Article published online: 2020-12-31

Emerging potential of parenteral estrogen as androgen deprivation therapy for prostate cancer

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Abstract

Androgen deprivation therapy (ADT) is a key management strategy for prostate cancer (PC), achieved commonly by administration of luteinizing hormone-releasing hormone agonist (LHRHa), ADT markedly suppresses both male and female sex hormones which results in "castration syndrome", a constellation of adverse events such as muscle weakness, impairment of glucose and lipid metabolism, impotence, osteoporosis, and fractures. Recent evidence suggests that estrogen, in the parenteral form, may emerge as an alternative to LHRHa as it offers potential benefits of arresting PC growth as well as avoiding some of the estrogen deficiency related toxicities of LHRHa by maintaining endogenous levels of estrogen.

Key words: Androgen deprivation therapy, parenteral estrogen, prostate cancer

Introduction

Prostate cancer (PC) is the most common malignancy and the second most common cause of cancer death affecting men in the western world.[1] PC incidence has risen rapidly in Asia where people are known to have the lowest risk of this disease. Factors responsible for this rapid rise include aging population, westernized dietary habits, and increasing use of prostate-specific antigen (PSA) testing.[2] Prostate cells, normal or cancerous, are dependent upon androgens for survival and growth. Consequently, androgen deprivation therapy (ADT) (commonly called hormone therapy) is the mainstay of PC treatment. Surgical or medical interventions resulting in the reduction of testosterone or blockade of the androgen receptor are referred to as ADT. ADT was initially achieved by orchiectomy as the testes are the principal source of circulating androgens (producing nearly 95% of total); the remaining 5% are produced by the adrenal glands. Luteinizing hormone-releasing hormone agonist (LHRHa) is the most widely administered contemporary ADT modality usually offered following a diagnosis of advanced (incurable) disease either at presentation, following failure of radical therapy with curative intent and as adjuvant or neo-adjuvant to radical radiotherapy for localized disease.[3] This review focuses on the potential of parenteral estrogen as an alternative option to LHRHa for ADT.

Luteinizing Hormone-Releasing Hormone Agonist and Castration Syndrome

Introduced in the 1980s, LHRHa acts by down-regulating gonadotrophin receptors in the pituitary, thereby causing central hypogonadism [Figure 1]. However, initial exposure to LHRHa leads to a "testosterone flare", which can exacerbate symptoms in a few patients like worsening bone pain from skeletal metastasis. The flare phenomenon is blocked by giving anti-androgens, a week before administering LHRHa.[4] Contemporary LHRHa as ADT delivers up to a 95% reduction in endogenous testosterone levels, which in turn results in suppression of endogenous estrogen (by about 80%) as it is derived from testosterone.[5]

The iatrogenic hypogonadism resulting from LHRHa therapy causes unwanted side effects including sarcopenia, anemia and erectile dysfunction (from testosterone deficiency) and osteoporosis (with high risk of fractures), hot flushes and probably, cognitive impairment (menopausal symptoms from estrogen deficiency) [Figure 2].[6] These LHRHa toxicities are labeled as "castration syndrome" which has a huge impact not only upon the quality-of-life (QOL) but also on the overall cost of treating PC and on the health economy.[7]

Oral Estrogen

Long before the advent of LHRHa, diethylstilbestrol (DES), a synthetic oral estrogen, was the first pharmacological agent used as an effective and inexpensive ADT for PC. DES acts by lowering androgen production via a negative feedback loop affecting the hypothalamic-pituitary-testicular axis [Figure 1]. The Veterans Administration Cooperative Urological Research Group (VACURG) conducted a series of randomized clinical trials between 1960 and 1975, comparing surgical orchiectomy, DES, and combination of both for the treatment of newly diagnosed PC.[8] Despite showing greater efficacy than orchiectomy, DES was discontinued from routine clinical use as results from the VACURG trials showed that DES caused cardiovascular (CVS) toxicity in up to 35% of patients with 15% experiencing a thromboembolic event. CVS mortality was shown to be lower after therapy with low dose DES (1 mg) as compared to high dose DES (5 mg) without any change in oncological effect. More recently, fosfestrol, another synthetic estrogen, was shown to be effective in controlling castration-resistant PC in terms of declining PSA levels but its toxicity profile needs elaboration.[9]

It is now known that the thromoboembolic and CVS complications of oral estrogen are a consequence of direct exposure of the liver to high concentrations of estrogen through the portal circulation which leads to hepatic overexpression of proteins, including those involved in coagulation.[10]

Parenteral Estrogen

Parenteral estrogen appears to be a more suitable alternative to both LHRHa and oral estrogen in the treatment of PC. Research over the last two decades suggests that parenteral administration of estrogen as ADT (intramuscular or transdermal) avoids first-pass through the liver, thereby avoiding hepatic induction of pro-coagulant proteins and circumventing the CVS toxicity. Several recent studies have demonstrated that castrate levels of testosterone for PC growth arrest can be achieved by this strategy, with little effect on hemostatic profile [Table 1].

