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Study shows additional role for abiraterone in blocking tumor growth in CRPC

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As part of an EU-supported IMI-PREDECT consortium (http://www.predect.eu), a Dutch study showed that anti-androgenic properties of the drug abiraterone may provide an additional mechanism of action in blocking tumour growth of castration resistant prostate cancer (CRPC).

The study, which won the first prize for best abstract in oncology at the 28th European Association of Urology (EAU) Congress to be held in Milan from March 15 to 19, demonstrated that although the use of abiraterone can potentially lead to an accumulation of precursor hormones, its anti-androgenic properties may stop precursor hormone-induced androgen receptor (AR) activation.

"Our results show that high concentrations of androgen precursors can drive CRPC growth through direct activation of (overexpressed) AR and not necessarily via the result of (intratumoural) CYP17-metabolism. This suggests that CRPC may not rely solely on de novo androgen synthesis," said lead author Dr. Jan Matthijs Moll of the Erasmus Medical Center, Dept. of Urology in Rotterdam, Netherlands.

Men with castration resistant prostate cancer are a difficult group to treat. Although metastatic prostate cancer may respond well to androgen ablation therapy initially, castration resistance usually develops within three years. Even though circulating testosterone levels are low in these patients, the androgen receptor reactivates, which indicates the AR remains an important target in CRPC.

The Rotterdam-based group has previously demonstrated that conversion of adrenal androgens into testosterone, rather than intratumoural de novo steroidogenesis, is the major source of testosterone in CRPC tumours. [1]

Clinical trials have demonstrated that abiraterone acetate plus prednisone /prednisolone can increase survival in CRPC patients even after chemotherapy [2]. "Blocking androgen synthesis (pregnenolone and progesterone are converted to androgens via CYP17A1 enzymatic activity) in CRPC patients has demonstrated a prolonged survival, but may eventually fail because androgen precursors can activate the AR directly," explained Moll.

In their study, the researchers generated castration resistant clones by long-term culture of VCaP and DuCaP cell lines in steroid-stripped medium (DCC), with or without addition of anti-androgens used in the clinic. Experiments were conducted with a subset of AR-overexpressing CRPC clones to test cell growth and AR-activation in the presence of adrenal androgen precursors, pregnenolone and progesterone or dihydrotestosterone in combinations with increasing levels of abiraterone.

The results showed that high (100 nM) levels of progesterone, but not of pregnenolone, induced cell growth in VCaP and DuCaP CRPC clones, which could not be blocked by low levels of abiraterone (0,1 μM) that are known to fully inhibit CYP17A1 activity (and thus potential subsequent testosterone production).

In a second experiment, the researchers showed that high levels of precursor androgens can directly activate the AR using a model with a fluorescent AR and that ligand-induced AR-translocation from the cytoplasm to the nucleus was slowed down by abiraterone.

"However, high levels of abiraterone (>5 mM) inhibited steroid-induced, but not basal growth of these (CRPC) cells. This finding, together with the observation that DHT-induced growth was inhibited by high levels of abiraterone, indicates that abiraterone can act as an anti-androgen," the researchers wrote.

"We show that abiraterone, a CYP17A1-blocking drug that has recently been approved in the treatment of CRPC, possesses an additional antiandrogenic property and can block androgen precursor-induced AR-activation at higher concentrations than what is needed for CYP17A1 specific inhibition. This may be a good argument to increase abiraterone exposure in the treatment of CRPC," added Moll.

Moll also said that "it is clear that the AR remains the most important target in the treatment of CRPC."

"Blockade of androgen synthesis seems not sufficient to prevent AR activation. New drugs that block AR activation irrespective of the activating ligand may provide new ammunition to last another 'round' for clinicians to treat CRPC," he said. "We believe it is vital to identify which metabolites have the potential to activate the mutated or overexpressed AR present in CRPC, which under normal conditions may not activate the AR. In that perspective, we are currently working together with our partner, Janssen, and other partners within the IMI-PREDECT consortium on developing new model systems for CRPC to further understand its biology and test new potential pathway perturbations that may benefit CRPC patients in the future."

Provided by European Association of Urology

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