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Current role of diethylstilbestrol in the management of advanced prostate cancer

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The aim of this review was to describe the most recent data from contemporary clinical trials of diethylstilbestrol (DES) to better determine its current role in advanced prostate cancer treatment as new hormonal therapies emerge. Relevant clinical studies using 1 mg of DES in castrate-resistant prostate cancer (CRPC) were identified from the literature, clinical trial databases, websites and conference abstracts. The efficacy and safety outcomes were summarized. DES in CRPC produced a biological response (change in PSA level) and improved the median survival of patients when used as a second-line hormone therapy after standard androgen deprivation with bicalutamide and LHRH analogues. These findings were for low doses of DES. The 1-mg dose is associated with a reduced toxicity, including fewer thromboembolic and cardiovascular events. Low-dose DES appears to be safe and effective for CRPC before initiating chemotherapy. The cost/efficiency ratio may encourage physicians to consider DES as a therapy option before chemotherapy in non-symptomatic CRPC.

What's known on the subject? and What does the study add?
Diethylstilbestrol (DES) has been found to have anti-tumour properties and clinical effectiveness in prostate cancer that is resistant to the first-line hormonal therapy.

This review found that low-dose DES has anti-tumour efficacy with limited cardiovascular side effects and should be considered for secondary hormone manoeuvres.

KEYWORDS

hormone-resistant prostate cancer, diethylstilbestrol, progression, PSA, low molecular weight heparin, androgen deprivation therapy

INTRODUCTION

Androgen deprivation therapy has been the standard approach for advanced prostate cancer treatment. In the 1940s, the two standard therapies were orchiectomy and diethylstilbestrol (DES). The Veterans Administration Cooperative Urological Research Group (VACURG) demonstrated that orchiectomy and DES have an equivalent efficacy; however, DES has an increased cardiovascular toxicity at a 5-mg dose in patients with metastatic prostate cancer, which limits the its use [1]. The advent of GnRH agonists, which showed an efficacy similar to 3 mg of DES without the cardiovascular toxicity, resulted in a decrease in the use of DES. However, results from further VACURG studies suggested that lower doses (1 mg daily) of DES had activity in prostate cancer that is similar to higher doses but with fewer cardiovascular side effects [2]. Although DES was seldom used in the USA, it was an important option in the armamentarium of European doctors, especially after the failure of first-line hormonal therapy [3]. The objective of the present review was to describe the most recent data from contemporary clinical trials of DES to better determine its current role in advanced prostate cancer treatment as new hormonal therapies emerge.

DIETHYLSTILBESTROL

Diethylstilbestrol is a synthetic ethinyl oestrogen. Its anti-tumour efficacy is attributable to different actions on the prostate cancer. First, the negative feedback exerted on the hypothalamic–pituitary complex causes a decrease in LH secretion, consequently decreasing androgen secretion [4]. DES also increases the levels of sex hormone-binding globulin and pituitary prolactin secretion which decreases testosterone production in the testes [1,5]. DES can also suppress the function of Leydig cells and inhibit the secretion of androgenic steroids. This effect decreases the secretion of testosterone, as shown by the *in vitro* work of Geisler *et al.* [6].

Recently, in CRPC, DES has been shown to act as a telomerase activity inhibitor [7]. It is well established that androgen receptors play a crucial role in CRPC and recently, it has been reported that DES exhibits a high binding affinity for these receptors and could play a mediating role in the disease [8].

TABLE 1 Recent major studies on the use of DES in hormone-resistant prostate cancer

Study, year	No. of patients	Therapy	Mean % PSA response	Mean (range) time to progression, months
Orlando *et al.*, 2000 [14]	38	DES 1 mg	79 (66-92)	7
Rosenbaum and Carducci, 2003 [15]	18/35	DES 1 mg/2 mg Aspirin 100 mg	66	7.5 (2–36)
Smith *et al.*, 1998 [12]	21	DES 1–2 mg	43 (22–64)	–
Clemons *et al.*, 2011 [13]	58	DES 1 mg	38.8	6.7 (4.8–15.2)
Shamash *et al.*, 2010 [3]	145	DES 1 mg	67.5	–

