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 procoagulant 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.

REFERENCES

Bourke L., Kirkbride P, Hooper R, Rosario AJ, Chico TJ, Rosario DJ (2013) Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness? Br J Cancer 108(1): 9–13.

Garnick MB (1986) Leuprolide versus diethylstilbestrol for previously untreated stage D2 prostate cancer. Results of a prospectively randomized trial. Urology 27: 21–28.
Hedlund PO, Damber JE, Hagerman I, Haukaa S, Henriksson P, Iversen P, Johansson R, Klarskov P, Lundbeck F, Rasmussen F, Varenhorst E, Viitanen J, the SPCG-5 Study Group (2008) Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. *Scand J Urol Nephrol* **42**(3): 220–229.

Langley RE, Cafferty FH, Alhasso AA, Rosen SD, Sundaram SK, Freeman SC, Pollock P, Jinks RC, Godsland IF, Kockelbergh R, Clarke NW, Kynaston HG, Parmar MKB, Abel PD (2013) Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: the randomised, phase 2 MRC PATCH trial (PR09). *Lancet Oncol* **14**(4): 306–316.

Ockrim JL, Lalani El-N, Kakkar AK, Abel PD (2005) Transdermal estradiol therapy for prostate cancer reduces thrombophilic activation and protects against thromboembolism. *J Urol* **174**(2): 527–533.

Ockrim JL, Lalani E-N, Banks LM, Svensson WE, Blomley MJ, Patel S, Laniado ME, Carter SS, Abel PD (2004) Transdermal estradiol improves bone density when used as single agent therapy for prostate cancer. *J Urol* **172**: 2203–2207.

The Leuprolide Study Group (1984) Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *New Eng J Med* **311**(20): 1281–1286.