The use of Transdermal Oestrogen in Castrate-resistant, Steroid-refractory Prostate Cancer

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Microabstract

We aimed to investigate the role and safety of transdermal oestrogen therapy in castrate resistant prostate cancer. Within this dose escalation study we observed reduction in PSA levels at all doses used. In addition, no venous thromboembolic events were detected making the use of transdermal oestradiol a safe treatment option for a subgroup of patients with castration-resistant prostate cancer.

Abstract

Background: Androgen-deprivation therapy is the mainstay of treatment for metastatic prostate cancer. Corticosteroids and oestrogens are also useful agents in castrate resistant prostate cancer. However, oral oestrogens are associated with thromboembolic events, which limits their use and transdermal oestrogens may offer a safer alternative. This study was carried out to determine the safety and effectiveness of transdermal oestrogens in castrate resistant prostate cancer.

Patients and Methods: 41 patients with castration and steroid-resistant prostate cancer were eligible for this dose-escalation study of transdermal oestradiol. A starting dose of 50mcg/24 hours was applied and increased if PSA rose >5ng/ml in steps to 300mcg/24hours. The primary endpoint was PSA response and secondary outcomes included incidence of thromboembolic events and progression free survival. Patients who progressed were offered diethylstilbestrol.

Results: 5/40 patients (13%) had >50% PSA reduction for at least 1 month at any transdermal oestradiol dose. No venous-thromboembolic events were observed and responses plateaued at 200mcg/24hours. A correlation between PSA response and rising sex hormone binding globulin was seen. 50% of patients subsequently responded to low dose diethylstilbestrol.

Conclusion: Transdermal oestradiol appears to be a low toxicity treatment option to control CRPC after failure of steroid therapy. Modulation of sex hormone binding

globulin by transdermal oestradiol may be one mechanism of action of oestrogens on castrate resistant prostate cancer. Oral oestrogens remain effective after the use of transdermal oestradiol.

Abbreviations:

TDE = Transdermal oestrogen

CRPC = castrate-resistant prostate cancer

PSA = prostate specific antigen

ADT = androgen deprivation therapy

Introduction:

Prostate cancer is the commonest cancer in men and the second most common cause of cancer-related death in men in the UK (1). The disease exhibits remarkable heterogeneity in clinical behaviour and outcome ranging from years of indolence to lethal disease despite similar histological features (2). Androgen deprivation therapy (ADT) is the standard of care for metastatic prostate cancer and it also has a role in the neoadjuvant and adjuvant settings. Initial response rates to ADT exceed 80%, however these are transient and patients invariably progress to the more aggressive phenotype of the disease termed castration-resistant prostate cancer or CRPC (3). ADT is most often achieved by administration of gonadotropin-releasing hormone (GnRH) analogues (4). Their use is associated with numerous long-term toxicities including hot flushes, gynaecomastia, increased cardiovascular events and reduced bone mineral density (4-6).

Even at the time of development of resistance to ADT, research has demonstrated that androgen receptor (AR) signaling remains crucial for the progression of CRPC. As a result, potent second generation anti-androgen drugs have been developed that target the AR pathway. More specifically, abiraterone acetate and enzalutamide have both been approved for use in the pre- and post-chemotherapy settings following improvements in OS in men with CRPC (7-10). Despite their impressive responses, however, these novel treatments are associated with numerous toxicities especially

within the elderly prostate cancer patient population who might not tolerate these treatments well. Toxicities include fatigue, oedema, hypertension and diarrhea. As a result, there has been a renewed interest in oestrogen therapy, particularly for patients who are less fit with relatively low volume disease and where chemotherapy and second generation anti-androgens may result in significant toxicity with associated effects on quality of life.

Oral oestrogen, in particular Diethylstilbestrol (DES), is an alternative agent used to induce medical castration (11), and prior to the development of GnRH analogues was the mainstay of treatment. Oestrogen decreases testosterone concentration in serum by suppressing LH production from the pituitary via negative feedback. Their use however, was abandoned due to their association with venous thromboembolism (VTE) and cardiovascular toxicity (12, 13). This VTE risk is attributed to the effects of first pass hepatic metabolism of oestrogen on coagulation proteins and lipids (14). Since the development of ADT using GnRH analogues, the main use of DES has been as second, third or consecutive line hormonal manipulation.