METHODS OF DOSE EFFICACY IN HORMONE-RESISTANT PROSTATE CANCER

Historically, DES was administered at a dose of 5 mg [9]. At this dose, the effectiveness of DES was obvious but not without many side effects (e.g. gynaecomastia, cardiovascular risk). A 1–3-mg DES dose in CRPC has been shown to provide the best relationship between effectiveness and side effects [10,11]. Major studies that used 1–3 mg of DES are listed in Table 1 [3,12–15]. Chang *et al.* [16] reported a 62% decrease of PSA with 3 mg/day DES in 48 patients. These results were consistent with earlier reports by Prout *et al.* [10] and Kent *et al.* [11].

Nevertheless, toxicity, including cardiac toxicity, remained with the 1-mg DES treatments for prostate cancer. The test dose of 1 mg/day of DES showed a promising effect on PSA in a phase 1–2 trial [12]. Nine of 21 (43%) patients had a PSA response, which was defined as a >50% decline from baseline at the end of the phase II trial. These results were identical after one or more hormonal manipulations, and the 2-year survival was 63% in a study by Klotz *et al.* [14]. The median PSA dropped from 95.4 μmol/L (baseline) to 1.5 μmol/L after 3 months of treatment with 1 mg of DES. DES use in their study was associated with warfarin in CRPC [17]. Of the 108 patients treated with 1 mg of DES for advanced prostate cancer (pT3, N0/1), 70 patients had a significant PSA response with a median of 21 months of treatment [18]. More recently, 38.8% of patients ($n = 49$) treated with 1 mg daily before chemotherapy had a PSA response, defined as a >50% decline from baseline, with a median time to progression of 30 months (95% CI, 21.9–68.7) [13]. Despite the number of previous hormonal manipulations, DES seemed to induce a biological response. Of the 34 patients who failed the androgen deprivation therapy, 56% biologically responded to 1 mg of DES, and similar results were observed with DES as second- and third-line therapies [12].

In addition to the pre-chemotherapy results, three out of nine patients treated after undergoing docetaxel treatment had a PSA response of >50%. This finding shows the effectiveness of DES in a different setting of prostate cancer [13]. The successful use of DES after chemotherapy had already been shown by Serrate *et al.* [19]. In this trial, a PSA decrease of >50% was observed in five of 20 patients. These data should have encouraged physicians to consider DES as a potential option after chemotherapy. A DES re-challenge could be a therapeutic option. In this situation, the mean (range) duration of treatment in four patients was 62.6 weeks (44.1–92) [13].

While DES was widely considered an old treatment, the present literature review has shown its efficacy in locally advanced or metastatic prostate cancer. Although DES has not been used widely in the USA, it has remained a therapeutic option, and meanwhile new hormone treatments are emerging (e.g. abiraterone, MDV3100, orteronel) [20–22]. The development of these new hormones and looking at the effectiveness of the old hormones blur the definition of hormone-resistant prostate cancer. In 2012, CRPC is commonly defined as a clinical (weight loss, increased pain), biological (new increase in PSA level) or radiological progression despite anti-androgen and castration (i.e. testosterone <50 ng/dL) treatments.

ADVERSE EVENTS FROM LOW DOSES OF DES

The dose escalation sought by Huggins [23] in 1941 was related to the cardiovascular toxicity of DES. Because the VACURG results showed a 36% increase in mortality in the 5-mg arm, he was looking for the ideal dose that would demonstrate efficacy while limiting its cardiovascular toxicity [2]. Hypercoagulability has been linked to the increased synthesis of the coagulation factors I, II, VII, IX and X resulting from the administration of oestrogen [24]; the increased synthesis of these coagulation factors would lead to a hypocoagulability, decreasing the plasminogen activator and cardiovascular effects.

