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Original Article

Oral ethinylestradiol in castration-resistant prostate cancer: A 10-year experience

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Abbreviations & Acronyms
CI = confidence interval
CRPC = castration-resistant prostate cancer
DES = diestylstilbestrol
EAU = European Urological Association
ECOG = European Cooperative Oncology Group
HR = hazard ratio
LHRH = luteinizing hormone releasing hormone
mCRPC = metastatic castration-resistant prostate cancer
PC = prostate cancer
PSA = prostate-specific antigen

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Objectives: To describe our 10-year experience with the use of oral ethinylestradiol in the treatment of metastatic castration-resistant prostate cancer.

Methods: From February 2000 to April 2010, 116 patients with a metastatic castration-resistant prostate cancer were prospectively submitted to oral ethinylestradiol monotherapy. Inclusion criteria were: diagnosis of castration-resistant prostate cancer after failure of at least two lines of androgen deprivation therapy and radiological evidence of metastases. Exclusion criteria were: symptomatic cases with a European Cooperative Oncology Group score >2 and severe or uncontrolled cardiovascular diseases. At inclusion in the study, all patients discontinued the previous androgen deprivation therapy and started oral ethinylestradiol at the daily dose of 1 mg. Aspirin (100 mg/daily) was concomitantly given.

Results: The median ethinylestradiol therapy duration was 15.9 months (range 8–36 months), whereas the median follow up of patients was 28 months (range 13–36 months). During ethinylestradiol therapy, a confirmed prostate-specific antigen response was found in 79 patients (70.5%). The median time to prostate-specific antigen progression was 15.10 months (95% confidence interval 13.24–18.76 months). A toxicity requiring treatment cessation was observed in 26 patients (23.2%) at a median time of 16 months (mainly thromboembolism).

Conclusions: Our 10-year experience shows that ethinylestradiol provides a prostate-specific antigen response in a high percentage of patients with metastatic castration-resistant prostate cancer. Cardiovascular toxicity can be managed through accurate patient selection, close follow up and a concomitant anticoagulation therapy.

Key words: advanced disease, castration resistant, estrogens, hormone therapy, prostate neoplasm.

Introduction

First-line medical treatment for advanced PC is represented by androgen withdrawal, mainly by the use of a LHRH agonist with or without the combination of an anti-androgen. High initial response rates are expected, but progression to a CRPC is inevitable after a variable follow up. Treatment options for CRPC mainly include palliative chemotherapy, such as docetaxel or cabazitaxel, but also adrenolytic agents, estrogenic compounds or other anti-androgenic manipulations.[1–3]

Recently, there has been a renewed interest in using estrogens as medical therapy for PC and CRPC, as also described by the EAU guidelines.[1] In contrast, it is also true that the development of new significant treatment strategies for CRPC might limit the use of an old therapy, such estrogens. The interest in estrogens, in particular for CRPC cases, is based on: (i) estrogens represent a different way of achieving castration, and it is possible that the beneficial effect of estrogens is also based on a direct cytotoxic effect on PC cells;[4,5] (ii) discovery of new estrogen receptors in PC tissue that can be upregulated by first-line castration therapies;[6] and (iii) clinical trials, in particular using DES, showing a high rate of PSA response in CRPC.[7]

The aim of the present study was to describe our 10-year experience with the use of oral ethinylestradiol in the treatment of mCRPC cases.

Methods

This was a single center prospective analysis. From February 2000 to April 2010, 116 patients with a mCRPC were detected and prospectively submitted to oral ethinylestradiol monotherapy at our department.