Parenteral oestrogens have been shown to avoid first-pass metabolism in the liver and are therefore not expected to be associated with the same frequency of

thromboembolic events as oral oestrogens (14). Langley et al conducted a randomized trial of GnRH analogues versus transdermal oestrogen (TDE) in treatment naïve locally advanced and metastatic prostate cancer (15). TDE achieved equivalent levels of castrate testosterone concentrations and had similar frequency of VTE complications. Rates of cardiovascular toxic effects were similar with the two treatments and were lower than those seen with oral oestrogen. As TDE may achieve castrate levels of testosterone with fewer cardiovascular and vascular thrombotic events it has also been trialed in CRPC. Furthermore, PSA response rates have been seen in Phase II studies using TDE with no increases in VTE or cardiovascular events (16). Response rates have also been demonstrated in chemo-refractory prostate cancer (17). However, the long-term efficacy of TDE versus DES is not known.

This dose-escalation study of TDE was therefore designed to assess the effectiveness of TDE in castrate resistant and steroid refractory advanced prostate cancer in patients who had declined or felt to be inappropriate for chemotherapy. Patients who came off study were offered DES to establish if there is any cross-resistance between TDE and DES. PSA was used as a marker for response.

Materials and Methods

Patients

Eligibility criteria included patients with confirmed locally advanced or metastatic prostate cancer with progression of disease to both GnRH analogues and steroid therapy equivalent to dexamethasone 2mg once a day, prednisolone 15mg per day or 20mg hydrocortisone per day. Patients were required to be biochemically castrate at baseline (serum testosterone <2nmol/l).

Men aged ≥ 18 years with an Eastern Co-operative Oncology Group (ECOG) performance status ≥ 3 were eligible. Men with pre-existing vascular conditions or history of VTE were included, with the exception of a cerebrovascular event within 3 months prior to study enrolment. Other exclusion criteria were prior oestrogen therapy or other active malignancy within the last 3 years. Patients had either declined docetaxel chemotherapy or felt to be inappropriate candidates for chemotherapy given their performance status.

Treatment

Transdermal Evorel® oestrogen patches delivering 50mcg oestradiol/24hours were given to all patients. GnRH analogues and steroids were discontinued at the start of the study. Patients who had been on long periods of steroids were reduced to maintenance levels. All patients were started on Aspirin 75mg daily unless previously

established on anti-platelet therapy. All patients received prophylactic Ranitidine (150mg twice daily).

Baseline investigations included a chest radiograph, electrocardiogram and a bone scan.

Blood tests included full blood count, urea and electrolytes, liver function, LDH, PSA, testosterone, LH, FSH, SHBG, and oestradiol levels. PSA levels were checked every 28 days. A rise of >5µg/l triggered a repeat test 7-14 days later. If this rise was confirmed, the Evorel® dose was increased initially to 100mcg/24 hours then to 200mcg/24hrs and finally to 300mcg/24hrs. At the start of each course, weight and ECOG performance status were recorded. If there was further PSA progression or symptomatic progression at any point, patients were taken off the transdermal patch. Patients without contra-indication due to thrombo-embolism were offered diethylstilbestrol 1mg/day following discontinuation of TDE.

Patients were reviewed every 28 days during treatment and then 3-monthly for 1 year. Subsequent follow-up was at the treating clinician's discretion.

Patients completed the European Organisation for Research and Treatment of Cancer QLQ C-30 questionnaire and PR25 prostate specific questionnaires to assess quality of life outcomes.

All patients gave written informed consent and the study was approved by the local Ethics Committee. The recruitment period for this study was between 2004 and 2010.

Statistics

Endpoints were measured on an intention-to-treat principle. The primary endpoint was PSA response rate as defined by consensus criteria (18). Secondary endpoints were incidence of thromboembolic events and progression free survival. Statistical considerations indicated that an open study of 14 patients was required initially for 95% chance of detecting at least one PSA response (>50% reduction of PSA maintained for one month). If one response was seen the trial size would increase to 21 and to 40 if further responses were seen (19). Stata statistical software was used for all statistical analyses.

Results

Patients

In this two centre study, 41 patients were enrolled in total. One patient withdrew prior to commencing therapy. Baseline patient characteristics are given in Table 1. Median age at enrollment was 76 years (inter quartile range 72-81). 26 patients (65%) had an ECOG PS of 0-1, and 12 patients (30%) 2-3. Data was missing for 2 patients. Prior to receiving Evorel®, all patients had received GnRH analogues or undergone bilateral orchidectomy. 39 patients (97%) received prior steroid therapy; 1 individual had an absolute contraindication to steroids due to ongoing osteomyelitis. No patients had received prior chemotherapy.

