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Comment

Transdermal oestradiol as a method of androgen suppression for prostate cancer within the STAMPEDE trial platform

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Androgen deprivation therapy (ADT) remains a cornerstone of the management of prostate cancer. The addition of ADT to radiotherapy improves disease-free and overall survival in the locally advanced setting and ADT forms the backbone onto which additional treatments may be added (either initially at first presentation or sequentially at disease progression). ADT is most commonly achieved with GnRH analogues that act through the hypothalamic–pituitary–gonadal axis to prevent testicular production of testosterone. The therapeutic benefits of ADT, however, are partially offset by its side effects, which include long-term osteopaenia, osteoporosis and fracture and increased risk of cardiovascular disease, weight gain and metabolic syndrome, reduced quality of life (including hot flushes, fatigue, sexual dysfunction and depression) and cognitive decline [1].

Although some of these unwanted effects result from the necessary reduction in testosterone levels, others are related to disturbance of the endocrine milieu, particularly oestrogen levels. Circulating oestrogens in men are produced through the peripheral conversion of testosterone. As a result of the testosterone reduction, oestrogens are therefore also suppressed, contributing to adverse effects (Fig. 1).

Exogenous oestrogens will also suppress LH production from the pituitary via negative feedback, lowering systemic testosterone production whilst avoiding the effects of a low oestrogenic state such as osteopaenia and dysregulation of lipid and glucose metabolism. Oral systemic oestrogens were amongst the first successful systemic therapies for advanced prostate cancer; however, systemic oral oestrogens in men are associated with an increased risk of cardiovascular and thromboembolic disease resulting from a first-pass effect in the liver with production of prothrombotic proteins. Transdermal application of oestradiol (E2) avoids this effect and offers an alternative, potentially safer, means of androgen suppression with oestrogens [2].

The PATCH trial (NCT00303784), currently recruiting, compares the efficacy and safety of transdermal E2 vs GnRH analogues in men with locally advanced and metastatic prostate cancer, and has so far recruited >1400 men. The initial pilot phase showed transdermal E2 achieved equivalent castration rates to GNRH analogues without the excess cardiovascular morbidity or mortality previously seen with oral oestrogen [3]. Subsequent analyses showed a number of other potential benefits of transdermal E2 compared with GNRH analogues, including improved bone mineral density [4], more favourable metabolic profiles and better quality of life over 6 months of ADT, although with increased likelihood of gynaecomastia [5].

Evaluating Transdermal E2 Within the STAMPEDE Trial

STAMPEDE (NCT00268476) is a platform (or 'living') protocol using multi-arm, multi-stage trial designs to investigate novel treatment approaches in locally advanced or metastatic hormone-sensitive prostate cancer. Opening in 2005, it has recruited nearly 10 000 patients across the UK

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Fig. 1 Transdermal oestradiol (E2) and testosterone metabolism. Transdermal E2 produces androgen suppression but replaces endogenous oestradiol lost (where 80% arises from the peripheral conversion of testosterone). Transdermal E2 therefore mitigates the oestrogenic side effects that arise with conventional androgen deprivation therapy (LHRH analogues). tE2, transdermal oestradiol.