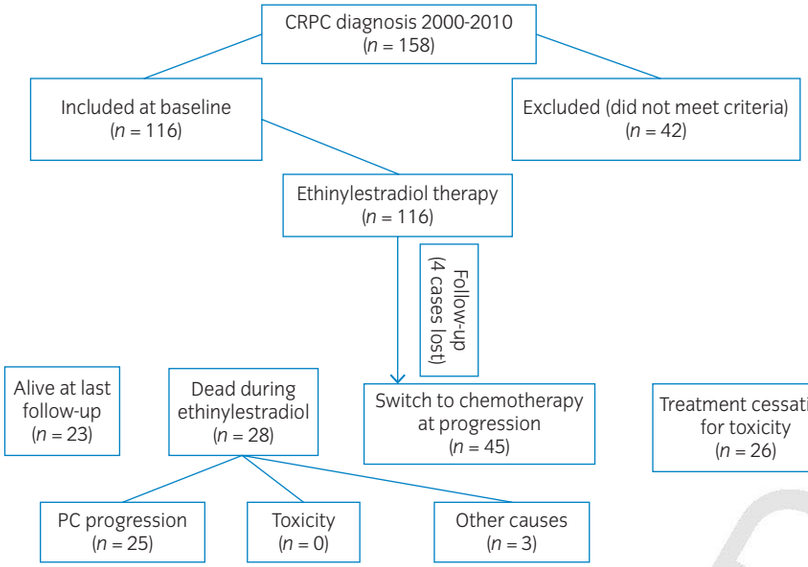


Fig. 1 Flow diagram of the study.

Patient selection

Inclusion criteria were: diagnosis of CRPC after failure of at least two lines of androgen deprivation therapy and radiological evidence of metastases. Exclusion criteria were: symptomatic cases with an ECOG score >2 (these cases were selected for immediate chemotherapy), severe or uncontrolled cardiovascular diseases (defined as New York Heart Association class III, or congestive heart failure, myocardial infarction within 6 months, unstable angina, deep venous thrombosis pulmonary embolism) and concomitant presence of other advanced malignancies or a life expectancy less than 3 months.[8] All patients had mCRPC defined as progressive disease (PSA rising and/or evidence of progression at imaging) despite castration testosterone levels (<50 ng/dL or <1.7 nmol/L).[1] Previous androgen deprivation therapies were: LHRH agonist monotherapy, at failure combination with a pure anti-androgen; and combination therapy with LHRH agonist and pure anti-androgen, at failure anti-androgen withdrawal for at least 6 weeks. Baseline data included age, previous local therapies (surgery or radiation therapy), type and duration of previous hormone therapies, ECOG score, PSA levels, hematological and biochemical variables, and number and site of metastases (defined at bone scan, magnetic resonance imaging or computer tomography scan).

Ethinylestradiol treatment

All 116 CRPC patients were treated as part of our clinical practice, on an outpatient basis following the Declaration of Helsinki principles, and all gave informed consent for treatment (informed on the possible different options and on the possible side-effects). The clinical protocol was approved by our internal institution's ethical committee. At inclusion in the study, all patients discontinued the previous androgen deprivation therapy and started oral ethinylestradiol at the daily dose of 1 mg. Aspirin (100 mg/daily) was concomitantly given to all patients at the exception of those who were already using warfarin for anticoagulation for other indications (18 cases).

Follow up and study end-points

Four patients with a lack of follow-up information were excluded from the analysis (Fig. 1). The remaining 112 patients were followed during ethinylestradiol treatment at approximately 60 days of intervals, including medical history, physical examination, hematological and biochemical variables and ECOG score assessment. Imaging was carried out at 6-month intervals or when clinically indicated (biochemical progression).

The primary end-points were time to PSA progression and PSA response rate. According to the PSA Working Group Criteria, a PSA response was defined as a 50% or greater decrease in serum PSA confirmed by two separate measurements at least 4 weeks apart.[1] PSA progression during therapy was defined as an increase of at least 50% above the nadir with an absolute increase of 5 ng/mL, or a PSA increase over 25% from the nadir or from baseline for those not meeting the PSA decline criteria.[1] After progression of the disease, patients were treated at the discretion of the physician (mainly using chemotherapy).

The secondary end-point was overall survival. Survival time was measured from baseline to date of death. Other end-points were represented by the toxicity rate, and need of estrogen therapy cessation, imaging progression in terms of number and sites of metastases.

