LETTER TO THE EDITOR

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Comment on 'Endocrine therapy in prostate cancer: time for re-appraisal of risks, benefits and cost-effectiveness?'

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Sir,

Bourke *et al* (2013) raise important and topical issues concerning the expanding literature and consequent increasingly informed debate surrounding the risks, benefits and cost-effectiveness of androgen deprivation therapy (ADT) in advanced prostate cancer (Bourke *et al*, 2013). It was disappointing, therefore, that their review did not incorporate a more detailed perspective on the potential for a revival of oestrogen, particularly in the face of accumulating knowledge about its pharmacology, toxicity and costs. As they state, following the discovery of the excess cardiovascular toxicity with oral oestrogens, its use as first-line treatment was 'all but forgotten for the next 30 years', to be replaced by luteinising hormone releasing hormone agonist (LHRHa) therapy.

Castration with LHRHa as ADT delivers up to a 95% reduction in endogenous testosterone (T) levels, but results in toxicity including, for example, sarcopenia and erectile dysfunction (sometimes referred to as the male menopause or andropause). As noted by Bourke *et al* (2013), there is now also some evidence indicating an increased risk of cardiovascular disease. Further, as endogenous oestrogen is derived from T, castrate T levels result in suppression of oestrogen (by about 80%) causing toxicity, including osteoporosis and bone fractures, cognitive impairment and hot flushes (like in the female menopause; The Leuprolide Study Group, 1984; Garnick, 1986).

Exogenous oestrogen for ADT offers two major theoretical therapeutic benefits. First, the route of administration of oestrogen is of paramount importance for the development of cardiovascular toxicity. Oral oestrogen undergoes first pass through the liver, which gets bathed in high concentrations switching on pro-coagulant proteins. This does not appear to occur, at least not to the same extent, when oestrogen is given parenterally (Ockrim *et al*, 2005; Hedlund *et al*, 2008; Langley *et al*, 2008). Second, exogenous oestrogen replaces endogenous oestrogen, which would be lost through contemporary LHRHa administration (Ockrim *et al*, 2004). By contrast with the alternatives, exogenous oestrogen is also cheap and can, as a single agent, not only treat the cancer through T suppression but also avoid the use of additional, usually expensive, drugs to counter the often unpleasant toxicities associated with the menopausal side effects of LHRHa.

The Cancer Research UK funded PATCH study (Prostate Adenocarcinoma TransCutaneous Hormone) compares LHRHa with transdermal oestrogen patches in a phase II randomised clinical trial of men with locally advanced or metastatic prostate cancer. Stage 1 of this study ($n = 254$) specifically addressed cardiovascular toxicity as the primary outcome and the data showed similar rates of cardiovascular events in both arms (Langley *et al*, 2013). The phase II trial continues to recruit with a new primary outcome of progression-free survival in order to gain data on efficacy and help inform the decision to proceed to a phase III study with overall survival as the primary outcome. Data from the study, which include changes in lipid profiles and other metabolic factors over time, will also contribute to the evidence-base regarding an association between cardiovascular risk and LHRHa.

Further research may yet establish the use of parenteral oestrogen as a safe, effective and cheap single therapy for the treatment of prostate cancer, which could avoid some of the toxicities of present-day castration.

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