EDITORIAL

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Is it time for everolimus-based combination in castration-resistant prostate cancer?

“...we deem that targeting the androgen receptor pathway, along with the PI3K/Akt/mTOR signaling in acquired PTEN loss metastatic castration-resistant prostate cancer, that is resistant to novel antiandrogenic therapies, maybe an interesting approach that needs to be tested in clinical studies.”

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Prostate cancer is the second leading cause of cancer-related death in men in most western countries [1]. Recently, several drugs with different mechanisms of action have been approved for the treatment of metastatic castration-resistant prostate cancer (CRPC). Specifically, enzalutamide, a second-generation androgen receptor (AR) antagonist, and abiraterone, an irreversible P450C17 (CYP17) inhibitor that blocks androgen biosynthesis, which have been approved in either chemotherapy naïve or not-chemotherapy-treated patients have given a significant survival advantage for men with metastatic CRPC [1]; cabazitaxel is a second-generation taxane, approved for the treatment of patients who progressed after a docetaxel-based chemotherapy; sipuleucel-T is the first immunotherapy which showed to prolong overall

survival among asymptomatic metastatic CRPC either treated with docetaxel than docetaxel-naïve, finally, the radium-223 is the first bone-seeking radionuclide that is reported to increase overall survival, and delay of time to first skeletal-related event in metastatic bone CRPC [1]. In addition, next-generation antiandrogens such as orteronel, ARN-509 and galeterone are under investigation in several trials [1]. The collective success of the AR-targeting agents reinforces the persistent dependence of AR signaling even in patients who have met the criteria of castration resistance [2] but, unfortunately, none of these agents are curative and patients ultimately progress. However, the collective success of the AR-targeting agents reinforces the persistent dependence of AR signaling even in patients who have met the criteria

KEYWORDS

- everolimus • mTOR pathway
- prostate cancer

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of castration resistance [2]. Therefore, there is the clinical need for developing new strategies in order to overcome drugs resistance, maximize survival and minimize side effects [3].

Mechanisms implicated in CRPC progression involve various steps in androgenic pathway including increased adrenal and/or intratumoral androgen biosynthesis in the castrate environment and acquisition of AR gene alterations such as AR amplification, AR mutations and AR splice variants that permit stabilized ligand-mediated activation or aberrant activation without a ligand [4]. Moreover, other pathways of carcinogenesis may be involved in conferring ligand-independent AR activity during CRPC progression [5]. Therefore, the development of treatment stratification based on predictive biomarkers that account for diversity in tumor biology will be crucial to inform treatment choices. One such biomarker that has emerged may be the androgen-receptor splice variant 7 mRNA (AR-V7) that lacks the ligand-binding domain [6]. AR-V7 confers resistance to abiraterone and enzalutamide in preclinical models [7] and in the clinic has been associated with a poor progression-free survival and overall survival to abiraterone and enzalutamide [6]. AR-V7 is a possible dynamic marker and its presence in the tumor is likely to reflect therapeutic selective pressure. While the AR-V7-positive status has been observed with both AR-directed therapies and taxane chemotherapies, the 'reversion' from positive to negative AR-V7 status has only been reported in relation to taxane therapies [8]. Moreover, AR-V7 does not seem to be associated with resistance to taxanes [9,10].

PTEN gene controls a number of cellular processes such as survival, metabolism and proliferation and suppresses cellular motility. In prostate cancer, *PTEN* is a common molecular aberration that has been correlated with a poor prognosis. Mutations in *PTEN* occur in up to 10% of primary prostate cancers while *PTEN* deletion occurs in 10–70% of surgically treated cancers and over 50% of metastatic prostate cancers. Preclinical data supported the role for *PTEN* loss in the regulation and expression of AR signaling [11,12]. In fact, AR transcriptional output is decreased in human and murine tumors with *PTEN* deletion and loss of *PTEN* function may facilitate activation of AR signaling and progression to androgen independence in prostate cancer [13].