Statistical analysis

Descriptive statistics (SPSS Statistics 19 system [SPSS, Chicago, IL, USA]) are reported as number and percentage of cases, mean ± SD, median and range. The relationship between possible predictive factors and survival was analyzed using univariate and multivariate logistic regression models (HR and 95% CI).

Kaplan–Meier survival curves were used to evaluate the median time for PSA progression and overall survival. Patients with no record of death or progression up to the end of the study

Table 1 Patients' characteristics at baseline

Patient characteristics	
No. patients	112
Age (years)	69.9 ± 3.8 (70) 60–77
PSA at baseline (ng/mL)	65.6 ± 30.1 (65.8) 20.1–150.7
Hemoglobin (>11 g/dL)	102 (91.1%)
Elevated alkaline phosphatase (>130 IU/L)	34 (30.3%)
ECOG score	
0	44 (39.3%)
1	45 (40.2%)
2	23 (20.5%)
Previous radical prostatectomy	41 (36.6%)
Previous radiotherapy	66 (58.9%)
Initial androgen deprivation therapy	
1. LHRH agonist; 2. at progression combination with pure anti-androgen (bicalutamide 50 mg/daily in 47 cases and flutamide 750 mg/daily in 15 cases)	62 (55.4%)
1. LHRH agonist + pure anti-androgen (bicalutamide 50 mg/daily in 42 cases and flutamide 750 mg/daily in 8 cases); 2. at progression anti-androgen withdrawal	50 (44.6%)
Duration of androgen deprivation therapy (years)	4.5 ± 2.3 (4.0); 2.0–6.5
Gleason score	
≤7 (3 + 4)	44 (39.3%)
≥7 (4 + 3)	68 (60.7%)
Bone metastases	
1 site	25 (22.3%)
2 sites	54 (48.2%)
>2 sites	33 (29.5%)
Lymph node metastases	36 (32.1%)
Visceral metastases	4 (3.6%)

Values are expressed as *n* (%) or mean ± SD (median); range.

were censored at their last date of follow up. A 5% level of significance was used for all statistical testing.

Results

Baseline characteristics

The present study was based on a population of 112 patients. All patients had a histologically confirmed diagnosis of prostate adenocarcinoma; patients' characteristics at baseline and histological grading are shown in Table 1. In particular, the median age was 70 years, median PSA was 65.8 ng/mL and median time of androgen deprivation therapy to start ethinylestradiol was 4 years. All cases received at least two previous hormone treatments, and all had confirmed testosterone levels <50 ng/dL or 1.7 nmol/L. All patients had documented bone metastases.

Survival end-point

The median ethinylestradiol therapy duration was 15.9 months (range 8–36 months), whereas the median follow up of patients was 28 months (range 13–36 months). All cases were observed for at least 12 months. A total of 23 patients (20.5%) were alive continuing ethinylestradiol therapy at the last follow up. Overall, 89 patients (79.5%) died during the follow up (28 cases [25.0%] died during ethinylestradiol therapy, whereas 61 (54.5%) died during the following chemotherapy regimens (Table 2). The number of deaths during ethinylestradiol therapy as a result of PC progression, treatment toxicity or other causes is shown in Table 2.

Table 2 Outcomes during ethinylestradiol therapy

No. patients	112
Alive at the last follow up	23 (20.5%)
Died during ethinylestradiol therapy	28 (25.0%)
PC progression deaths	25 (22.3%)
Cardiovascular toxicity deaths	0 (0)
Other causes	3 (2.7%)
PSA response	79 (70.5%)
PSA <4 ng/mL	24 (21.4%)
No PSA progression at 12 months	72 (64.3%)
No PSA progression at 24 months	8 (7.1%)
Clinical progression (imaging evidence)	44 (39.3%)
Median Time to clinical progression (months)	16.50 (95% CI 14.48–19.65)
ECOG score at PSA response	(79 cases)
Improvement	38 (48.1%)
Stabilization	41 (51.9%)
Deterioration	0 (0)
Other treatments after ethinylestradiol progression (45 cases) or treatment cessation for toxicity (16)	
Docetaxel + prednisone	13
Docetaxel + prednisone + zoledronic acid	48

Values are expressed as *n* (%) or mean ± SD (median); range.