A series of studies was conducted by the Scandinavian PC Group (SPCG) using polyestradiol phosphate (PEP) administered

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/2278-330X.155699

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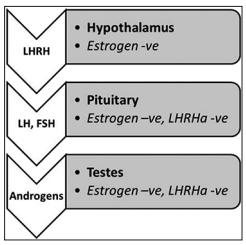

Figure 1: Inhibition of hypothalamic-pituitary-gonadal axis; estrogen inhibits testicular androgen production by negative feedback, luteinizing hormone-releasing hormone agonist down-regulates anterior pituitary receptors and suppresses release of luteinizing hormone and follicle-stimulating hormone, subsequently diminishing androgen formation in testes

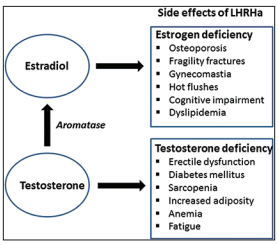

Figure 2: Luteinizing hormone-releasing hormone agonist-induced hypogonadism causes adverse effects related to both testosterone and estrogen deficiencies

Table 1: Characteristics of recent studies on parenteral estrogen for treating prostate cancer

Study title and design	Estrogen type	Patient number	Median follow-up	Toxicity outcomes
SPCG-5, randomized clinical trial	Intramuscular PEP versus CAB	*n*=910	18.5 months	No significant difference between groups in terms of overall and CVS mortalities
Ockrim *et al*. pilot study	Transdermal estradiol	*n*=20	12 months	No significant CVS toxicity from baseline
PATCH Phase II Stage 1, randomized clinical trial	Transdermal estradiol versus LHRHa	*n*=254	19 months	Similar rates of CVS events in the trial arms

SPCG=Scandinavian Prostate Cancer Group, PATCH=Prostate Adenocarcinoma TranCutaneous Hormones, PEP=Polyestradiol phosphate, CAB=Combined androgen blockade, LHRHa=Luteinizing hormone-releasing hormone agonist, CVS=Cardiovascular

intramuscularly. In the largest SPCG trial (*n* = 910), no significant difference was observed in progression-free survival, overall or disease-specific survival and CVS mortality between the two groups of PC patients randomized to receive either combined androgen blockade (LHRHa/orchiectomy plus anti-androgen) or intramuscular estrogen (PEP 240 mg).[11]

Topical Estrogen

Topical application of estrogen as a transdermal patch, gel or cream has potential advantages over other injections as it can be conveniently self-administered and readily withdrawn if toxicities occur. Ockrim *et al*. used transdermal estrogen (estradiol skin patches) in a small study (*n* = 20) on hormone naïve patients with advanced PC. Castrate levels of testosterone and effective tumor response (decrease in PSA levels) were achieved without significant CVS toxicity as seen with oral estrogen administration.[12] Recent results from the first stage of the phase II randomized clinical trial Prostate Adenocarcinoma TransCutaneous Hormone (PATCH) comparing LHRHa with transdermal estrogen patches in men with locally advanced or metastatic PC showed similar rates of CVS events in both arms. The rates of testosterone suppression were also similar in the two trial arms.[13]

Potential Benefits of Parenteral Estrogen

With parenteral estrogen, there is a benefit of not only treating the cancer (by suppressing testosterone to castrate levels), but also of maintaining endogenous levels of estrogen (through exogenous estrogen replacement), potentially avoiding menopausal symptoms.[14] Estrogen receptors are present in brain regions that mediate cognitive functions including memory.[15] Estrogen has an integral role in maintaining bone health through its anti-resorptive actions mediated by estrogen receptors.[16] Atheroprotective role of estrogen has also been suggested which may be mediated through the improvement in lipid profile (reduced low-density lipoprotein and elevated high-density lipoprotein [HDL]) seen with estrogen.[17] Some of these beneficial effects of estrogen have been widely studied in females particularly the setting of the menopause, but very little work has been done in men suffering from PC.[18,19]

In a study of men treated with transdermal estrogen patches for newly diagnosed locally advanced or metastatic PC, Ockrim *et al*. showed that of 12 baseline osteoporotic/osteopenic regions (in five patients), four showed improvement based on the World Health Organization grading after a year of therapy and bone mineral density increased at all measured sites over time.[20] None of the patients on intramuscular PEP in the SPCG trial developed serious skeletal complications compared to 18 on combined androgen blockade.[11]

Recent results from the PATCH trial showed blood glucose and lipid profiles to be more favorable in the estrogen arm than in the LHRHa arm. At 6 and 12 months, mean fasting cholesterol increased in the LHRHa arm but decreased in the estrogen arm whereas HDL cholesterol increased in both. Mean fasting glucose showed increase in the LHRHa group at 6 months and again further at 12 months, but it decreased in the estrogen group at 6 months which was maintained unchanged at 12 months. Patients in the estrogen patches group also reported less hot flashes (25%) than in the LHRHa group (56%). Gynecomastia was observed on both treatments, but more frequently in the estrogen-patches group.[13]

Conclusion

From the limited evidence available, parenteral estrogen appears to be a potentially important alternative to LHRHa in the management of PC. However, before it is inducted into the clinical setting, there is a need to institute research trials aimed at evaluating the benefits of parenteral estrogen as ADT for PC. Future results from such investigations may establish parenteral estrogen as an inexpensive and effective monotherapy for both treating PC and eliminating some of the serious adverse events that occur following castration with LHRHa (including osteoporosis with increased risk of fracture, cognitive impairment, and hot flushes). This potential development will not only improve the QOL of PC survivors, but its cost-effectiveness will also have considerable health-economic benefits.

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How to cite this article: Ali Shah SI. Emerging potential of parenteral estrogen as androgen deprivation therapy for prostate cancer. South Asian J Cancer 2015;4:95-7.
Source of Support: Nil. **Conflict of Interest:** None declared.