At baseline, the median PSA measured 151ng/dl. 35 patients (88%) had evidence of bony metastases. All patients were biologically-castrate except for 2 (with elevated serum testosterone 2.2 and 5.7nmol/l). These 2 patients did not meet eligibility criteria but were included according to intention-to-treat analysis. Median time from diagnosis to development of castration resistant disease was 38 months (inter quartile range 20-67 months). The median time on corticosteroids prior to the study was 4.5 months (interquartile range 2.5-7.5 months). The median time from

castration resistant disease to entry to the study was 12 months (inter quartile range 7.2-18 months).

Castration was maintained in all patients throughout the study with the exception of the patient with the baseline serum testosterone of 5.7nmol/l.

Table 1: Baseline characteristics of patients receiving transdermal estradiol at treatment randomisation:

Number of patients	40
Median age (range)	76 (58-87)
Median time from castration resistance to starting TDE (range), months	12 (2-32)
Median duration on dexamethasone (range), months	5 (1-17)
ECOG Performance status	
0	7/38 (18%)
1	20/38 (53%)
2	8/38 (21%)
3	2/38 (5%)
Median PSA (ng/dL) (range)	151 (25-1386)
Median alkaline phosphatase level (range)	135 (39-2187)
Median haemoglobin level (g/dL) (range)	11.1 (8.3-16.4)
Gleason score at diagnosis	
<8	18/40
8-10	14/40
NA	8/40
Presence of bony metastases	35/40 (88%)
Previous therapy	
GnRH agonist	39/40 (98%)
Bilateral orchiectomy	1/40 (3%)
Steroid therapy	39/40 (97%)

Toxicity

After 4 months on treatment, self-reported gynaecomastia had increased from 4% to 58% (p=0.001), however hot flushes had reduced from 25% to 8% (p=0.03). Nausea reporting increased from 10% to 18% (p=0.05) (see Table 2). There were no venous thrombo-embolic events. There was one vascular event (retinal artery occlusion). There were no skeletal events and no patients were on i.v. bisphosphonates or denosumab during the study. There were no treatment related deaths.

Table 2: Symptoms reported at baseline and after 4 months on treatment (EORTC-QLQ-C30 and EORTC-QLQ-PR25):

	At baseline	After 4 months on study	
Hot flushes	(7/28) 25%	(2/26) 8%	(p=0.03)
Gynaecomastia	(1/28) 4%	(15/26) 58%	(p=0.001)
Loss of masculinity	(11/28) 39%	(9/26) 35%	(p=0.29)
Insomnia	(11/31) 35%	(11/27) 42%	(p=0.19)
Nausea and vomiting	(3/31) 10%	(5/27) 18%	(p=0.05)
Diarrhoea	(3/30) 10%	(3/27) 13%	(p=0.81)
Constipation	(5/29) 17%	(9/27) 33%	(p=0.04)
Anorexia	(4/31) 14%	(9/27) 33%	(p=0.02)
Fatigue	(13/31) 41%	(15/27) 55%	(p=0.02)
Dyspnoea	(8/31) 26%	10/27) 38%	(p=0.03)
Pain	(11/31) 36%	(14/27) 51%	(p=0.02)
Weight loss	(4/29) 14%	(2/24) 8%	(p=0.69)
Weight gain	(6/29) 21%	(3/26) 12%	(p=0.37)
Oedema	(8/29) 28%	(12/27) 44%	(p=0.05)

Oestradiol and Sex Hormone Binding Globulin

Increasing TDE dose resulted in increasing oestradiol and SHBG concentrations across all groups (p<0.001). By the end of treatment 39 patients (97.5%) went onto

100mcg/day patch, 33 patients (82.5%) onto 200mcg/day and 24 patients (60%) went onto 300mcg/day patch (Table 3).