Median overall survival during ethinylestradiol therapy was 19.52 months (95% CI 18.53–21.47 months) and Kaplan–Meier curves are shown in Figure 2a.

PSA response and progression

During ethinylestradiol therapy, an initial and confirmed PSA response was found in 79 patients (70.5%). PSA levels lower than 4 ng/mL were found in 24 patients (21.4%; Table 2).

PSA progression during therapy was reported in 63 patients (56.2%). The median time to PSA progression was 15.10 months (95% C I 13.24–18.76 months). The proportion of patients without PSA progression at 12 months and 24 months of therapy was 64.3% (72 patients) and 7.1% (8 patients) respectively. Kaplan–Meier curves for time to PSA progression are shown in Figure 2b.

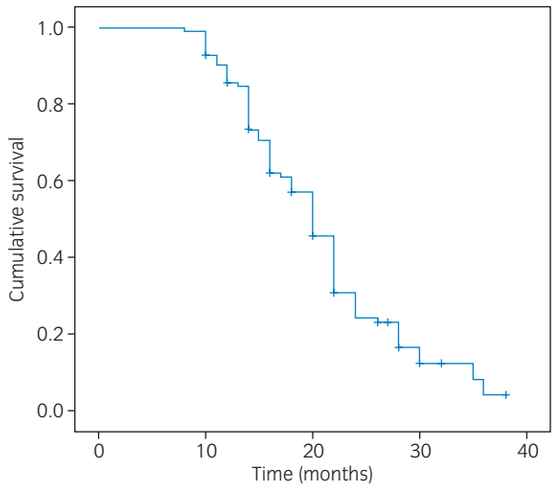
During ethinylestradiol therapy, a clinical progression in terms of new sites of distant metastases (imaging definition) was found in 44 patients (39.3%), and the median time to clinical progression was 16.50 months (95% CI 14.48–19.65 months; Table 2).

At progression, 45 of 63 patients discontinued ethinylestradiol, and all started chemotherapy regimens.

Performance status

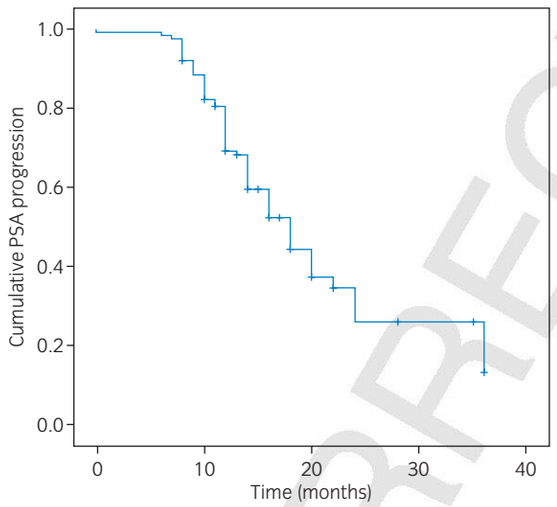
A total of 68 patients (60.7%) had at baseline an ECOG score higher than 0. During ethinylestradiol therapy, at PSA response, 48.1%, 51.9% and 0% of patients had an improvement, a stabilization and a deterioration of this parameter, respectively (Table 2).

(a)



Survival time (months)	0	10	20	30	40
Number at risk	112	112	54	8	0

(b)



Survival time (months)	0	10	20	30	40
Number at risk	112	98	27	3	0

Colour

Fig. 2 Kaplan–Meier curves on (a) overall survival and (b) time to PSA progression.

Toxicity

Side-effects and toxicity related to ethinylestradiol treatment are described in Table 3.

A toxicity that required treatment cessation was described in 26 patients (23.2%) at a median time of 16 months. In no patient was a dose reduction applied.

The main severe toxicity requiring treatment cessation was thromboembolism (18 patients). No patient died as a result of treatment toxicity.

