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REPLY

Cardiovascular toxicities of systemic treatments of prostate cancer: is oestrogen to the rescue?

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We thank Shah and colleagues for their interest in our article (Cardiovascular toxicities of systemic treatments of prostate cancer. *Nat. Rev. Urol.* **14**, 230–243 (2017))[1], which raised some important points regarding the administration route for oestrogen therapy for prostate cancer (Cardiovascular toxicities of systemic treatments of prostate cancer: oestrogen to the rescue? *Nat. Rev. Urol* http://dx.doi.org/10.1038/nrurol.2017.126 (2017))[2].

In our Review[1] we analysed the cardiovascular adverse events of all drugs commonly used to treat prostate cancer, including targeted and hormonal therapies that are not approved for use in clinical practice, such as oestrogens. The use of oestrogens is currently not considered as a therapeutic hormonal option by all guidelines for prostate cancer, as noted by Shah and colleagues[2]. Oestrogens were usually administered by oral route but their use in this form was associated with severe thromboembolic effects owing to procoagulant molecules produced after being metabolized by the liver[3]. More recently, alternative routes of administration were tested in order to reduce adverse effects and to improve patient compliance.

Shah *et al.*[2] comment that in a large Scandinavian phase III trial the administration of intramuscular oestrogens did not increase cardiovascular mortality, but the treatment did considerably increase the risk of nonfatal cardiovascular events[4]. Ockrim *et al.*[5] tested transdermal administration of oestrogens for treating prostate cancer in a small, single-arm, phase II study with just 20 patients.

This route of oestrogen administration is being investigated in the large, phase III Prostate Adenocarcinoma TransCutaneous Hormones (PATCH) trial, a multistep study started in 2007 in the UK[6]. The first results of this study confirmed the good tolerability of oestrogen patches without excessive cardiovascular toxicity[7]. Based on these results, the study was extended to assess survival outcomes. Moreover, recently published data from the study showed improved 6-month self-reported quality of life, although an increased incidence of gynaecomastia was observed with oestrogen patches in comparison with luteinising-hormone-releasing hormone (LHRH) agonists[8].

These data show that different adverse effects can influence patients' quality of life in different ways, and cardiovascular safety is only one of the potential adverse effects of treatment for prostate cancer. All potential adverse effects must be evaluated together to establish the risk:benefit ratio when palliative therapy is proposed to patients.

The role of oestrogens via transdermal administration for prostate cancer treatment will clearly be definitively assessed only on the basis of the final results of the PATCH trial in terms of treatment efficacy and safety in a large population.

In conclusion, oestrogen therapy cannot currently be considered standard of care according to international guidelines, and more data from prospective clinical trials are needed to better define its role in prostate cancer treatment.

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Competing interests statement
O.C. has received honoraria from Sanofi Aventis, Astellas and Janssen. The other authors declare no competing interests.