Table 3: PSA, estradiol, SHBG, testosterone, LH/FSH at start of increasing TDE dose:

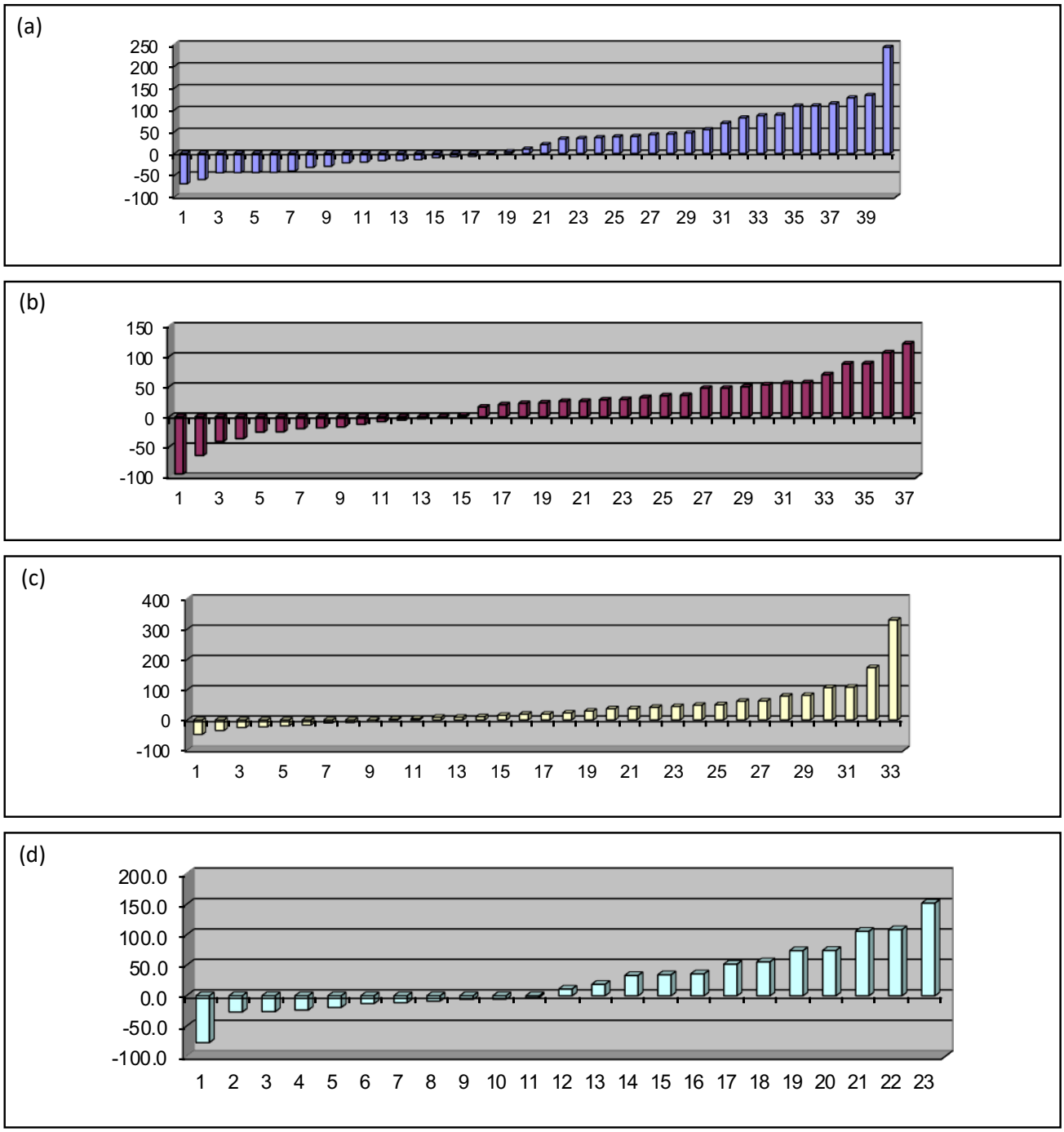
	50mcg/day	**100mcg/day**	**200mcg/day**	**300mcg/day**	**End of treatment**
n	40	39	33	24	40
Median PSA (mg/ml)	151 (25-1386)	149 (42-2135)	160 (15-1777)	163 (14-1506)	441 (21.8-2650)
Median plasma estradiol (pg/ml)	41 (0-137)	117 (25-323)	187 (66-1109)	577 (135-1801)	573 (37-3094)
Median plasma SHBG (nmol/l)	40 (14-70)	54 (18-148)	63 (17-113)	76 (42-120)	76 (40-157)
Plasma testosterone (nmol/l)	0.7 (0.4-5.7)	0.7 (0.4-4.6)	0.6 (0.4-4.3)	0.6 (0.2-2.5)	0.7 (0.4-2.1)
LH (IU/l)	0.3 (0.1-23.2)	0.3 (0.1-17.3)	0.3 (0.2-15.8)	0.2 (0.1-4.8)	0.2 (0.1-0.5)
FSH (IU/l)	3.8 (1.4-83.7)	3.0 (0.2-29.2)	1.4 (0.2-33.1)	0.5 (0.2-6.2)	0.2 (0.1-2.5)