At a 3-mg dose of DES, a 9.6% rate of thromboembolic events was found in the European Organisation for the Research and Treatment of Cancer (EORTC) trial, protocol 30761, vs 2.7% in the other arm, which included cyproterone acetate and medroxyprogesterone acetate [25]. The results were similar in EORTC protocol 30762, which included a thromboembolic event incidence of 17%, 16% of which were lethal. In the present study, the risk increased with age, a weight >75 kg and a history of cardiovascular disease [26]. More recent studies using 3 mg of DES have reported similar results. In a phase III comparison of 3 mg of DES vs goserelin, 16 cardiovascular events occurred in the DES arm, which included 126 patients [27]. Overall, there was an 8–12.6% incidence of cardiovascular events observed in the contemporary studies that used 3 mg of DES [1].

The final analysis of EORTC protocol 30805, which compared orchiectomy plus cyproterone acetate and low-dose DES (1 mg daily) in patients with metastatic disease, evaluated the clinical efficacy and toxicity of low-dose DES in a multicentre, prospective, randomized trial [26]. In the DES arm, 14.8% (16/108) of patients reported thromboembolic events vs 8.3% (9/108) in the orchiectomy-only arm. This population had no known cardiovascular history. Only two of 63 patients reported a deep vein thrombosis that was confirmed by

a Doppler in the most recent study [13]. These results were obtained by adding 2 mg of warfarin to the diethylstilbestrol for 15 patients with cardiovascular risk. Six patients were previously treated with warfarin for other indications.

Similar results were found in the recent literature, with thromboembolic complication rates of 5–8% [12,28]. Consequently, DES was combined with 75 mg of aspirin (Table 2 [12,13,18,26,28]). This increased risk of thromboembolic complications was investigated with androgen deprivation. DES with aspirin resulted in a rate of cardiovascular events (e.g. stroke, deep vein thrombosis) almost identical to that of any androgen blockade. The latter was estimated to be >40% when compared with a bilateral orchiectomy and should be considered in the therapeutic decision [29].

Another side effect reported by patients was gynaecomastia. This side effect appeared quickly and may be experienced in up to 60% of patients, with 25% of patients having grade 3 gynaecomastia [16]. This side effect may be managed with external irradiation of the breast or preventatively [30]. Other side effects were anecdotal, including nausea, vomiting, rash and asthenia [1].

The most recent European guidelines have emphasized that DES is the most commonly used oestrogen in PCa. In addition, there was a renewed interest in using oestrogens to treat PCa for the following reasons: LHRH agonists have a number of deleterious side effects, and their long-term widespread use is costly, and oestrogens suppress testosterone levels and do not lead to bone loss or cognitive decline. In phase II trials of patients diagnosed with hormone-refractory PCa, oestrogenic compounds (DES, DES-diphosphate) have induced PSA response rates as high as 86%. DES is one of the classic forms of hormonal therapy. The efficacy of DES was demonstrated many years ago and was recently re-confirmed in a meta-analysis in which DES was found to have results similar to a bilateral orchiectomy [14]. However, there is still concern about the significant cardiovascular side effects of DES, even at lower doses. Further data are needed before oestrogens can return to clinical practice as a standard first-line treatment option.

TABLE 2 Thromboembolic events with low-dose DES

Study, year	Percentage of thromboembolic events	Previous treatment
Smith *et al.*, 1998 [12]	5 (1/21 patients)	Aspirin 75 mg
Clemons *et al.*, 2011 [13]	3.1 (2/63 patients)	Warfarin 2 mg (25% patients)
Bishop *et al.*, 1996 [18]	7.5 (8/106 patients)	Nothing
Robinson *et al.*, 1995 [26]	14.8 (16/108 patients)	Nothing
Manikandan *et al.*, 2005 [28]	7.5 (2/26 patients)	Aspirin 75 mg

CONCLUSION

In summary, low-dose DES remains a feasible, inexpensive and effective option for CRPC treatment before chemotherapy. Thromboembolic events occur in <5% of all patients receiving DES, therefore, it should still be considered for the treatment of CRPC as third generation hormonal therapies emerge.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **DES**, Diethylstilbestrol; **CRPC**, castrate-resistant prostate cancer; **VACURG**, Veterans Administration Cooperative Urological Research Group; **EORTC**, European Organisation for the Research and Treatment of Cancer.