RE: STATE-OF-THE-ART TREATMENT IN CASTRATION-RESISTANT PROSTATE CANCER - FORWARD TO THE PAST - AGAIN

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Castration-resistant prostate cancer (CRPC) management is enjoying a renaissance following the marginal but significant beneficial impact of recent novel advances in medication on progression-free and overall survival, timely reviewed by Castro et al.1 The Nobel prize-winning work of Huggins in the 1940s revealed the prostate to be hormone-sensitive and to shrink when androgen-deprived, and this was the inspiration for the era that followed and what has taken us through to this point in time.2 Androgen deprivation therapy (ADT), as first-line therapy in the management of advanced prostate cancer (PrC), was initially prescribed in the form of oral oestrogen (diethylstilbestrol [DES]; i.e. medical orchiectomy at a very high dose of 5 mg three times per day) or surgical orchiectomy. However, the use of DES was abandoned when it was shown to be associated with serious and often fatal thromboembolic and cardiovascular (CVS) events in more than one-third of men.2 This outcome was later shown to be due to the effect of oral oestrogen absorption via the hepatic–enteric circulation, which bathes the liver in a high concentration of oestrogen and induces pro-coagulation factors. The VACURG studies later showed this effect to be markedly reduced when oral DES was used at lower doses (1-3 mg once daily), which led to oestrogen regaining some of its reputation as ADT in certain instances. Consequently, it is now often forgotten that (low-dose) DES has also played a role in second-line treatment for CRPC and has been reported to lead to improved outcomes in some men. For example, Wilkins et al.3 described how almost 30% of 231 men with CRPC treated with DES at a dose between 1-3 mg once daily exhibited a prostate-specific antigen response for a median duration of 4.6 months. So it is disappointing, if unsurprising, that once again and despite many supportive data,2,4-7 the long-established and still-evolving contemporary literature demonstrating a role for oestrogen as effective and possibly safer therapy in men with CRPC received no mention in this review.

Oestrogen acts on PrC cell growth by several mechanisms. One example is suppression of the hypothalamic–pituitary–gonadal axis through feedback inhibition, which is the same mechanism through which contemporary ADT (luteinising hormone receptor hormone analogue [LHRHa], the compound which replaced DES as first-line medical orchiectomy) acts.8 However, with the passage of time, LHRHa is itself increasingly recognised to be associated with major toxicity because it leads not only to a reduction in testosterone levels of up to 95%, but also to suppression of endogenous oestrogen by about 80%.9,10 This suppression is due to oestrogen in men being derived from testosterone through the action of the enzyme aromatase. In contrast, if sufficient oestrogen is applied parenterally, then not only are castration-associated levels of testosterone reached, but exogenous oestrogen replaces the lost endogenous oestrogen so that overall oestrogen levels remain high, with the liver being avoided and the CVS effects minimised.5,11 This allows for the potential mitigation of toxicities due to oestrogen deficiency itself, such as osteoporosis, improving bone mineral density,12 cognitive impairment, and disturbances of lipid metabolism,13 and thus makes it possible to reconsider oestrogen as an attractive option in hormonal therapy.
Several recent studies in cytotoxic chemotherapy-naïve patients have demonstrated that low-dose oral DES (1-3 mg) is well tolerated and appears to have a clinically acceptable toxicity profile with a 5-10% rate of thromboembolic events.\(^1\)\(^,\)\(^5\)\(^,\)\(^14\)\(^,\)\(^15\) Thus, DES seems generally safe and effective for CRPC before initiation of cytotoxic chemotherapy, and can offer palliative benefit to men unfit for chemotherapy.\(^6\)\(^,\)\(^7\) Furthermore, the cost-effectiveness of DES\(^6\) at a time of economic strain throughout healthcare\(^18\) greatly favours its use as a therapeutic option prior to chemotherapy in non-symptomatic CRPC.\(^7\) Low-dose DES has also been shown to be as effective as salvage therapy in patients with progressive CRPC in a post-chemotherapy setting.\(^5\)\(^,\)\(^7\)

As healthcare costs continue to grow, it will become increasingly important not only to control the cost of primary treatments, but also to mitigate any additional iatrogenic toxicities.\(^8\) Treating PrC and its treatment-associated toxicities currently costs the UK over £100 million per annum, with a total global health bill estimated at >£2 billion.\(^18\) Therefore, whilst Castro et al.\(^1\) report on the development and effectiveness of several new agents for CRPC (namely abiraterone, enzalutamide, and cabazitaxel), there are few data on the cost of these new drugs. Abiraterone is estimated to cost around £50,000 per quality-adjusted life-year.\(^19\) Furthermore, whilst abiraterone seems to offer incremental gains by extending median survival by about 3-5 months, it is associated with further and profound reduction in sex hormone activity that will likely only exacerbate the problem of the increasingly recognised toxicities of iatrogenic hypogonadism of LHRHa alone.\(^19\)

In the face of these new developments and toxicity concerns, and given the recent safety and efficacy data with regard to oestrogen as well as its potential in avoiding associated morbidity and its significantly lower cost, it seems reasonable to invest more into studies on the evolving role of parenteral oestrogens in CRPC, not least by utilising oestrogen as a control arm in future studies. We therefore suggest oestrogen undergo re-purpose assessment. Sometimes in order to move forwards, perhaps we must look to the past.

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