PSA Change

5/40 patients (13%) had >50% reduction for at least 1 month at any TDE dose. The median progression-free survival was 4.6 months (95% CI 1.7 to 6.2 months). 2/39 patients (5%) had a confirmed PSA reduction >50% at 50mcg/day and a further 2 patients (5%) at 100mcg/day. There were no reductions in PSA at 200mcg/day. 1/24 patients (4.3%) had a reduction of >50% at 300mcg/day (Figure 1). Correlation was seen between a rise in SHBG and PSA decline as well as between plasma oestradiol and PSA response except at 50mcg/day.

The median maximum change in PSA was -21% (range -94.8 to +242.7%). The percentage achieving PSA control i.e. stable or reduction in PSA for at least 1 month was 53% (21/40 patients) at 50mcg/day, 53% (21/39 patients) at 100mcg/day, 52% (17/33 patients) at 200mcg/day and 50% (12/24 patients) at 300mcg/day and 55% (22/40 patients) as a whole. 18 patients (45%) developed symptomatic progression and dropped out prior to maximum dose escalation.

Figure 1 - Waterfall plots for the changes in PSA for each dose of transdermal oestradiol: Graphs demonstrate respective PSA changes at (a) 50, (b) 100, (c) 200 and (d) 300 mcg of oestradiol.



Survival

Median time on treatment measured 5.5 months (4.6-8.6 months 95% C.I.). Median survival was 19.3 months (interquartile range 5.2-16.7 months). Patients with normal alkaline phosphatase had significantly longer time on treatment and overall survival (OS) 9.1 versus 4.2 months (p=0.0005) and 24.5 versus 13.1 months (p=0.001) respectively.

Time on treatment and OS were also significantly longer in patients whose baseline Hb was greater than the cohort median: 8.15 months vs 4.65 months (p=0.005) and 24 vs 13.1 months (p=0.066) respectively.

Patients with baseline PSA less than the median also had a longer time on treatment and OS: 8.7months vs 4.35 months (p=0.007) and 24.5 vs 9.5 months (p=0.0008) respectively.

Diethylstilbestrol

20 patients received diethylstilbestrol post TDE. 16 (80%) had a decline in PSA and 10 (50%) had a >50% decline. The median survival from the start of diethylstilbestrol

was 46 months in those who had a 50% response (range 6.2 – NR) vs 6.9 months for those who did not (range 1.6-26.3) (p=0.13)

Quality of Life

Mean standardized Quality of Life (QOL) scores initially deteriorated on treatment compared to baseline (QOL global score = 55.3 at start of study, 44.7 at 1 month, p=0.04) but this was not significant at 4 months of treatment (QOL global score = 46, p=0.18). In addition, hot flushes were significantly reduced by the treatment.

Discussion

Traditionally the hormonal targets for prostate cancer have focused on negating androgen action; however recent evidence from epidemiological and experimental data have elucidated a role of oestrogens in prostate development and progression. The prostate expresses both oestrogen receptor alpha (ERα) and oestrogen receptor beta (ERβ) and the mechanism of action of oestrogen in prostate cancer is likely to be multi-factorial (20). Most evidence suggests that ERα mediates the harmful effects of oestrogen in the prostate (21). Furthermore, ERα has been correlated with the tumour promoting function of TMPRSS2-ERG fusion, a major driver of prostate carcinogenesis (22). In addition, the progressive emergence of ERα and ERα-regulated genes during prostate cancer progression and hormone refractory disease suggests that these tumours can bypass the AR by using oestrogens for their growth (21). The role of ERβ in the prostate remains unclear with most evidence suggesting that ERβ is tumour suppressive (23), however, there is increasing evidence that isoforms of ERβ may be oncogenic (24, 25). Finally, it has been shown that oestradiol suppresses tissue growth in vitro via ER-independent mechanisms as well (26). Clinical trials using oestrogen receptor-selective agents have not shown any improvements in clinical outcomes so far (20).

