Review Article

The resurgence of estrogens in the treatment of castration-resistant prostate cancer

H. Krishna Moorthy, G. G. Laxman Prabhu[1], P. Venugopal[1]*

Department of Urology, Lourdes Hospital, Kochi, Kerala, [1]Department of Urology, Kasturba Medical College (A Unit of Manipal Academy of Higher Education), Mangalore, Karnataka, India

*E-mail: peeveegee@gmail.com

ABSTRACT

Use of exogenous estrogens in manipulating the androgenestrogen equilibrium was one of the earliest therapeutic strategies developed to treat prostate cancer which followed close on heels the discovery of hormone dependence of this tumor. Despite its well-documented benefit, estrogen therapy fell out of favor with the advent of other forms of androgen deprivation therapy (ADT) as the former registered a higher incidence of cardiovascular complications and poorer overall survival. Clearer understanding of the mechanism of action of estrogen coupled with the adoption of alternative routes of administration has triggered a renewed interest in estrogen therapy. Since then, many studies have not only proved the therapeutic benefit of estrogens but also explored the ways and means of minimizing the dreaded side effects deterring its use. Further, the fact that estrogen therapy offered a clear advantage of reduced cost of treatment over other treatments has led many countries to readopt it in the treatment of advanced prostatic cancer. We reviewed the published data on the use of estrogens in CRPC, which may affect its revival as an efficacious treatment option having minimal side effects, with modified dosage and route of administration. Estrogen therapy would be a less expensive option having equivalent or even better therapeutic effect than ADT in advanced carcinoma of prostate.

INTRODUCTION

Testosterone and 5 α dihydrotestosterone stimulate the growth of prostate cells, though they do not induce prostate cancer *per se*. Prostate cancer metastases in men with progressive castration-resistant prostate cancer (CRPC) have been found to contain higher levels of testosterone receptors than those in prostate cancer tissue from eugonadal men which clearly underscores the testosterone dependency of this disease. Endogenous estrogens work in synergy with androgens for the malignant transformation of prostate epithelial cells through a complex mechanism.[1,2]

Androgen deprivation therapy (ADT) has long been recognized as the corner stone for the treatment of locally advanced and metastatic carcinoma of prostate. However, ADT is associated with major side effects such as skeletal-related events (osteopenia, osteoporosis, and fracture of bones), increased risk of cardiovascular diseases, weight gain, metabolic syndrome, reduced quality of life (due to hot flushes, sexual dysfunction, fatigue, and mental depression), and cognitive decline.[3] These side effects are due to the reduction in testosterone levels which in turn result in reduced peripheral conversion of testosterone to estrogen. The reduction in testosterone level in ADT is up to 95% with a concurrent reduction in endogenous estrogen by about 80%.

Usefulness of exogenous estrogen therapy in the management of advanced and CRPC has been known for several decades. It is possible that exogenous estrogen suppresses pituitary luteinizing hormone (LH) production via negative feedback

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.IJU_56_19

Received: 17.02.2019, **Accepted:** 26.05.2019

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

thereby reducing systemic testosterone production. Concurrently, the exogenous estrogens replace the lost endogenous estrogens so that the overall estrogen levels remain high, thus avoiding the undesired side effects of estrogen reduction seen with ADT. The role of estrogen in the coagulation cascade which is also the pharmacologic basis of its adverse events is depicted in Figure 1.

Despite its well-documented benefit, estrogen therapy fell out of favor with the advent of other forms of ADT as the former had a higher incidence of cardiovascular complications and poorer overall survival. Most of the toxicity caused by exogenous estrogen therapy is a consequence of the first pass portal circulation which facilitates the hepatic metabolism of hormones, lipids, and coagulation proteins. Administration of estrogen by routes which bypass the hepatic enzyme induction can significantly reduce its side effects. Clearer understanding of the mechanism of action of estrogen coupled with the adoption of alternative routes of administration has triggered a renewed interest in estrogen therapy, particularly in CRPC. We reviewed the published articles on treatment of CRPC with exogenous estrogens by searching the Medline PubMed databases from 2000 to 2018.

ROLE OF ENDOGENOUS ESTROGENS IN PROSTATE CANCER

While some studies have shown that elevated plasma estrogens increase the risk of prostate cancer,[4,5] certain others have observed contradictory findings.[6] Estrogen mediates its biological effects in prostate tissue by binding to the intracellular estrogen receptor (ER) β, with minor effects on ER α.[7,8] The principal ERs, namely ER α and ER β are expressed by prostate in health and disease. They exhibit functional specificity, and any imbalance in their expression can significantly alter the estrogenic effect on target cells in the prostate. Loss of expression of ER β has been reported to be associated with development of prostate cancer.[9]

