Androgen Receptor Signaling In Prostate Cancer

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By Hans Van Der Slikke, MD [1]


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Dr. Hans van der Slikke: "Good morning, we're here at the Analogue Conference in Geneva and next to me is Zoran Culig, he is a research worker and MD at the Department of Urology in Innsbruck. You're doing a lot of research on prostate cancer cells and prostate cells, tell me what your main topic of research is today."

Dr. Zoran Culig: "Our main topic is working on androgen receptor signaling in prostate cancer, and we have been working on this study since 1991. At that time it was thought that the androgen receptor had a less important role in prostate cancer and this hypothesis was based mainly on studies on various animal models in which tumor cells derived from late stages do not express androgen receptors. We and others have shown that in human tissue, and even in a metastatic lesion, there is androgen receptor expression and even metastases from patients who failed endocrine therapy still express androgen receptor. This led us to studies on structure and function of these receptors, and we have found that mutant androgen receptors do exist in prostate cancer tissue. They are not very frequent in early stages of prostate cancer, but their percentage increases especially in metastases of prostate cancers, and we know that these mutants in prostate cancer shows a gain of function. That means that in contrast to mutations, which are detected in patients with, for example, the sequel of immunizations and which show a loss of function, mutants detected in prostate cancer patients show a gain of function. That means that other steroids and even non-steroidal anti-androgens such as hydroxy-flutamide, which are used in clinical therapy for advanced prostate cancer, switch to agonists. This was very important for the understanding of tumor progression and also for understanding of the so-called anti-androgen withdrawal syndrome, which will cure in sub group of patients with prostate cancer. That means if there is a cessation of anti-androgen during therapy that some of these patients show a paradoxical improvement in clinical symptoms and also a decline in PSA levels. Furthermore, we also work on non-steroidal activation of the androgen receptor, and it clearly exhibits non-steroidal activation and some growth factors analogues of cyclin and see-ma-tha (some other) phosphate, LHRH hormone itself, and interleukin-6 are among substances that induce function of the androgen receptor in a ligand-independent manner. This also may be important in patients with prostate cancer because these patients have low androgen levels and these low androgen doses in combination with, for example, GnRH or interleukin-6 reduce maximal concentration of androgen that is needed for maximal activation of the androgen receptor. That means that the androgen receptor does not need a high concentration of androgen to be fully activated in prostate cancer."

Dr. Hans van der Slikke: "So these are findings over the last few years that you and your group with Professor Bartsch did. Can you tell us what this will mean for the therapy and treatment of prostate cancer?"

Dr. Zoran Culig: "We know there are several problems with applications of anti-androgens especially because of these mutations and generation of hypersensitivity of the androgen receptor during long-term androgen ablation. Therefore, we have to clearly distinguish between beneficial effects of anti-androgens, which are short-term effects, and long-term effects, which might be harmful. We have initiated an experimental approach to treat prostate cancer cells and en-cup with antisense oligonucleotides which are directed against the androgen receptor and with this antisense oligos we have achieved down regulation of androgen receptor expression. So this might be a novel approach that should be perhaps tested in patients with late prostate cancer, and perhaps in..."
combination with another experimental therapy, for example, application of BCL-2 antisense oligonucleotides or anti-androgenic treatment because I believe that because of the multi-hormonal nature of prostate cancer that the successful therapy must target not only one signaling pathway. We need to target most signaling pathways and the androgen receptor is a good target for these new therapies because the androgen receptor is implicated in communication with some other signaling pathways."

**Dr. Hans van der Slikke:** "We are now using GnRH analogues and you started the trial with GnRH antagonists. Could you tell us what in theory could be the advantages of these antagonists?"

**Dr. Zoran Culig:** "We now know that there were some synergistic effects of GnRH agonists on the androgen receptor activity. How these agonistic effects are related to proliferation of prostate cells is still not clear but we now test if the LHRH receptor antagonist has an effect on androgen receptor activity, and if not, there may be one additional improvement in therapy where we use these new compounds. So I think we are now in the initial stage of these studies, and I hope that in a couple of months we shall know more about the local effects of GnRH antagonists."

**Dr. Hans van der Slikke:** "You told me before that there's also an advantage of the antagonists that are working immediately and not having this initial surge in androgen activity."

**Dr. Zoran Culig:** "Yes, androgen receptor antagonists, their immediate effect is inhibitory but the problem in prostate cancer is there is adaptation of cells and the cells adapt to these conditions with low androgen involvement. One of these mechanisms includes adaptation of androgen receptors and because of this we are now looking for new ways for inhibition of androgen receptor expression and function."

**Dr. Hans van der Slikke:** "Thank you very much."

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