A randomised phase 3 evaluation of transdermal oestradiol (tE2) versus luteinising hormone releasing hormone agonists (LHRHa) for androgen suppression in non-metastatic (M0) prostate cancer; efficacy results from the PATCH and STAMPEDE trials.

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Background: Androgen deprivation is a key component in the management of patients with prostate cancer, usually achieved using LHRH analogues (LHRHa). As an alternative, transdermal estradiol (tE2) lowers testosterone more rapidly, avoiding side-effects attributable to loss of estragens, maintains bone mineral density, and improves metabolic outcomes and quality of life (QL). Transdermal administration avoids the cardiovascular (CVS) toxicity of oral oestrogen.

Methods: Open-label, randomised phase 3, non-inferiority (NI) comparison of LHRHa v tE2 patches with oncological efficacy outcome measures. Eligibility: histologically confirmed newly diagnosed high-risk M0 [locally advanced or node positive (+)] prostate cancer or those relapsing with PSA≥4ng/ml and doubling in <6 months, PSA ≥20ng/ml or N+. Treatment: standard LHRHa v tE2 100mcg/24h patches changed twice weekly for ≥2 years, (prostate radiotherapy and docetaxel permitted). Primary outcome: metastasis-free survival (MFS) defined as time from randomisation to metastatic disease or death from any cause, designed to exclude >4% reduction in 3-year MFS (85% power, 1-sided 5% α). Secondary outcomes: overall survival (OS), castration rates and toxicity.

Results: 1360 men, [639 LHRHa 721 tE2 (randomisation ratio 1:2 then 1:1)] were recruited from PATCH (NCT00303784, n=1082) and STAMPEDE (NCT00268476, n=278) trial sites between 2007-2022. Baseline characteristics were well-balanced between randomised groups. The 3-year MFS in patients randomised to LHRHa was 86% (giving a target NI hazard ratio (HR) of 1.31). Patients randomised to tE2 had a 3-year MFS of 87% HR 0.96 (95% CI 0.81-1.14), excluding a 2% reduction in MFS in favour of tE2. OS HR was 0.89 (CI 0.74-1.07) in favour of tE2. Prostate cancer, CVS and 2nd malignancy deaths were similar between randomised groups. Sustained castration rates (testosterone ≤1.7nmol/L over 1 year (n=1066), with tE2 use (confirmed oestradiol ≥250 pmol/L), were 85% in both arms. LHRHa v tE2 any grade: gynaecomastia was 42% v 85%, and hot flushes 89% v 44%.

Conclusion: In the treatment of men with locally advanced prostate cancer, outcomes are non-inferior when tE2 as opposed to LHRHa is used as ADT; this approach should be considered a standard of care. tE2 provides men with choice about expected side-effects and route of administration.

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