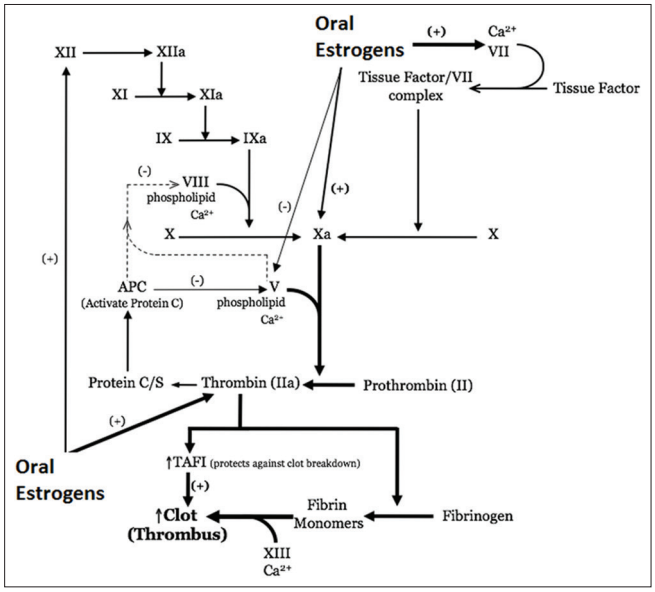

Figure 1: The role of estrogens in coagulation cascade which is the pharmacologic basis of adverse events

There is growing evidence to believe that endogenous estrogens exert their effect on carcinogenesis through a genotoxic mechanism that protects against catechol estrogen and redox cycle.[10,11] In contrast, the natural estrogens from plants products (phytoestrogens, like soy isoflavones such as genistein) and dietary estrogen analogs have been proposed to retard prostate cancer development and therefore have the potential for use as anticancer agents.[12]

HISTORICAL PERSPECTIVE OF EXOGENOUS ESTROGEN THERAPY

The first description of the role of exogenous estrogen therapy in advanced prostate cancer was given by Huggins and Hodges in 1942.[13,14] Subsequently, over the next four decades, estrogens and orchiectomy became the standard of care for the treatment of all patients with advanced carcinoma of prostate. However, the Veterans Administration Cooperative Urological Research Group (VACURG) study published their results in late 1960s which showed significant discrepancy between cancer specific survival and overall survival of cancer prostate patients with exogenous estrogens.[15-17] These studies also revealed significantly increased risk of cardiovascular mortality in 36% of patients and thromboembolism in up to 15% of patients receiving diethylstilboestrol (DES) at a dosage of 5 mg daily. These alarming results combined with development of luteinizing hormone-releasing hormone (LHRH) agonists (LHRHa) and nonsteroidal antiandrogens with equivalent oncological effects and lower cardiovascular toxicity pushed estrogens to the back seat in therapeutics of advanced carcinoma of prostate.

Interestingly, the subsequent VACURG studies using DES at lower doses and studies using transdermal estradiol (E2) reported significant therapeutic response in selected patients with CRPC associated with lesser cardiovascular side effects and delayed mortality. Other studies have also reported significant effect of 17 β E2 in suppressing CRPC growth and delayed mortality.[18] These studies have rekindled a new interest in exploring the potential for safer use of estrogens in the management of advanced carcinoma of the prostate.

MECHANISM OF ACTION OF EXOGENOUS ESTROGENS

The various mechanisms that are postulated for the beneficial effects of exogenous estrogen in patients with carcinoma of prostate are as follows:[19-21]

Suppression of circulating androgens

- Inhibition of LHRH from hypothalamus with subsequent suppression of LH and testicular production of testosterone
- Strong binding activity to the androgen receptors
- Suppression of androgens (dehydroepiandrosterone sulfate and androstenedione) from extra gonadal sources
- Nonhormonal pathways.

Effects on cell cycle/intracellular apparatus

- Inhibition of growth of primary cultures of benign prostatic hyperplasia and carcinoma of prostate cell lines
- Interaction with cellular and mitochondrial ATP synthase
- Interaction with cellular microtubules
- Promotion of cell cycle arrest and apoptosis through a non-ER mechanism
- Alteration in levels and stability of tubulin (mitotic apparatus component)
- Induction of cell cycle arrest G2-M phase by microtubule polymerization
- Downregulation of genes involved in tumorigenesis and upregulation of insulin-like growth factor binding protein 6 gene expression and protein levels
- Effects of telomerase activity and gene expression
- Antiangiogenic effects by inhibiting the growth and migration of vascular smooth muscle cells
- Inhibition of enzymes of androgen steroidogenesis in tissues to suppress local androgen levels
- Direct cytotoxic effects on prostate cells
- Induction of immune surveillance
- Metabolism of 17 β E2 to cytotoxic estrogens such as 2-methoxyestradiol which has significant antiangiogenic and proapoptotic effects
- Direct suppression of Leydig cell function and androgen steroidogenesis
- Antiandrogen action in prostate cancer cell lines with a mutated androgen receptors.