Predictors of PSA response

At univariate analysis, tumor Gleason score, duration of previous androgen deprivation therapies, presence of lymph node metastases and number of bone metastases were significant ($P < 0.05$) predictors of PSA response during therapy. Multivariate analysis using the Cox model (Table 4) showed that tumor Gleason score, duration of previous androgen deprivation therapies and concomitant presence of lymph nodes metastases were significant predictors of PSA response during ethinylestradiol treatment. In particular, patients with an absence of lymph nodes progression, more than 4 years of previous androgen deprivation therapy and a Gleason score ≤7 (3 + 4) were more likely to have a PSA response. Similarly, the same parameters were significantly associated to overall survival (Table 4).

Discussion

In the present 10-year experience of metastatic CRPC cases, estrogen therapy using ethinylestradiol showed to have a clinical therapeutic effect, either in terms of PSA response or as survival.

Our population was represented by mCRPC patients, all with bone metastases and an ECOG score ≤2. All patients progressed after at least two steps of androgen deprivation therapy.

The concept of PSA progression or PSA response was evaluated following guideline indications.[1]

The oral administration of ethinylestradiol monotherapy was associated with a very high PSA response rate (70.5%) and a high percentage (21.4%) of patients with an initial "normalization" (<4 ng/mL) of PSA levels. Therefore, the present study sustains that a high percentage of CRPC patients initially respond to ethinylestradiol therapy.

The second point is the duration of this positive response. We found that the proportion of mCRPC cases without a PSA progression at 12 and 24 months was 64.3% and 7.1%, respectively, and the median time for PSA progression was 15 months. Considering the oncological characteristics of our population (CRPC metastatic patients), ethinylestradiol was able to produce a significant time in which patients were free from PC progression. The results in terms of survival sustain these data. The response to ethinylestradiol therapy was also associated with an improvement (48.1%) or stabilization (51.9%) in the performance status of the patients.

The rationale for a positive oncological response in CRPC using estrogen therapy is based to different possible mechanisms of action: (i) a new way of achieving castration in cases resistant to LHRH agonist activity; (ii) a direct cytotoxic effect on PC cells; (iii) hyperexpression of estrogen receptors in PC that can be upregulated by previous androgen deprivation therapies;[9] and (iv) effect on sex hormone-binding globulin and free testosterone.[10]

Table 3 Toxicities

Parameter	No. cases	No. cases requiring treatment cessation	Time to treatment cessation (months)
Gastrointestinal events	74 (66.1%) (all grade 1–2)	0 (0)	–
Painful gynecomastia	34 (30.3%) (all grade 1–2)	0 (0)	–
Fluid retention	74 (66.1%) (all grade 1–2)	0 (0)	–
Cardiac failure	8 (7.1%) (all grade 3)	8 (7.1%)	14 (8–22)
Thromboembolic events	31 (27.7%) (13 cases grade 2 and 18 cases grade 3)	18 (16.1%)	18 (14–22)

Number (%) of events and CTCAE grading; number (%) of cases requiring ethinylestradiol cessation; median (range) time (months) for treatment cessation.

Table 4 Multivariate Cox model for predictors of PSA response and overall survival

Variables	PSA response		Overall survival	
	HR	*P*-value	HR	*P*-value
Age (years)	0.88 (0.60–1.10)	0.62	0.75 (0.50–1.05)	0.54
PSA at baseline (ng/mL)	1.35 (0.86–2.14)	0.08	1.40 (0.90–2.15)	0.08
Haemoglobin at baseline (g/dL)	0.94 (0.70–1.25)	0.15	1.35 (1.04–1.95)	0.08
Alkaline phosphatase at baseline (IU/L)	0.84 (0.54–1.12)	0.68	0.82 (0.50–1.02)	0.66
Sequence in androgen deprivation treatment	0.42 (0.20–0.95)	0.72	0.48 (0.25–0.98)	0.75
Duration of initial androgen deprivation therapy (months)	1.74 (0.95–2.15)	0.04	1.67 (0.92–2.06)	0.04
Gleason score	1.85 (1.15–2.34)	0.04	2.14 (1.45–3.07)	0.02
Bone metastases (no. sites)	1.13 (0.64–1.85)	0.34	1.18 (0.72–1.94)	0.25
Presence of lymph node metastases at baseline	1.82 (1.20–2.76)	0.04	2.05 (1.54–2.80)	0.02
Previous radical prostatectomy or radiotherapy	0.96 (0.44–1.45)	0.34	0.94 (0.41–1.37)	0.30

HR (95% CI) and *P*-values.

