Hormonal control of cancer: an outdated topic?

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As a medical oncologist today, the topic of endocrine control of cancer seems overshadowed by recent successes and developments in immunotherapy and targeted therapy. However, after careful consideration, one might argue that (anti-)hormonal therapy for cancer is one of the initial, and maybe first ever used targeted oncological treatments. In no way is the concept of endocrine therapy outdated, with numerous trials ongoing and their results eagerly awaited.

Ever since the observations by Beatson, that bilateral oophorectomy induced remissions in advanced breast cancer, and by Huggins and Hodges, that canine prostate cancer responded to mechanical castration, growing evidence suggested multiple roles of sex hormones in the control, progression and treatment of various entities of cancer. The most common non-cutaneous malignancies in women and men, breast and prostate cancer, being amongst them.

In the last decade, for instance, aside from chemical castration using gonadotropin-releasing hormone analogues, targeted inhibition of the androgen receptor (AR) by small molecules such as apalutamide, enzalutamide or abiraterone has greatly improved outcomes in both hormone-sensitive and castration-resistant prostate cancer. The notion that cancer cell dependency on AR signalling remains in the castration resistant setting is a major discovery that should lead to a discussion about endocrine treatment resistance in general and not just for the entity of prostate cancer. Although some mechanisms of resistance against the aforementioned second-generation AR inhibitors such as (neuroendocrine) transdifferentiation and AR splice variants like AR-V7 are known, their underlying causes and consequences will need further clinical examination.

In the field of breast cancer treatment, the definition of endocrine sensitivity criteria has certainly changed the way luminal breast cancer progression is perceived and treated—especially in the metastatic setting. Again, some underlying mechanisms potentially affecting response to endocrine treatment such as mutations of ESR1 or PIK3CA are known. Although aromatase inhibitors continue to be a standard of adjuvant and palliative treatment strategies—with and without cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, that had a tremendous impact on overall survival and delay of chemotherapy when added to endocrine therapy in metastatic breast cancer—the endeavour of developing novel selective oestrogen receptor (ER) degraders or modulators such as fulvestrant or tamoxifen is of highest importance. Can one observe a similar dependency of cancer cells on sustained steroid receptor (ER) signalling as seen in prostate cancer? And what role would this dependency play in progression after CDK4/6 inhibition?

For both entities, targeted endocrine treatments have replaced cytostatic chemotherapy as parts of treatment protocols in the advanced stages of disease and most likely will continue to do so once ongoing trials in adjuvant and neoadjuvant settings and in combination with other treatment modalities, such as immunotherapy, targeted therapy and radiotherapy, have reported their results.

Certainly, the topic of hormonal control of cancer is not sufficiently covered by discussing the role of steroids in prostate and breast cancer, as there is practically no malignant disease completely independent from endocrine stimuli: cancer progression highly depends on signalling pathways mediating growth, often mediated through hormones and their receptors, such as insulin-like growthfactor-I or somatotropin. Besides, both the immune system and the tumour microenvironment are highly susceptible to hormonal influences.

Therefore, the oncological community should not forget about the hormonal axis, when looking for novel targets and approaches—even in an era with a heavy focus on immune checkpoint inhibition and targeted therapy. Multimodal combination...
therapies including hormonal agents and other targeted agents against Her2, PIK3CA, PARP or immune checkpoint proteins could lead to a further decrease in the use of cytostatic chemotherapy, ameliorated patient outcome and reshape the way we treat hormone-dependent cancer in the future.

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