MECHANISM OF ESTROGENIC SIDE EFFECTS

These are various mechanisms by which exogenous estrogens exert their side effects in the body.[19]

- Induction of hypercoagulability by increasing synthesis of coagulation factors I, II, VII, IX, X
- Increasing the serum level of factor VII
- Reduction in plasminogen activation levels, thereby reducing fibrinolysis
- Reduction in antithrombin III
- Alteration in platelet function
- Alteration in serum lipid profile.

LOW-DOSE DIETHYLSTILBOESTROL IN THE TREATMENT OF CRPC

There are several studies which have proved that low-dose DES would be beneficial in the treatment of CRPC. The phase II trial with 1 mg of oral DES in 21 patients showed a prostate-specific antigen (PSA) response in 43% patients with confirmed adenocarcinoma of prostate and distant metastasis refractory to first-line androgen deprivation.[22] These authors reported only 5% of patients developing deep vein thrombosis (DVT), 14% developing gynecomastia though 90% of patients had minimal nipple hypersensitivity. Baseline PSA, hemoglobin, lactate dehydrogenase, alkaline phosphate, and length of time on first hormonal treatment did not correlate with the response. The estimated survival at 2 years of treatment was 63%.

In a review article, Malkowicz has reported that 0.1 mg of DES/day was quite effective as much as 3 mg/day as an anticancer agent with lesser side effects, although subsequently, 1 mg of DES three times a daily evolved as the standard form of treatment.[23]

Wilkins *et al*. in 2012 reported a PSA response rate of 28.9%, median time to PSA progression of 4.6 months, improvement in European Organization for the Research and Treatment of Cancer pain score in 18% and thromboembolic complication in 9.9% of patients in their study involving 231 patients with CRPC using DES.[24] The patients received initial daily dose of 1 mg of DES with titration up to 3 mg. 75 mg of aspirin was also given to all patients with the exception of those who were already on Warfarin. Single fraction of 8 cGY external radiation was given to the breast buds before starting DES to prevent painful breast enlargement. Similar beneficial effects of low dose DES have also been reported by other authors using the drug in the treatment of CRPC before initiating chemotherapy.[25]

In a retrospective single center study on 43 CRPC patients with oral DES in a daily dose of 1–4 mg/day, there was >50% decline in serum PSA levels with durable responses (>1 year) in 31% of patients. Only 9% of patients in this study developed thromboembolic complications when thromboprophylaxis was given along with the treatment.[26]

The review article by Turo *et al*. also highlighted the usefulness of low-dose DES in many clinical trials for the treatment of CRPC with minimal side effect profiles.[19] These authors also proposed a synergistic effect of DES on tumor cells when used in conjunction with the newer therapies for cancer of prostate.

Aggarwal *et al*. reported that there was a significant reduction in serum testosterone levels in 12 weeks of treatment with DES at 3 mg/day or a herbal supplement (PC-SPES 960 mg TID) in patients with CRPC.[27] The patients in this study also received Warfarin 2 mg/day continuously as thromboembolism prophylaxis.

There are reports that 1 mg DES combined with dexamethasone resulted in more than 50% PSA decline

in 64%–68% patients, although venothromboembolism occurred in 22% of patients.[28] These authors reported that DES would be an alternative in patients with failed abiraterone treatment in patients with CRPC.

Shamash *et al*. in their multicenter randomized phase III trial compared the use of dexamethasone (2 mg/day), aspirin (75 mg/day), and ranitidine (150 mg twice a day) along with immediate addition of DES (1 mg/day) or deferred (until disease progression) addition of DES in CRPC.[29] They concluded that immediate or deferred use of DES in the management of CRPC did differ neither in terms of PSA response nor in terms of progression free survival. Therefore, deferring DES until failure of dexamethasone would be the preferred strategy when using these agents in CRPC to reduce the toxicity of DES.

Oral ethinyl E2 at 1 mg/day along with aspirin (100 mg/day) was found to be effective in 116 CRPC patients in a single center prospective analysis done by Sciarra *et al*.[30] They confirmed PSA response in 70.5% of patients and a median time to PSA progression of 15.1 months. About 23.2% of patients required treatment cessation due to toxicity at a median time of 16 months mainly due to thromboembolism.

