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Testosterone Therapy in Castrate-Resistant Prostate Cancer: A Possible New Approach

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Manipulation of patients' androgen status pervades so much of the management of prostate cancer (PCa). It commences with neoadjuvant androgen deprivation therapy (ADT) in combination with radiation therapy for intermediate-risk and high-risk organ-confined disease and extends to various modulations of ADT in patients with nonlocalised and metastatic disease. Permutations include continuous and intermittent monotherapy as well as combined androgen blockade for hormone-responsive cancer, with both the addition and subtraction of single therapeutic agents for short-term responses in castrate-resistant PCa (CRPC).

Although initial response to ADT is excellent (>90%), these therapies inevitably fail with the emergence of CRPC. Extensive preclinical and clinical data indicate that the androgen receptor (AR) signalling pathway is not only present but continues to mediate androgen signalling after failure of androgen agonist therapy, despite castrate levels of circulating androgens [1]. AR overexpression, amplification, mutation, and altered coregulator interactions may sensitise the AR to lower levels of ligand, thereby contributing to failure of hormonal therapies. It has been documented recently that intratumoural androgen levels in CRPC are sufficient to stimulate tumour growth [2], indicating that local synthesis of androgens is another mechanism for maintaining AR signalling in the castrate environment. The clinical importance of these findings is highlighted by the recent reports of clinical efficacy of abiraterone acetate, an irreversible inhibitor of 17 α -hydroxylase/C17,20 lyase that

blocks androgen synthesis in patients with advanced prostate cancer [3].

Thus, in men with CRPC, administration of testosterone seems counterintuitive. In this issue of the journal, however, Morris et al [4] from Memorial Sloan-Kettering Cancer Centre report a phase 1 trial of high-dose exogenous testosterone in patients with castrate-resistant metastatic PCa (CRMPC). Their research is based on preclinical studies of both androgen-independent cell lines [5] and findings in an animal model [6]. Consistent with reports of the safety of exogenous androgen priming to enhance chemotherapeutic efficacy in advanced PCa [7], Morris et al's trial demonstrates that administration of exogenous testosterone to men with CRMPC is safe, provided that very careful monitoring is employed.

Following submission of Morris et al's manuscript to the journal [4], an electronic publication of another study by Szmulewitz et al [8] from the University of Chicago has become available. Their participants, who were at an earlier phase of castrate resistance than those enrolled into Morris et al's study, also used topically administered testosterone. Both studies were designed to assess the safety of the exogenous testosterone administration strategy. Only 1 of 15 patients from Szmulewitz et al's cohorts was withdrawn due to grade 4 cardiac toxicity; the Morris et al trial withdrew one man who had a prior history of epidural disease and developed spinal compression but without neurological symptoms. Because there was an indication of a tumour effect in both studies (with a fall in serum

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prostate-specific antigen in 7 of 12 patients in the Morris et al trial and in 3 of 15 patients [up to 43%] in the Szmulewitz et al trial), these findings pave the way for further studies to examine potential therapeutic benefits from exogenous testosterone therapy in selected CRPC patients.

A notable finding from Morris et al's manuscript is that despite administering three times the usual replacement dose of testosterone, serum levels did not, on average, exceed normal levels [4]. Szmulewitz et al experienced similar findings [8]. This may partially explain the fact that none of the 12 patients in Morris et al's study exhibited an objective response. As pointed out by these authors, PCa growth is stimulated by lower doses of androgens than those that result in growth repression [5]. Thus, while a failure to reach supraphysiological testosterone serum levels may have adversely affected tumour responses in both of these trials, it may have inadvertently served to test the prime objective of safety. Indeed, particularly in Morris et al's report, the oncological therapeutic effect is very difficult to evaluate, since patients were heterogeneous because of different pretrial progression rates (not detailed). Five of 12 patients progressed through previous taxane chemotherapy in addition to different treatment and monitoring regimens pursued for the three cohorts.

Morris et al provide a careful analysis of these and other confounding limitations in their manuscript, with a 5 α -reductase inhibitor being proposed as a possible method for bolstering serum testosterone levels. Another alternative would be to deliver testosterone parenterally by intramuscular injections. The most easily available preparations, however, are depot, which provide supraphysiological doses for >14 d, but unlike transdermal daily dosing, depot dosing cannot be *turned off* if a patient encounters testosterone-driven clinical symptomatic progression. This concern could be minimised by only treating patients with no radiographic evidence of disease, and it would address the question of whether pulsed supraphysiological levels are more cytotoxic than continuously released replacement testosterone with the transdermal approach. Of necessity, such an evaluation would need to be done in a formal clinical trial with structured safeguards in place.

Morris et al also suggest strategies to identify patients prior to therapy who may be more likely to respond, so that therapy might be tailored [4]. One proposition, based on the assumption that responders will be those with upregulation of the AR, is the use of fluorinated dihydrotestosterone positron emission tomography tracers to image and to identify patients with upregulation of the AR in CRPC. A

further strategy is evaluation of AR gene amplification in circulating CRPC cells, since approximately 40% of patients with progressive CRPC have AR amplification in their circulating tumour cells [9,10].

Clearly, further analyses of perversions of AR signalling in CRPC needs to be undertaken to identify those patients who will benefit from high-dose testosterone therapy and to circumvent the need for a trial-and-error approach to identify responders. Thus, an integrated molecular and clinical research collaboration is required to maximise the potential of this avenue of AR-targeted therapy before translation is recommended to the clinic as a routine treatment.

Conflicts of interest: The authors have nothing to disclose.

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