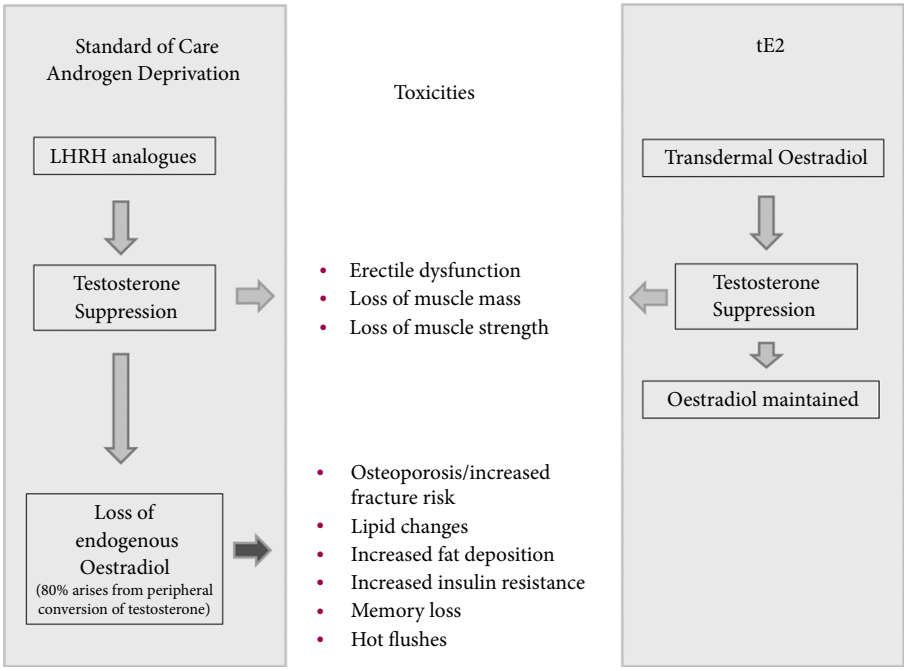
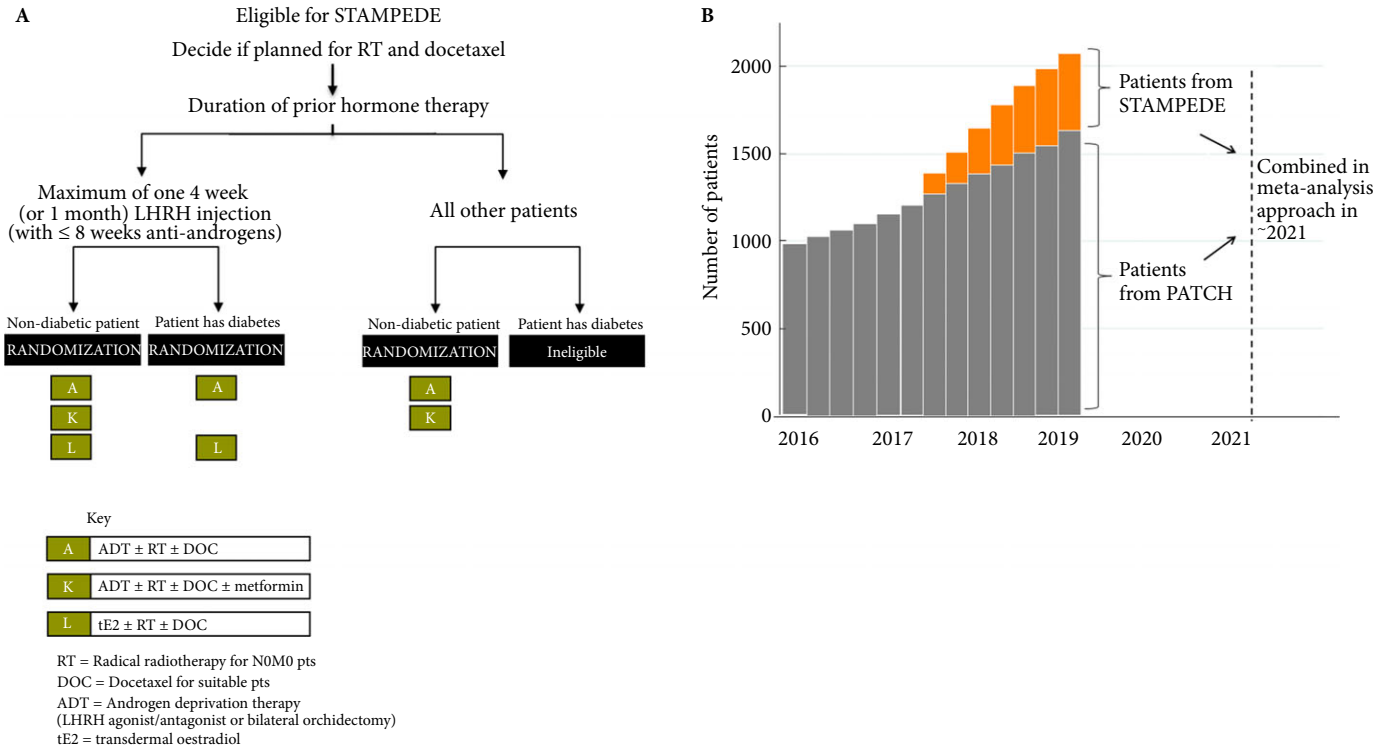