Another important function of *PTEN* is the negative regulation of intracellular levels of PI3K which causes a subsequent overactivation of protein kinase B (Akt) and mTOR pathway. Therefore, subsequently, the loss of *PTEN*, the PI3K/Akt/mTOR pathway is constitutively active in the majority of CRCP [14]. It has been estimated that PI3K/Akt/mTOR pathway is mutated in the about the 40% of primary site of prostate tumors and in the totality of metastatic lesions [15]. In addition, it has been shown that the PI3K/Akt/mTOR pathway is linked to resistance to primary androgen deprivation therapy [16]. Therefore, it is reasonable to think that *PTEN* loss may also be involved in resistance to the new hormonal agents such as abiraterone or enzalutamide and the PI3K/Akt/mTOR may play a role in CRPC as a possible pathway involved in hormonal treatment resistance.

In addition, it seems the deregulation of *PTEN* is associated with worse survival and shorter time of drug exposition during new antiandrogenetic therapies [17]. In 2015, the outcome of a retrospective analysis on a total of 144 patients who had received abiraterone postdocetaxel was analyzed according the presence or loss of *PTEN* protein expression. *PTEN* protein expression was determined by immunohistochemistry on prostate cancer tissue. *PTEN* loss occurred in 38% (54 of 140) of the primary tumor samples and 50% (30 of 60) of the metastatic CRPC samples. The loss of *PTEN* was associated with a shorter median overall survival, 14 months for the group of patients with *PTEN* loss versus 21 months for patients without *PTEN* loss [17]. In the multivariate Cox regression model, the loss of *PTEN* was found as an independent factor for overall survival with a hazard ratio of 1.56. High lactate dehydrogenase levels and the presence of visceral metastases were found also to have a negative effect on overall survival with a hazard ratio of 1.59 and 1.967, respectively. Other efficacy and points such as confirmed prostate-specific antigen declines of at least 50% were observed in the 32% of patients with *PTEN* loss and the 43% of patients without *PTEN* loss ($p = 0.02$). In addition, the median duration of treatment with abiraterone was shorter in the *PTEN* loss group.

Everolimus (RAD001) is an oral inhibitor of mTOR, inhibiting the PI3K/Akt/mTOR pathway and approved for the treatment of breast, renal and neuroendocrine tumors. Several

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preclinical studies and some clinical studies suggested everolimus is active in metastatic CRPC [18]. Although everolimus efficacy in unselected patients with metastatic CRPC is moderate, patients with a deletion of PTEN showed a longer progression-free survival and response [19].

Based on these data and on previous data from other settings as showed in the BOLERO trial [20], it is reasonable to speculate that the combination of new hormonal agents such as abiraterone and enzalutamide with everolimus may offer a new therapeutical option to overcome resistance to the novel hormonal agents. More recently, a preclinical study has confirmed this issue [15]. In fact, Kato *et al.* have evaluated the combination of EPI-002 (an AR N-terminal domain antagonist) and mTOR inhibitors, such as BEZ235, in enzalutamide-resistant cell lines. In this study, the combination of EPI-002 and BEZ235 resulted in a decrease of the growth of enzalutamide-resistant cells *in vitro* and *in vivo* models. Interestingly, the inhibition of mTOR decreased the proliferation of enzalutamide-resistant human prostate cancer cells which are considered to be driven by AR-V7 and

decreased levels of expression of AR-V7 target genes [15].

Understanding tumor biology will become increasingly important for therapeutic decisions in the near future. Considering all these data, we deem that targeting the AR pathway, along with the PI3K/Akt/mTOR signaling in acquired PTEN loss metastatic CRPC, that is resistant to novel antiandrogenic therapies, maybe an interesting approach that needs to be tested in clinical studies. There are several potential predictive biomarkers which may help in the identification and selection of patients suitable for this novel therapeutical approach.

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