PARENTERAL ESTROGENS IN THE TREATMENT OF CRPC

To mitigate the cardiovascular complications of oral estrogen by avoiding first-pass hepatic metabolism and avoid the complications caused by estrogen deprivation, an alternate approach using parenteral estrogens has been proposed. The Scandinavian Prostate Cancer Group-5 trial study evaluated the results of intramuscular injections of 240 mg polyestradiol phosphate (PEP) every 2nd week for the first 8 weeks followed by a maintenance dose of 240 mg monthly in 915 patients with advanced prostate carcinoma. It was concluded that parenteral estrogen regimen had comparable efficacy and cardiovascular safety to medical or surgical orchiectomy in patients with advanced cancer of prostate with lesser skeletal side effects, although the nonfatal complications such as gynecomastia were more pronounced in the PEP group.[31]

Norman *et al*. in their systematic review[32] and Phillips *et al*.[33] in their study on use of parenteral estrogen in the treatment of cancer of prostate reported the efficacy of this form of drug regimen in advanced prostate cancer compared to LHRH analog with the added advantage of lower cost of treatment.

TRANSDERMAL ESTROGENS IN THE TREATMENT OF CRPC

It is recognized that transdermal application of estrogens can eliminate cardiovascular and thromboembolic complications resulting from first-pass effect in the liver with production of prothrombotic proteins.

Langley *et al*. assessed the hormonal effects of Fem 7 (100 mg transdermal estrogen patches) on men undergoing first-line ADT for advanced prostate cancer.[34] They found that the estrogen patches produced castrate levels of testosterone with concomitant PSA reduction at 12 weeks of therapy, with lesser side effects. The testosterone levels in eight of the 13 patients studied were <1.7 nmol/l, two were 1.7–2 nmol/l, and three were more than 2 nmol/l. All patients had a PSA response, with eight having a PSA level <4 ng/ml. Therefore, early evidence from these studies supports estrogen patches as viable alternatives to LHRH.

Stein *et al*. also proved in their study involving 22 patients, who had advanced, heavily pretreated castrate and chemotherapy refractory cancers that transdermal E2 patches (0.4 mg/24 h total) applied at weekly intervals to be effective with significant PSA responses.[35] In another study, an average of two patches per day (0.6 mg/24 h of 17 β E2) for 8 weeks was found to be sufficient to maintain androgen ablation in 20 men with locally advanced or metastatic prostate cancer.[36] Ockrim *et al*. in their study observed that transdermal E2 therapy resulted in increase in mean and peak systolic velocities and photoplethysmography in arterial blood flow at 6 months of treatment.[37] Arterial compliances initially decreased but got normalized after 12 months. However, the venous variables were unaffected by therapy. This study probably pointed to the cause for increase in cardiovascular toxicity in early phase of estrogen patch therapy and the cardioprotective effect that accrued thereafter.

The PATCH trial (NCT00303784) is currently being under taken to compare the efficacy and safety of transdermal E2 agonists versus gonadotropin-releasing hormone analogs in men with locally advanced and metastatic prostate cancer with reduced cardiovascular side effects.[38] Transdermal E2 has also been found to be beneficial in improving bone mineral density.[39] This form of therapy has been reported to produce more favorable metabolic profiles with better quality of life although there has been increased chance of gynecomastia.[40] The STAMPEDE trial (NCT00268476) is also currently recruiting patients to compare transdermal E2 with standard ADT as a compliment to the PATCH trial.[41]

These studies strongly support the use of transdermal E2 as a potential alternative to LHRH analog for the suppression of androgens in the treatment of locally advanced and metastatic prostate cancer. This form of treatment is probably less thrombogenic as it avoids hepatic first-pass mechanism which increases the synthesis of thrombophilic coagulation factors. The treatment is also significantly cost-effective in comparison to LHRHa.

OTHER FORMS OF ESTROGEN THERAPY

Estramustine phosphate, a nitrogen mustard derivative of E2-17 β-phosphate, has been found to have antitumor properties. Ravery *et al*. reviewed the studies on combination therapy with estramustine and docetaxel in the treatment of advanced prostate cancer.[42] The studies revealed that use of estramustine with adjunctive low molecular weight heparin could be used as an effective second-line treatment strategy in hormone refractory prostate cancer.

Fosfestrol, a DES prodrug developed to achieve higher water solubility and lower toxicity, was found to produce higher intracellular levels of DES with significant anti-tumor activity.[43] Fosfestrol 100 mg thrice a day was given orally in a continuous schedule until the appearance of progressive disease or excess toxicity. In 38 patients with hormone refractory prostate cancer, the median time to progression with oral fosfestrol was 7 months; in 34% of patients, pain remained stable, and in another 53%, there was improvement in pain score. Toxicities such as worsening of gynecomastia, peripheral edema, and DVT were observed in 8% of patients. There was no treatment-related deaths reported in the trial. The authors proposed concomitant prophylaxis with anticoagulants in patients with predisposing factors during the therapy.