The primary hormonal effect of estrogens is through a feedback inhibition of the hypothalamic–pituitary–testicular axis. Furthermore, estrogens administration has been associated with a significant decrease in adrenal androgens, such as dehydroepiandrosterone and dehydroepiandrosterone sulphate synthesis.[11,12] A direct cytotoxic effect on PC cells is sustained by evidence on castrate xenograph models *in vivo*[5] and PC cell lines.[4]

Recently, there has been a renewed interest in using estrogens. In contrast, it is also true that the development of new significant treatment strategies for CRPC limits the use of an old therapy, such as estrogens.

DES is probably the most commonly used estrogen in PC.[7,13] However, other estrogen or anti-estrogen therapies have been recently analyzed in clinical trials including ethinylestradiol[14–16] or fulvestrant.[17,18] In our opinion, at present there is no real reason or rationale to prefer one form of estrogen therapy over the others. We started our experience with ethinylestradiol and homogeneously continued it for 10 years. No direct comparison of the activity of the different estrogen therapies or on the different routes of administration (parenteral, oral, transdermal) has been carried out. Similarly, differences in the selection of the populations and in treatment regimens limit the possibility to compare the present results with those obtained in previous experiences with estrogen treatments.

In particular, a recent long-term experience with estrogens in CRPC was reported in the study of Wilkins *et al*. of 231 CRPC patients treated with DES.[7] The authors described a PSA response in 30% of cases, a median time for PSA progression of 4.6 months and a median overall survival of 9.3 months. The population treated with DES by Wilkins *et al*. included either metastatic (80%) or non-metastatic (20%) cases.[7]

A phase 3 trial compared dexamethasone and immediate DES with dexamethasone and deferred DES in 270 CRPC patients.[13] In the group treated with immediate DES, a PSA response was achieved in 68% of patients, median time to PSA progression was 8.6 months and median overall survival was 19.4 months.

On the basis of the results of the clinical trials published in the literature, EAU 2013 guidelines concluded that DES (as estrogen therapy) can be an effective form of therapy; however, there is still concern about the significant cardiovascular side-effects.[1] At present, fewer data are available regarding ethinylestradiol use, but the present study can represent a significant experience with positive oncological results in metastatic CRPC. In a previous experience, Izumi *et al*. administered ethinylestradiol 1.5 mg/daily in a limited number[24] of patients with a CRPC.[15] The proportion of cases achieving a PSA response was 70%, and the median time to PSA progression was 300 days.

Toxicity related to estrogen treatments is probably the main problem to be more commonly re-admitted into clinical practice. As underlined by the EAU guidelines, DES is associated to a high cardiovascular and thromboembolic toxicity, also reducing the daily dose.[1]

Two main strategies have been used to reduce estrogen toxicity: a parenteral or transdermal route of administration and the concomitant use of cardiovascular protective agents.[1] The rate of cardiovascular toxicity in more recent studies was considerably lower than in earlier studies on estrogens where

anticoagulation was not used routinely.[7] In the present study, a selection of patients on the basis of a history for severe cardiovascular diseases has been carried out. Furthermore, aspirin was concomitantly given to all patients at the exception of those who were already using other forms of anti-coagulation. In our experience with ethinylestradiol, thromboembolism remained the main reason of severe toxicity and treatment cessation, but with limited rates, and in particular after long periods of treatment (16.1% of patients at a median of 18 months). Also, in the recent study by Wilkins *et al*., a concomitant anticoagulation with aspirin was used and the rate of thromboembolism was limited to 10% (4.8% required cessation of DES).[7] Considered together, cardiovascular side-effects requiring treatment cessation were reported in 23% of our patients; this remains a significant rate to be considered in the treatment choice.

