Evaluation of New Generation Drugs for Advanced Prostate Cancer Treatment Necessitates Further Understanding of the Underlying Molecular Modes of Action

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LETTER TO EDITOR

With development and approval of new generation prostate cancer (PC) drugs, new treatment options have proven significant benefit for patients with advanced PC. Novel therapeutic agents, like Abiraterone (Zytiga), Enzalutamide (Xtandi, previously known as MDV-3100), and Radium 223 (Xofigo), recently expand the treatment options in the castration-resistant post-docetaxel setting. Besides, several other drugs are currently being evaluated, including inhibitors of new targets like the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), the epidermal growth factor (EGF) receptor, as well as the heat shock protein 27 (HSP27) [1,2]. Unfortunately, the clinical benefit of recently approved drugs remains temporary and chemoresistance cascades frequently re-initiate tumor growth and progression. With regard to numerous new potential PC drugs, it is doubtful that current treatment options already reached the optimum of therapeutical benefit. More likely, there are significant challenges regarding optimal therapeutical sequences and combinations of the novel agents, as well as the question of how to apply the ideal anticancer therapy in different settings of PC.

In the near future, molecular characterization of cellular response to drug treatment could represent an opportunity to improve our understanding of advanced PC. Epithelial cells have to acquire several traits to become malignant, elegantly grouped by Hanahan and Weinberg [3] as: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissues invasion/metastasis. During the last years, a growing body of literature describes various molecular pathways being responsible for progression to malignancy, as well as effector proteins, which are critical and propellent for each of these traits. So far, these data have been mainly analyzed in terms of two objectives: (1) identification of molecular markers, potentially predicting the response to anticancer treatment, and (2) identification of new molecular targets, enabling the design of novel anticancer strategies. Each of these approaches was exceedingly beneficial for therapy development, but of short duration with regard to progress of the disease.

In our opinion, however, a third approach, based on intracellular molecular drug mechanisms, would enrich the current therapy regimes and further strengthen the evaluation of new drugs entering the market. Beyond required approval studies for any of the novel pharmaceutical agents there is a lack of evidence about the molecular mode of action, as well as the cellular mechanisms counteracting drug efficacy. For this reason, a basis for rational therapy design based on molecular pathways is missed. These are the great unknowns which should be thoroughly investigated for early prediction and auxiliary evaluation of novel therapies.

Selection of drug combinations with known complementary mechanisms of action may do not only provoke synergistic effects; but also delay treatment resistance by induction of absorbing cellular pathways. Thus, this approach can be applied for the rational design of alternative drug therapies before starting substantial clinical trials. Recently, the group of Martin Gleave (Vancouver Prostate Centre, Canada) qualifies HSP27 as an appropriate molecular target for new anticancer strategies in PC treatment [2]. Currently, our working group described for the first time, that HSP27 regulates the proliferative androgen receptor and the tumor suppressor microRNA-1. Both of them are contributing to the cytoprotective properties of the heat shock protein [4-6]. Thus, co-factors of HSP27 signaling represent promising co-targets of HSP27 targeting combination therapies for advanced PC.

In conclusion, our understanding of novel drugs mode of action and treatment resistance, regrettably, is still limited, especially in context of individualized medicine concepts.
Therefore, further in vitro analysis and pre-clinical studies for mapping intracellular drug-induced signaling pathways in PC cells are required to embed novel agents into current therapy strategies.

REFERENCES