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Transdermal Estradiol as an Alternative to LHRH Agonists in Prostate Cancer Management

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Background: Standard androgen deprivation therapy (ADT) for advanced prostate cancer (PCa) utilizing luteinizing hormone-releasing hormone agonists (LHRHa) induces severe castrate-state side effects, notably bone mineral density (BMD) loss and metabolic dysfunction, due to concurrent estradiol depletion. Parenteral oestradiol, such as transdermal estradiol (tE2), avoids the hepatic first-pass metabolism that caused the cardiovascular (CV) toxicity of historical oral estrogens. This synthesis evaluates the therapeutic efficacy, safety and metabolic impact of tE2 in prostate cancer.

Methods: Data was synthesised from 5 clinical trials evaluating tE2 in PCa, including phase II studies in castration-resistant cohorts and large-scale RCTs in hormone-sensitive advanced diseases. Efficacy, CV safety, BMD fluctuations and quality of life (QoL) outcomes were studied across both these subtypes.

Results: Evidence from the large-scale, multi-stage PATCH and STAMPEDE trials (1,362 M0 and 1,128 M1 patients) confirms that tE2 patches achieve testosterone suppression equivalent to LHRHa (1.7 nmol/L), featuring a faster initial testosterone decline. Crucially, tE2 did not cause excess CV toxicity compared to LHRHa (HR 1.11, 95% CI 0.80- 1.53; P = 0.54). Regarding skeletal health, a key preplanned substudy demonstrated that while LHRHa caused a -3.0% lumbar spine BMD loss at 2 years, tE2 treated patients experienced a +7.9% BMD increase (P<0.001) - mitigating the risk of osteoporotic fractures without adding complex bone protection agents. Furthermore, tE2 improved metabolic profiles, reducing fasting glucose and total cholesterol relative to LHRHa. From a QoL perspective, tE2 significantly reduced hot flushes (8% vs. 46%) but increased gynecomastia incidence (37% vs. 5%). However, the utility of tE2 is restricted to hormone sensitive settings; a phase II study combining low-dose tE2 (0.2 mg/24 h)

with paclitaxel poliglumex in heavily pretreated mCRPC patients demonstrated no clinical activity, with zero patients achieving a ≥ 50% PSA decline and a median time to progression of 4 weeks.

Conclusions: tE2 represents a viable, cost-effective single-agent alternative to LHRHa for hormone sensitive advanced PCa. It successfully induces castrate levels of testosterone while distinctly preserving BMD, improving metabolic markers and mitigating hot flushes, without increasing the risk of CV toxicity.