In the present 10-year experience of metastatic CRPC cases, the use of ethinylestradiol showed a high percentage of PSA response. Possible cardiovascular toxicity can be managed through an accurate patient selection and follow up, and a concomitant anticoagulation therapy.

Conflict of interest

None declared.

References

1 Mottet N (chair), Bastian PJ, Bellmunt J *et al*. EAU Guidelines for prostate cancer. 2014. 1–168.

2 Tannock IF, de Wit R, Berry WR. Docetaxel plus prednisone ormitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* 2004; **351**: 1502–12.

3 de Bono JS, Oudard S, Ozguroglu M. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. *Lancet* 2010; **376**: 1147–54.

4 Montgomery B, Nelson PS, Vessalla R, Kalhorn T, Hess D, Corey E. Estradiol suppresses tissue androgens and prostate cancer growth in castration resistant prostate cancer. *BMC Cancer* 2010; **10**: 1–7.

5 Corey E, Quinn JE, Emond MJ, Buhler KR, Brown LG, Vessella RL. Inhibition of androgen-independent growth of prostate cancer xenografts by 17beta-estradiol. *Clin. Cancer Res.* 2002; **8**: 1003–7.

6 Limonta P, Montagnani MM, Moretti RM. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. *Expert Opin. Investig. Drugs* 2001; **10**: 709–20.

7 Wilkins A, Shahidi M, Parker C *et al*. Diethylstilbestrol in castration resistant prostate cancer. *BJU Int.* 2012; **110**: 727–35.

8 Beer TM, Ryan C, Alumkal J, Ryan CW, Sun J, Eilers KM. A phase II study of paclitaxel poliglumex in combination with transdermal estradiol for the treatment of metastatic castration resistant prostate cancer after docetaxel chemotherapy. *Anticancer Drugs* 2010; **21**: 433–8.

9 Bonkhoff H, Berges R. The evolving role of estrogens and their receptors in the development and progression of prostate cancer. *Eur. Urol.* 2009; **55**: 533–42.

10 Kitahara S, Umeda H, Yano M *et al*. Effects of intravenous administration of high dose-diethylstilbestrol diphosphate on serum hormonal levels in patients with hormone-refractory prostate cancer. *Endocr. J.* 1999; **46**: 659–64.

11 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**: 71–6.

12 Takezawa Y, Nakata S, Kobayashi M *et al*. Moderate dose diethylstilbestrol diphosphate therapy in hormone refractory prostate cancer. *Scand. J. Urol. Nephrol.* 2001; **35**: 283–7.

13 Shamash J, Powles T, Sarker SJ *et al*. A multicentre randomized phase III trial of Desamethasone vs Desamethasone plus diethylstilbestrol in castration resistant prostate cancer: immediate versus deferred diethylstilbestrol. *Br. J. Cancer* 2011; **104**: 620–8.

14 Stein M, Goodin S, Doyle-Lindrud S *et al*. Transdermal estradiol in castrate and chemoresistant prostate cancer. *Med. Sci. Monit.* 2012; **18**: 260–4.

15 Izumi K, Kadono J, Shima T *et al*. Ethinylestradiol improves prostate specific antigen levels in pretreated castration resistant prostate cancer. *Anticancer Res.* 2010; **30**: 5201–6.

16 Di Silverio F, Sciarra A. Combination therapy of ethinylestradiol and somatostatin analogues reintroduces objective clinical response and decreases chromogranin A in patients with androgen ablation refractory prostate cancer. *J. Urol.* 2003; **170**: 1812–16.

17 Chadha MK, Ashraf U, Lawrence D *et al*. Phase II study of fulvestrant in castration resistant prostate cancer. *Prostate* 2008; **68**: 1461–6.

18 Gasent Blesa JM. Experience with fulvestrant acetate in castration resistant prostate cancer. *Ann. Oncol.* 2010; **21**: 1131–2.

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