Toremifene, as a second generation of selective ER modulators, was reported to have lesser cardiovascular side effects compared to ADT when administered at 80 mg dose.[44]

The analogue of 2-Methoxyoestradiol named as ENMD-1198 was found to be beneficial in patients with advanced prostate cancer.[45]

The agonist of ER α, Tx 758 was also found to decrease the estrogen deficiency side effects during ADT though it increased the risk of venous thromboembolic complication.[46]

ESTROGEN IN THE MANAGEMENT OF HOT FLUSHES IN MEN RECEIVING ANDROGEN-DEPRIVATION THERAPY

Hot flushes are characterized by a subjective sensation of rise in cutaneous temperature due to vasodilation predominantly in the face; throat and extremities usually followed by perfuse sweating. Following the administration of ADT, there is steep decline in serum LH and *follicle-stimulating hormone* resulting in the release of hypothalamic catecholamines, particularly that of norepinephrine. This affects the thermoregulatory center in upper hypothalamus resulting in abnormal peripheral vasodilatation. About 80% of patients on ADT will experience hot flushes, of which 27% is likely to have persistent troublesome effects.

There are many drugs including cyproterone acetate, gabapentin, clonidine, selective serotonin reuptake inhibitors, and various herbal products containing phytoestrogens recommended for the treatment of hot flushes. Megestrol acetate 20 mg twice a day has been reported to produce complete resolution of symptoms in 70% of men on ADT and reduction in the severity of symptom in another 20%.[47]

Oral DES in the dose of 0.25–0.5 mg/day was found to be effective in reducing hot flushes though gynecomastia remained a notable side effect.[48] Transdermal DES in the dose of 0.1 mg/h was also found to reduce the number and severity of hot flushes significantly.[49]

In a Japanese study conducted in 2004, it was observed that estramustine phosphate also reduced the hot flush score significantly in patients undergoing ADT.[50]

COST OF THERAPY

The cost of treatment at this advanced stage of the disease is yet another limiting factor. Treating prostate cancer and treatment-associated toxicities has been reported to cost the UK over £100 million per annum with a total global health bill estimated at more than £2 billion. Abiraterone was estimated to cost around £50, 000 per quality adjusted life years, when it extended the median survival by a mere 3–5 months.[51]

The cost-effectiveness of ADT in advanced prostate cancer has been analyzed by Bayoumi *et al*. which is shown in Table 1.[52] These authors questioned the cost-effectiveness of wide spread use of expensive androgen suppression strategies based solely on biochemical evidence of disease progression in men with advanced prostate cancer. ADT was found to be the least economically attractive option yielding small health benefits at relatively higher cost.

DISCUSSION

The selection of treatment options for CRPC is often linked to poor prognosis prediction since the reduction in PSA level observed in these patients need not necessarily correlate with the outcome of treatment, especially in the first 3 months of treatment. Shamash *et al*. reported a validated prognostic index predicting the response of dexamethasone and DES in the treatment of CRPC which could have some clinical relevance.[53] However, the distressing side effects of currently used ADT still continue to cast doubts on the therapeutic judgment of treating physician in advanced carcinoma of prostate.

It is well known that with the advent of LHRH analogues, estrogen therapy which was far more cost effective receded from the therapeutic armamentarium for a while. However,

Table 1: Cost-effectiveness estimates in carcinoma of prostate Bayoumi *et al*.[52]

Strategy	Costs and life years	
	Cost in USD	Effective life years
DES	4100	6.86
Orchiectomy	7500	7.58
NSAA	18,400	7.39
NSAA + orchiectomy	23,200	7.54
LHRHa	30,900	7.54
NSAA + LHRHa	46,200	7.52

DES=Diethylstilboestrol, NSAA=Nonsteroidal antiandrogens, LHRHa=Luteinizing hormone-releasing hormone agonist

since 2010, there has been a renewed interest in revisiting this mode of therapy as an alternative to ADT or even as an option before chemotherapy in CRPC. Hongo *et al*. in 2014 reported complete response to ethinyl E2 administered for almost 2 years in patients with CRPC.[54] There is an interesting article on a urologist's personal experience with multiple surgical, hormonal, and radio/immunotherapeutic options for the treatment of advanced prostate cancer and thoughts on the role of old and new therapies.[55] The author narrated that in 2008, he was advised transdermal E2 patch which he began and continued to the present. E2 slowed his PSA doubling time but of equal importance, improved his sense of well-being. The author finally concluded that estrogen was barely mentioned in the guidelines of the major oncology societies and was being essentially overlooked and very much underappreciated.

For patients with metastatic castration-resistant prostate cancer on androgen receptor signaling inhibitors and standard chemotherapy, it is now reported that those who harbored circulating tumor cells that had AR-V7 protein in the cellular nuclei were very likely to survive longer on taxane-based chemotherapy.[56] There are also reports that detection of AR-V7 in circulating tumor cells from patients with CRPC has been reported to be associated with resistance to enzalutamide and abiraterone.[57] Estrogens would be a good alternative in these situations, if AR-V7 proteins could be detected before the administration of the newer forms of ADT.

