Transdermal oestrogen therapy as a second-line hormonal intervention in prostate cancer: a bad experience

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OBJECTIVE

To compare transdermal oestrogen with oral diethylstilbestrol (DES) as a second- or third-line hormonal therapy in the treatment of prostate cancer.

PATIENTS AND METHODS

In all, 32 assessable patients who, having already had a relapse on at least one line of hormonal therapy, received transdermal oestrogen therapy as an alternative to oral DES, when DES became unavailable.

RESULTS

Whereas DES had controlled the prostate-specific antigen (PSA) level for a median of 29 weeks in a group of 15 patients in remission, all but one had an increase in PSA level (median 86% increase above the starting PSA level) within a median of 8 weeks after introducing transdermal therapy. This increase was reversed in seven of the 12 patients who recommenced DES therapy.

INTRODUCTION

Carcinoma of the prostate is the commonest cancer in men in the UK [1], and accounts for ≈ 10 000 deaths every year [2]. In most patients with locally advanced or metastatic disease the treatment involves hormonal therapy [3]. Historically, this often consisted of oestrogens but due to the cardiovascular side-effects [4] this class of drugs lost favour. LHRH analogues are now commonly used as primary hormonal therapy but, unlike oestrogens, these can cause osteoporosis and hot flushes [5]. Transdermal oestrogen has produced satisfactory oestradiol levels, with a reduction of hot flushes, in patients with prostate cancer [6]. In 2003, Ockrim et al. [7] reported the successful use of transdermal oestrogen as a first-line hormonal therapy in the treatment of prostate cancer. The thromboembolic side-effects of oestrogen therapy appear to be avoided by transdermal administration [8], presumably because the liver is not exposed to the high concentrations of oestradiol found in the portal vein with oral dosing.

Oestrogen agonists (such as diethylstilbestrol, DES) are currently widely used in our practice as second- or third-line therapy in the management of castration-resistant prostate cancer. In November 2003, the manufacturer of DES informed the NHS professionals that the drug would become temporarily unavailable. This precipitated a need for an alternative oestrogen preparation; it was decided that transdermal oestrogen might provide a good alternative in the setting of second- or third-line hormonal therapy, given the success of this preparation as first-line hormone therapy. Here we report on the effect of changing from oral DES to transdermal oestrogen on PSA levels, which are monitored regularly for the early identification of relapses.

CONCLUSION

Although the use of transdermal oestrogen is currently attracting enthusiasm as a first-line treatment for prostate cancer, these results show that for second- or third-line therapy further cautious research with careful monitoring is necessary.

KEYWORDS

transdermal oestrogen, hormone therapy, prostate cancer
DES treatment was 29 (6–200) weeks. Thirteen patients had biochemically progressive disease (i.e. their PSA levels were rising) on DES treatment, with a median (range) duration of DES treatment of 102 (12–200) weeks. Four patients had had no previous oestrogen therapy when starting to use the patches.

Of 15 patients with stable PSA levels at the time of treatment switch, 14 had an increase of >40% of their previous PSA levels after starting transdermal oestrogen. This increase took a median (range) of 8 (3–26) weeks to become apparent and the median rise was 86 (44–215)%. Only one of 15 patients had a decrease in PSA level, to 55% of the level before transdermal therapy, over 12 weeks.

A plot of the duration of PSA control by DES before the switch against the duration of control by the skin patch after the switch showed that the latter was much shorter (Fig. 1).

Twelve patients in the stable remission group restarted DES treatment once it became available again. Seven of these responded to the change in treatment with a decrease or stabilization in PSA level lasting ≥8 weeks. An example of this series of events is given in Fig 2. Four of the 12 patients had either a transient response (<8 weeks) or a decrease in PSA level with chemotherapy as well as DES. Only one patient who restarted DES had continued biochemical progression.

Of those with progressive disease, all 17 had further increases in PSA level after switching to transdermal therapy; 11 of them restarted DES. Interestingly, four of these had a decrease or stabilization in PSA level and a further three had a transient response (<8 weeks) or a response with additional chemotherapy. Of the patients previously untreated with oestrogen therapy, all four had increases in PSA level while on the oestrogen patches.

DISCUSSION

All but one of the present patients had an increase in PSA level after starting transdermal oestrogen therapy. For those patients with increasing PSA levels on DES treatment, it is unclear whether the increase was as a result of oestrogen-independent disease progression or a failure of the patches to confer any additional therapeutic benefit. For the patients with stable disease or in remission, these findings were unexpected. Some of these had been in remission for up to 4 years (median 29 weeks), but only a short time after the transdermal therapy started, their PSA levels increased.

In an individual patient, disease progression after the change in treatment does not automatically imply decreased treatment efficacy, as that patient’s disease could have been approaching the end of his oestrogen-induced remission. However, that there was progression in 14 of 15 stable patients after introducing transdermal therapy suggests that the patches were the cause of the biochemical deterioration. The commonest response to DES reinstatement was a decrease in the PSA level, which reinforces this view.

The number of patches prescribed could have been insufficient, leading to a sub-therapeutic amount of oestrogen being delivered, although the advice of a centre with previous prescribing experience had been sought. This might have been because hormone-resistant prostate cancer requires higher doses of oestradiol than earlier stages of disease. Some of the patients had their blood testosterone and oestradiol levels measured, and on every occasion the testosterone was suppressed to undetectable levels and the oestradiol was higher than or within the normal range for a woman. However, these results are difficult to interpret, as the patients’ testosterone levels would already have been suppressed by other means, and there is no consensus on a therapeutic blood oestradiol level in the treatment of prostate cancer.

DES, in addition to its anti-gonadotrophic effect, has been shown to have a direct action on cancer cells [9]. Is it possible that this last action is not shared with oestradiol, which is therefore a less effective second-line agent?
Interestingly, a recent study of transdermal oestradiol as a second-line hormonal therapy showed modest results, with three of 24 patients having reductions in their PSA levels and only six remaining free of disease-progression at 28 weeks [10].

In conclusion, with the recent optimism over the use of transdermal oestrogen in the treatment of prostate cancer, we felt it was important to report our unexpected findings, so that in future others might exercise caution and careful monitoring if deciding to study the use of transdermal oestrogen preparations in men with prostate cancer. These results should not prejudice any trials of transdermal oestrogen therapy at an earlier stage of the disease, where this intervention might still be a valuable tool in lowering testosterone levels. Further research is necessary to achieve appropriate dosages of transdermal oestrogen therapy in castration-resistant prostate cancer.

CONFLICT OF INTEREST
None declared.

REFERENCES

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Abbreviations: DES, diethylstilbestrol.