Fig. 2 **A**, Trial schema and **B**, projected trial enrolment and contribution of data from PATCH and STAMPEDE, ADT, androgen deprivation therapy; DOC, docetaxel; E2, oestradiol; RT, radiotherapy; tE2, transdermal oestradiol.



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and Switzerland, testing 10 approaches thus far, and demonstrating that the addition of docetaxel and abiraterone to standard ADT each improve overall survival as well as demonstrating a lack of significant benefit with zoledronic acid and celecoxib [6]. Randomized cohorts investigating radiotherapy (to the primary tumour in the face of metastatic disease) and the combination of abiraterone and enzalutamide have completed recruitment and are in active follow-up. STAMPEDE is currently recruiting to the 'metformin comparison' and since June 2017, a new 'transdermal E2 comparison' has been added, comparing transdermal E2 with standard ADT to complement the PATCH trial.

The clinical efficacy of transdermal E2 will henceforth be assessed using data from ~2000 contemporaneously randomized patients from the PATCH and STAMPEDE trials, using a meta-analysis approach (Fig. 2). This strategic decision, taken by the Trial Management Groups of the trials together, and with the approval of the appropriate funding bodies, allows faster recruitment to the comparison and activation of the comparison at additional UK sites. Competing or overlapping trials tend to be discouraged by Hospital Research and Development departments, so this expands recruitment efficiently. This combined approach also reduces the number of patients allocated standard treatment (across both trials overall), thereby increasing the proportion of patients receiving a novel treatment.

Within both STAMPEDE and PATCH, and in accordance with current recommendations, radiotherapy will be mandated (unless contraindicated) for all patients with N0 M0 disease and encouraged for those with N+M0 disease; use of docetaxel is permitted for all patients, including those randomized to transdermal E2. So far, no additional toxicity has been observed in patients receiving upfront docetaxel with transdermal E2 within PATCH (permitted since 2016). This will continue to be monitored in both trials.

A practical challenge in recruiting to a transdermal E2 comparison is the requirement to limit exposure to GnRH analogues prior to randomization. Prolonged duration of testosterone suppression can be seen with 12-week depot GnRH analogue injections. Ideally, all patients would be recruited and randomized whilst still on their pre-GnRH analogue, anti-flare anti-androgen, as done in PATCH; however, in STAMPEDE, trial entry is permitted within 12 weeks of starting LHRH. To accommodate this difference in approach, patients who have only received a single 4-week injection are eligible for randomization to the transdermal E2 comparison.

Conclusions

Accumulating data from the PATCH trial is building a case in support of transdermal E2 as a potential alternative to GnRHa for the suppression of androgens in the treatment of locally advanced and metastatic prostate cancer. The incorporation of the transdermal E2 comparison within STAMPEDE allows the efficacy and toxicity questions to be answered in the most efficient manner possible for patients, trialists and funders alike. The evolving STAMPEDE platform allows integration of updates in the standard of care with ongoing research questions to maximize benefits to future patients by understanding how these improvements can be combined. More broadly, if the combined analysis of PATCH and STAMPEDE confirms transdermal E2 as a method for ADT on prostate cancer with benefits over GnRH analogues, this therapeutic method could be investigated in other situations requiring ADT, such as short-term androgen suppression in combination with radiotherapy in the treatment of high-risk localized disease. Transdermal oestradiol patches may also add a cost benefit: they are considerably cheaper that other systemic approaches to ADT. This could potentially have important implications for improving access to prostate cancer treatment in low- and middle-income countries where primary presentation with metastatic disease is common and prostate cancer incidence is rising as populations age.

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Conflict of Interest

Ruth E. Langley has served as an advisor for, and received honoraria from Bayer. The remaining authors have no conflicts of interest to declare.

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