Recent study by Pramesh *et al*. highlighted that delivery of affordable and equitable cancer care as one of India's greatest public health challenges.[58] These authors calculated that the public expenditure on cancer in India as below $ 10 per person (compared with more than $100 per person in high-income countries), with overall public expenditure on health care being only slightly above 1% of gross domestic product. Interestingly, out-of-pocket payments, which accounted for more than three-quarters of cancer expenditures in India, was regarded as one of the greatest threats to patients and families. A cancer diagnosis was increasingly responsible for catastrophic expenditures that negatively affected not only the patient but also the welfare and education of several generations of their family.

Yet another interesting study by Haddad *et al*. highlighted that there existed a social gradient in community as far as healthcare delivery was concerned in India, which was not solely explained by differences in material deprivation, but was dependent on other factors, such as social exclusion and caste discrimination.[59] Therefore, we believe that effective treatment with low cost using estrogens in advanced cancer prostate in a country like India with wide social, economic, developmental and cultural stratifications, and ramifications would be a boon to the families to avert the economic drain on them caused by the disease and its treatment.

It is now well recognized that oral estrogens, due to the first pass though the liver, has been responsible for the alarming cardiovascular and thromboembolic setbacks of estrogen. Low dose estrogen, especially given parenterally or transdermally appears to be well tolerated with minimal side effects and highly cost-effective. Estrogens in low doses may not cause osteoporosis and has beneficial effect in patients with CRPC compared to ADT. Estrogen and their analogs could also be used to alleviate the distressing side effect of hot flushes in patients on ADT.

CONCLUSIONS

There is currently enough evidence to support the efficacy of estrogen therapy in the management of CRPC. The resurgence of estrogen therapy would be a less expensive option having equivalent or even better therapeutic effects than ADT in this disease scenario.

REFERENCES

1. Santti R, Newbold RR, Mäkelä S, Pylkkänen L, McLachlan JA. Developmental estrogenization and prostatic neoplasia. Prostate 1994;24:67-78.
2. Thomas JA, Keenan EJ. Effects of estrogens on the prostate. J Androl 1994;15:97-9.
3. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, *et al*. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 2015;67:825-36.
4. Barrett-Connor E, Garland C, McPhillips JB, Khaw KT, Wingard DL. A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. Cancer Res 1990;50:169-73.
5. Modugno F, Weissfeld JL, Trump DL, Zmuda JM, Shea P, Cauley JA, *et al*. Allelic variants of aromatase and the androgen and estrogen receptors: Toward a multigenic model of prostate cancer risk. Clin Cancer Res 2001;7:3092-6.
6. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118-26.
7. Jensen EV, Jacobson HI, Walf AA, Frye CA. Estrogen action: A historic perspective on the implications of considering alternative approaches. Physiol Behav 2010;99:151-62.
8. Lai JS, Brown LG, True LD, Hawley SJ, Etzioni RB, Higano CS, *et al*. Metastases of prostate cancer express estrogen receptor-beta. Urology 2004;64:814-20.
9. Oh WK. The evolving role of estrogen therapy in prostate cancer. Clin Prostate Cancer 2002;1:81-9.

