Epworth Sleepiness scale with a score of 8/24, a severe AHI of 35.7 per hour, and a high Oxygen Desaturation index (ODI) of 16.3 per hour. Enzalutamide was immediately stopped, and a treatment by continuous positive airways pressure (CPAP) was not initiated, due to a dramatic decrease of symptoms in a few days. Four months after enzalutamide discontinuation, the AHI had dropped to 14.9 per hour and ODI to 8.1 per hour, with complete resolution of excessive daytime sleepiness and diurnal apnea. Brain magnetic resonance imaging (MRI) was normal. Pharmacovigilance reporting was done, and enzalutamide was not reintroduced.

Seizures are the most frequently discussed CNS adverse event associated with enzalutamide with a dose-dependent toxic effect [1, 5]. The lowering of the seizure threshold may be due to the active enzalutamide metabolite crossing the blood–brain barrier, and inhibiting γ-aminobutyric acid (GABA) -gated chloride channel activity [5]. In both phase III studies, the incidence of seizures remained lower than 1% and occurred in at-risk patients [1]. Although there is a reciprocal interaction between sleep and seizures, the link between SA and seizures remains unclear, and seizures were not detected in the patient reported here (no electroencephalogram recordings). SA includes obstructive sleep apnea (OSA) and central sleep apnea (CSA), depending on whether or not respiratory efforts are reported, respectively [3]. Regarding CSA, there were no specific risk factors, brain MRI was normal and CPAP titration was not done to better characterize the mechanism of SA [3]. In contrast, most of apneas reported in polysomnography were obstructive (obstructive: 164; central: 19; mixed: 2) arguing for an OSA. A potential explanation could be an inhibitory effect on the hypoglossal motoneurones, inducing pharyngeal hypotonia [4]. At first glance, it is difficult to hypothesize a role of GABA pathway, considering that an activation could be more involved—but still debated [4]—in the pathophysiology of OSA than the inhibition reported for enzalutamide [5]. Finally, chronological arguments remain strongest for relating SA to enzalutamide. Such observation leads us to consider consequences in daily practice, especially the interest to perform an Epworth sleepiness scale or polysomnography in patients reporting high levels of fatigue, cognitive impairment, or seizures. Furthermore, some drugs potentially used in this setting (antiepileptic or opiate) may worsen or induce SA.

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disclosure

GR, YL, PS: National Board Astellas, all the remaining authors have no conflict of interest.

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doi: 10.1093/annonc/mdv481
Published online 7 October 2015

PD-L1 copy number gain in nonsmall-cell lung cancer defines a new subset of patients for anti PD-L1 therapy

In contrast to the impressive clinical efficacy of PD-1/PD-L1 checkpoint inhibitors, comparably little is known about their biology in nonsmall–cell lung cancer (NSCLC) [1–3]. Owing to substantial differences in companion diagnostics, it remains challenging to establish a common definition of eligible patients [4, 5]. Therefore, we analyzed copy number gain of the PD-L1 gene in NSCLC.

Two hundred twenty-one specimens were enrolled, comprising 115 adenocarcinomas (ADC), 86 squamous cell carcinomas (SCC), 12 large cell carcinomas (LCC), 6 carcinoids and 2 adeno-squamous carcinomas with ethical permission (University Lübeck ref. nr. 12–220). According to TNM staging, we included 29 (13.1%) stage IA, 43 (19.5%) IB, 40 (18.1%) IIA, 21 (9.5%) IIB, 55 (24.9%) IIIA, 23 (10.4%) IIIB and 10 (4.5%) IV. Tissue microarrays were constructed from formalin-fixed, paraffin-embedded tissues with 2-mm-diameter double punches for each case and A549 cells as internal controls. Fluorescence