Our cohort of patients' response to TDE was modest but significant. This group had been pre-treated with GnRH analogues and steroid therapy and had advanced cancer as demonstrated by resistance to castrate levels of testosterone and a median PSA of 151. A significant proportion (26%) were Performance Status (PS) 2-3 and were thus inappropriate for, or had declined Docetaxel chemotherapy. The majority of patients had been on treatment for some time, with median time from diagnosis to development of castration resistant disease of 38 months.

A PSA response of >50% was seen in 13% of patients at any TDE dose. In 56% of patients, TDE use at any dose was associated with either a fall in PSA or stable PSA. This study commenced prior to the adoption of PCWG-2 criteria (6), which advises 12 weeks of drug therapy prior to a confirmed rise in PSA rather than the 35-42 days followed in this study. This may have resulted in underestimation of response to TDE.

Median time on treatment was 5.5 months while the median time to progression using Kaplan-Meier estimates was 4.6 months (1.7-6.2 months). Median overall survival for this cohort was 19.3 months which compares favourably with overall survival in patients with metastatic CRPC receiving Docetaxel in the TAX-327 trial (27). Some better prognostic groups were identified: patients with a normal alkaline phosphatase, or Hb >median were predictive factors for longer time on treatment

and greater overall survival. In those patients who had a 50% PSA response, overall survival was excellent at 46 months.

Oestrogens are also known to have bone protective effects (28). Prostate cancer patients with a high incidence of bony metastases and prolonged LHRH agonist use are at high risk of pathological fractures (4). Reassuringly no skeletal events were recorded in this study.

Oral DES has been shown to have activity in CRPC (29). Shamash et al, conducted a Phase III trial using immediate or deferred DES in conjunction with dexamethasone in CRPC (30). Immediate DES was not superior to delayed DES with regards to PSA response rate or progression free survival (RR 68% immediate vs 64% deferred, p=0.49). Given the high incidence of VTE with immediate DES (22% vs 11%), DES use was not recommended until failure of dexamethasone. In our cohort, there was one vascular event recorded; a retinal artery occlusion which was not a VTE. This supports the belief that TDE has a lower VTE side effect profile than DES. TDE may therefore be an option prior to DES therapy and a trial in conjunction with dexamethasone may be appropriate.

Furthermore, there was significant response to DES after TDE treatment indicating there possible lack of cross resistance between these two treatments. The activity of DES after TDE suggests that the mechanism of action of transdermal and oral oestrogens upon CRPC is not equivalent and warrants further investigation. There is evidence of endocrine re-sensitisation on discontinuing GnRH analogues whilst on alternative therapy.In another study by Shamash et al, for example, there is evidence of re-sensitisation to hormonal therapy by discontinuing GnRH analogues during docetaxel chemotherapy (31). Therefore, it is possible that this re-sensitization also applies to discontinuation of GnRH due to oestrogen use and would be very interesting to study in more detail.

In addition, in this study we have shown that TDE affected SHBG in a dose-dependent fashion, and increased SHBG levels were associated with a PSA response. This suggests that SHBG may play a role in driving the prostate cancer response and correlates with the fact that at the lowest dose, a rise in SHBG correlated with a fall in PSA. Alterations in SHBG can alter the equilibrium between bound and free androgens affecting the availability of androgens to induce androgen receptor responses (32) and this may be a pathway for oestrogen to exert its influence on CRPC. The significance of SHBG remains under-investigated in CRPC but the association seen in this trial suggests it should be investigated further.

Increasing the TDE dose above 200mcg/day did not increase the PSA response observed. The number of patients included in the trial was small and a dose response may have been observed had more patients been included. In addition, it may be that for some patients where a PSA response at a lower dose was not seen, resistance to TDE had already developed and this could not be overcome with dose increases.

There are a number of limitations to our study. This was a small Phase II study involving 40 patients in 2 institutions and drawing conclusions as to the efficacy of TDE in the wider population of patients with CRPC is difficult. In addition, there was no use of routine radiological assessment during therapy. In fact, in many studies of second generation agents, PSA response is still an important and easy way to assess early response however it is clear that benefit is sometimes seen when PSA remains stable or only slowly increases. The dose titration in the study design meant that it was much harder to show large PSA responses as TDE, was only increased if PSA rose. In addition, patients came off the study with predefined rises in PSA which may not have been clinically significant again, leading to possible under reporting of efficacy. Furthermore, this study was conducted prior to the routine use of second generation anti-androgens and clearly it would be interesting to know whether there was any cross-resistance between them and transdermal oestradiol. None of the patients

received prior chemotherapy for castration-resistant disease which would also be standard nowadays for fit patients.