10. Cavalieri E, Frenkel K, Liehr JG, Rogan E, Roy D. Estrogens as endogenous genotoxic agents – DNA adducts and mutations. J Natl Cancer Inst Monogr 2000;27:75-93.
11. Cavalieri EL, Devanesan P, Bosland MC, Badawi AF, Rogan EG. Catechol estrogen metabolites and conjugates in different regions of the prostate of noble rats treated with 4-hydroxyestradiol: Implications for estrogen-induced initiation of prostate cancer. Carcinogenesis 2002;23:329-33.
12. Bosland MC. The role of estrogens in prostate carcinogenesis: A rationale for chemoprevention. Rev Urol 2005;7 Suppl 3:S4-10.
13. Huggins C. Effect of orchiectomy and irradiation on cancer of the prostate. Ann Surg 1942;115:1192-200.
14. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972;22:232-40.
15. Treatment and survival of patients with cancer of the prostate. The Veterans Administration Co-Operative Urological Research Group. Surg Gynecol Obstet 1967;124:1011-7.
16. Bailar JC 3rd, Byar DP. Estrogen treatment for cancer of the prostate. Early results with 3 doses of diethylstilbestrol and placebo. Cancer 1970;26:257-61.
17. Byar DP. Proceedings: The veterans administration cooperative urological research group's studies of cancer of the prostate. Cancer 1973;32:1126-30.
18. Montgomery B, Nelson PS, Vessella R, Kalhorn T, Hess D, Corey E. Estradiol suppresses tissue androgens and prostate cancer growth in castration resistant prostate cancer. BMC Cancer 2010;10:244.
19. Turo R, Smolski M, Esler R, Kujawa ML, Bromage SJ, Oakley N, *et al.* Diethylstilboestrol for the treatment of prostate cancer: Past, present and future. Scand J Urol 2014;48:4-14.
20. Gomella LG. Effective testosterone suppression for prostate cancer: Is there a best castration therapy? Rev Urol 2009;11:52-60.
21. Qadan LR, Perez-Stable CM, Anderson C, Dilppolito G, Herron A, Howard GA, *et al*. 2 methoxyestradion induces G2/M arrest and apoptosis in prostate cancer. Biochem Biophys Res Commun 2001;285:1259-66.
22. Smith DC, Redman BG, Flaherty LE, Li L, Strawderman M, Pienta KJ. A phase II trial of oral diethylstilbesterol as a second-line hormonal agent in advanced prostate cancer. Urology 1998;52:257-60.
23. Malkowicz SB. The role of diethylstrilbesteron in the treatment of prostate cancer. Urology 2001;58 Suppl 2A: 108-13.
24. Wilkins A, Shahidi M, Parker C, Gunapala R, Thomas K, Huddart R, *et al.* Diethylstilbestrol in castration-resistant prostate cancer. BJU Int 2012;110:E727-35.
25. Bosset PO, Albiges L, Seisen T, de la Motte Rouge T, Phé V, Bitker MO, *et al.* Current role of diethylstilbestrol in the management of advanced prostate cancer. BJU Int 2012;110:E826-9.
26. Grenader T, Plotkin Y, Gips M, Cherny N, Gabizon A. Diethylstilbestrol for the treatment of patients with castration-resistant prostate cancer: Retrospective analysis of a single institution experience. Oncol Rep 2014;31:428-34.
27. Aggarwal R, Weinberg V, Small EJ, Oh W, Rushakoff R, Ryan CJ. The mechanism of action of estrogen in castration-resistant prostate cancer: Clues from hormone levels. Clin Genitourin Cancer 2009;7:E71-6.
28. Omlin A, Pezaro CJ, Zaidi S, Lorente D, Mukherji D, Bianchini D, *et al.* Antitumour activity of abiraterone and diethylstilboestrol when administered sequentially to men with castration-resistant prostate cancer. Br J Cancer 2013;109:1079-84.
29. Shamash J, Powles T, Sarker SJ, Protheroe A, Mithal N, Mills R, *et al.* A multi-centre randomised phase III trial of dexamethasone vs. dexamethasone and diethylstilbestrol in castration-resistant prostate cancer: Immediate vs. deferred diethylstilbestrol. Br J Cancer 2011;104:620-8.
30. Sciarra A, Gentile V, Cattarino S, Gentilucci A, Alfarone A, D'Eramo G, *et al.* Oral ethinylestradiol in castration-resistant prostate cancer: A 10-year experience. Int J Urol 2015;22:98-103.
31. Hedlund PO, Henriksson P; The Scandinavian Prostatic Cancer Group-5 Trial Study. Parenteral estrogen v/s total androgen ablation in the treatment of advanced prostate carcinoma: Effects on overall survival and cardiovascular mortality. Urology 2000;55:328-33.
32. Norman G, Dean ME, Langley RE, Hodges ZC, Ritchie G, Parmar MK, *et al.* Parenteral oestrogen in the treatment of prostate cancer: A systematic review. Br J Cancer 2008;98:697-707.
33. Phillips I, Shah SI, Duong T, Abel P, Langley RE. Androgen deprivation therapy and the re-emergence of parenteral estrogen in prostate cancer. Oncol Hematol Rev 2014;10:42-7.
34. Langley RE, Godsland IF, Kynaston H, Clarke NW, Rosen SD, Morgan RC, *et al.* Early hormonal data from a multicentre phase II trial using transdermal oestrogen patches as first-line hormonal therapy in patients with locally advanced or metastatic prostate cancer. BJU Int 2008;102:442-5.
35. Stein M, Goodin S, Doyle-Lindrud S, Silberberg J, Kane M, Metzger D, *et al.* Transdermal estradiol in castrate and chemotherapy resistant prostate cancer. Med Sci Monit 2012;18:CR260-4.
36. Ockrim JL, Lalani EN, Laniado ME, Carter SS, Abel PD. Transdermal estradiol therapy for advanced prostate cancer – Forward to the past? J Urol 2003;169:1735-7.
37. Ockrim JL, Lalani el-N, Aslam M, Standfield N, Abel PD. Changes in vascular flow after transdermal oestradiol therapy for prostate cancer: A mechanism for cardiovascular toxicity and benefit? BJU Int 2006;97:498-504.
38. Langley RE, Cafferty FH, Alhasso AA, Rosen SD, Sundaram SK, Freeman SC, *et al*. 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 2013;14:306-16.
39. Langley RE, Kynaston HG, Alhasso AA, Duong T, Paez EM, Jovic G, *et al.* A randomised comparison evaluating changes in bone mineral density in advanced prostate cancer: Luteinising hormone-releasing hormone agonists versus transdermal oestradiol. Eur Urol 2016;69:1016-25.
40. Gilbert DC, Duong T, Kynaston HG, Alhasso AA, Cafferty FH, Rosen SD, *et al.* Quality-of-life outcomes from the prostate adenocarcinoma: TransCutaneous hormones (PATCH) trial evaluating luteinising hormone-releasing hormone agonists versus transdermal oestradiol for androgen suppression in advanced prostate cancer. BJU Int 2017;119:667-75.
41. Gilbert DC, Duong T, Sydes M, Bara A, Clarke N, Abel P, *et al.* Transdermal oestradiol as a method of androgen suppression for prostate cancer within the STAMPEDE trial platform. BJU Int 2018;121:680-3.
42. Ravery V, Fizazi K, Oudard S, Drouet L, Eymard JC, Culine S, *et al.* The use of estramustine phosphate in the modern management of advanced prostate cancer. BJU Int 2011;108:1782-6.
43. Orlando M, Chacón M, Salum G, Chacón DR. Low-dose continuous oral fosfestrol is highly active in 'hormone-refractory' prostate cancer. Ann Oncol 2000;11:177-81.
44. Smith MR, Malkowicz SB, Brawer MK, Hancock ML, Morton RA, Steiner MS. Toremifene decreases vertebral fractures in men younger than 80 years receiving androgen deprivation therapy for prostate cancer. J Urol 2011;186:2239-44.
45. Zhou Q, Gustafson D, Nallapareddy S, Diab S, Leong S, Lewis K, *et al.* A phase I dose-escalation, safety and pharmacokinetic study of the 2-methoxyestradiol analog ENMD-1198 administered orally to patients with advanced cancer. Invest New Drugs 2011;29:340-6.
46. Yun H, Xie J, Olumi AF, Ghosh R, Kumar AP. Activation of AKR1C1/ERβ induces apoptosis by downregulation of c-FLIP in prostate cancer cells: A prospective therapeutic opportunity. Oncotarget 2015;6:11600-13.

47. Khan A, Lewis R, Huger S. Managing hot flush in men receiving androgen deprivation therapy for prostate cancer. Trends Urol Mens Health 2014;5:31.
48. Smith JA Jr. A prospective comparison of treatments for symptomatic hot flushes following endocrine therapy for carcinoma of the prostate. J Urol 1994;152:132-4.
49. Gerber GS, Zagaja GP, Ray PS, Rukstalis DB. Transdermal estrogen in the treatment of hot flushes in men with prostate cancer. Urology 2000;55:97-101.
50. Fukuhara S, Yokoyama S, Tsutahara K, Mori N, Hara T, Yamaguchi S. A clinical study of estramustine phosphate sodium for the treatment of hot flushes in men with prostate cancer. Nihon Hinyokika Gakkai Zasshi 2004;95:761-5.
51. Wilson HC, Sahah SI, Price P, Abel PD. Re-state of the art treatment in castration-resistant prostate cancer-forward to the past-again. EMJ 2014;2:100-5.
52. Bayoumi AM, Brown AD, Garber AM. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. J Natl Cancer Inst 2000;92:1731-9.
53. Shamash J, Stebbing J, Sweeney C, Sonpavde G, Harland S, Dawkins G, *et al*. A validated prognostic index predicting response to dexamethasone and diethylstilbestrol in castrate-resistant prostate cancer. Cancer 2010;116:3595-602.
54. Hongo H, Kosaka T, Oya M. Complete response to ethnylestradiol prolonged for almost two years in patients with castration-resistant prostate cancer. Can Urol Assoc J 2014;8:E921-3.
55. Schellhammer PF. A urologist's personal view of prostate cancer. Turk J Urol 2016;42:121-6.
56. Scher HI, Graf RP, Schreiber NA, McLaughlin B, Lu D, Louw J, *et al*. Nuclear-specific AR-V7 protein localization is necessary to guide treatment selection in metastatic castration-resistant prostate cancer. Eur Urol 2017;71:874-82.
57. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Rosser JC, *et al*. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028-38.
58. Pramesh CS, Badwe RA, Borthakur BB, Chandra M, Raj EH, Kannan T, *et al*. Delivery of affordable and equitable cancer care in India. Lancet Oncol 2014;15:e223-33.
59. Haddad S, Mohindra KS, Siekmans K, Màk G, Narayana D. "Health divide" between indigenous and non-indigenous populations in Kerala, India: Population based study. BMC Public Health 2012;12:390.

How to cite this article: Moorthy HK, Laxman Prabhu GG, Venugopal P. The resurgence of estrogens in the treatment of castration-resistant prostate cancer. Indian J Urol 2019;35:189-96.