Finally, clinical trials are currently investigating the use of TDE in metastatic prostate cancer in the hormone sensitive setting. For example, the PATCH trial (NCT00303784) compares the efficacy and safety of TDE vs GnRH analogues in men with locally advanced and metastatic prostate cancer and has so far recruited >2000 patients (33). The initial pilot phase showed that TDE achieved equivalent castrate levels of testosterone to GnRH analogues without the previously observed rates of cardiovascular toxicity seen with oral oestrogen (15). Furthermore, the STAMPEDE trial (NCT00268476) now includes a 'TDE arm' since 2017 and this will compare TDE to ADT and together with the PATCH trial will be able to define the role of this treatment in metastatic hormone sensitive prostate cancer (34).

Conclusion

This study demonstrated that TDE is a low toxicity treatment that may provide control of CRPC after failure of steroid therapy and that a dose of 200mcg/day - 300mcg/day has an acceptable efficacy / toxicity profile. The low toxicity and lack of cross reaction with DES suggest it is a reasonable pre-DES therapy and could be considered as an alternative to novel anti-androgen therapies or as alternative to

Docetaxel chemotherapy particularly in less fit patients. The most significant adverse effect is gynaecomastia. The correlation of SHBG levels with TDE dose and PSA response suggest that modulation of SHBG level by oestrogens may play an important role in the effect of oestrogens on CRPC. In addition, the finding that DES remains active after TDE suggests differing mechanisms of action on CRPC dependent on the route given. It would therefore appear that TDE is a safe and valid therapy and that there is much more to learn about the role of oestrogens in CRPC.

Clinical practice points

Oral systemic oestrogen treatment, in the form of diethylstilbestrol (DES), was widely used in prostate cancer and castration-resistant disease. Their use, however, was associated with increased risk of cardiovascular and thromboembolic events resulting from the first-pass metabolism in the liver. TDE avoids this effect and offers an alternative and potentially safer means of androgen suppression.

TDE used in this population of patients with CRPC post GHRHa and DES treatment was found to be safe and well tolerated. Importantly TDE lead to PSA decline of >50% in 13% of patients with a median progression-free survival of 4.6 months.

Optimal inhibition of the AR signaling pathway remains an important target in the setting of CRPC and the use of TDE as an alternative modality of maintaining castrate

levels of testosterone is a possible option especially for the older and less fit patients who might not tolerate chemotherapy or second-generation anti-androgens and should always be considered. These results are also significant in the rapidly evolving treatment setting of metastatic castration-resistant prostate cancer. Given that this study was conducted during a period where second-generation anti-androgens were not approved or available, the optimum treatment sequence of TDE and other novel that modulate the AR pathway is currently unclear and further trials will need to be performed to determine this.

Declarations of interests

None Declared

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Clinical practice points

Oral systemic oestrogen treatment, in the form of diethylstilbestrol (DES), was widely used in prostate cancer and castration-resistant disease. Their use, however, was associated with increased risk of cardiovascular and thromboembolic events resulting from the first-pass metabolism in the liver. TDE avoids this effect and offers an alternative and potentially safer means of androgen suppression.

TDE used in this population of patients with CRPC post GHRHa and DES treatment was found to be safe and well tolerated. Importantly TDE lead to PSA decline of >50% in 13% of patients with a median progression-free survival of 4.6 months.

Optimal inhibition of the AR signaling pathway remains an important target in the setting of CRPC and the use of TDE as an alternative modality of maintaining castrate levels of testosterone is a possible option especially for the older and less fit patients who might not tolerate chemotherapy or second-generation anti-androgens and should always be considered. These results are also significant in the rapidly evolving treatment setting of metastatic castration-resistant prostate cancer. Given that this study was conducted during a period where second-generation anti-androgens were not approved or available, the optimum treatment sequence of TDE and other novel that modulate the AR pathway is currently unclear and further trials will need to be performed to determine this.

Microabstract

We aimed to investigate the role and safety of transdermal oestrogen therapy in castrate resistant prostate cancer. Within this dose escalation study we observed reduction in PSA levels at all doses used. In addition, no venous thromboembolic events were detected making the use of transdermal oestradiol a safe treatment option for a subgroup of patients with castration-resistant prostate cancer.