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Low-dose diethylstilbestrol for the treatment of advanced prostate cancer

Julia Clemons¹, L. Michael Glodé¹, Dexiang Gao², and Thomas W. Flaig¹

¹Department of Medicine, Division of Medical Oncology, University of Colorado Denver, School of Medicine, Aurora, CO

²Research Institute, The Children's Hospital, Aurora, CO

Abstract

Objectives—The purpose of this study was to assess the efficacy and safety of low-dose (1mg) daily diethylstilbestrol (DES) for the treatment of castrate-resistant prostate cancer (CRPC).

Methods and Materials—A retrospective chart review was performed on patients treated with low-dose DES who had CRPC despite anti-androgen withdrawal. The study population consists of 63 patients treated in the pre- and post-chemotherapy settings based on a database review; 58 had sufficient data for efficacy, all were analyzed for safety.

Results—A PSA decrease of $\geq 50\%$ was observed in 19 of 49 pre-chemotherapy patients (39%) with a median time to progression (TTP) of 30 weeks (95% CI, 21.9, 68.7). A PSA decrease of $<50\%$ was seen in another 16 patients (33%) with a median TTP of 16.4 weeks (95% CI, 13.0, 37.6). Fourteen patients (29%) had progressive disease by PSA testing; their median TTP was 6.9 weeks (95% CI, 5.6, 12.9). Thromboembolic events included 2 patients with DVTs and 1 patient who developed primary fibrinolysis syndrome. Additional adverse events included gynecomastia in 37 of 63 patients (59%). Secondary observations include PSA responses in 3 of 9 patients treated with DES after chemotherapy progression and a high rate of PSA responses in patients retreated with DES after a drug holiday.

Conclusions—Low-dose DES is safe and effective in a modern cohort of men with CRPC despite anti-androgen treatment. Its potential role in the post-chemotherapy setting and the suggestion of efficacy on re-challenge merits additional consideration.

Keywords

diethylstilbestrol; castrate resistant prostate cancer

Introduction

Diethylstilbestrol (DES) is a synthetic ethinyl estrogen with established activity in prostate cancer dating back to the 1940s [1]. DES and orchiectomy were the mainstays of therapy for prostate cancer until the Veteran's Administration Cooperative Urological Research Group

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Corresponding Author: Thomas W. Flaig, M.D, Division of Medical Oncology, University of Colorado Denver, School of Medicine, Mail Stop 8117, 12801 E. 17th Avenue, Room L18-8117, Aurora, CO 80045, Phone: 303-724-3888, Fax: 303-724-3889, Thomas.Flaig@ucdenver.edu.

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(VACURG) studies demonstrated that DES at a dosage of 5 mg daily significantly increased cardiovascular mortality [2]. The use of DES further fell out of favor when GnRH agonists demonstrated equal efficacy compared with 3mg of DES with less cardiovascular toxicity, particularly thromboembolic events [3].

However, results from the ensuing VACURG studies suggested that lower doses of DES (1 mg daily) had similar activity to higher doses in prostate cancer with considerably fewer cardiovascular side effects [4,5]. This finding was supported in another large European study that compared the use of low-dose DES to orchiectomy for metastatic prostate cancer [6]. More recently, multiple smaller studies mainly examining the use of 1mg of DES daily as second line hormonal therapy found DES to be as effective and with a much smaller risk of cardiovascular toxicity compared to higher doses of DES [7,8]. Although DES no longer enjoys widespread use in the United States, these studies, along with the low financial cost of DES, formed the rationale for our continued use of DES as a secondary hormonal manipulation in castrate-resistant prostate cancer (CRPC). Of note, DES remains in regular use for CRPC in Europe after failure of initial hormone therapy [9].

The mechanism of action of DES in prostate cancer appears to be multifold. The primary mechanism is the effect of DES on serum hormone and sex hormone binding globulin levels: testosterone, DHEA-S, and estrone are decreased, while sex hormone binding globulin and prolactin levels are increased [10–12]. DES exerts these effects through negative feedback on the hypothalamic-pituitary axis resulting in decreased LH secretion and consequent decreased androgen production [10]. *In vitro* studies also suggest that DES directly suppresses Leydig cell function and inhibits androgen steroidogenesis, further decreasing serum testosterone [13]. Additionally, there is some evidence DES acts as an anti-androgen in a prostate cancer cell line with a mutated androgen receptor, suggesting it may have this effect *in vivo* [14]. However, DES also has activity in patients with CRPC; potential mechanisms for this activity have been suggested in recent studies. In a xenograft model, DES was shown to suppress tumor androgen levels, which can remain elevated in CRPC and this effect was not estrogen receptor dependent [15]. Furthermore, in prostate cancer cell lines it was found that DES is a potent inhibitor of the enzyme telomerase, which is often up-regulated in malignant cells [16]. Finally, DES also induces apoptosis and has a direct cytotoxic effect on prostate carcinoma cells *in vitro* [17,18].

An intriguing area of ongoing research and interest is the role androgen and estrogen receptors have in this disease [19,20]. Androgen receptor activity appears to continue to be important in mediating growth during CRPC. Recent computer models suggest that DES has a relatively strong binding affinity to the androgen receptor and can be viewed as an androgenic effector [21].

Materials and Methods

A retrospective chart review was performed to extract efficacy and safety data from patients with CRPC, including failure of anti-androgen withdrawal, treated with low-dose DES. Patients were given 1 mg of DES by mouth and aspirin (ASA) daily (81 or 325mg) at the University of Colorado Hospital urologic oncology clinic. The study population was generated by reviewing DES prescriptions filled at a local compounding pharmacy that supplied DES between January 1, 2004, and March 1, 2008. All patients remained on a GnRH agonist, had undergone bilateral orchiectomy, or underwent regular monitoring of their testosterone levels and were restarted on GnRH agonist therapy if they achieved a non-castrate level (e.g. testosterone > 50 ng/dL), therefore ensuring that all subjects remained medically castrate.

A total of 63 patients filled one or more DES prescriptions during the study time period. Their charts were examined for demographic data, tumor characteristics, treatment history, PSA responses, testosterone levels, radiologic studies, adverse events, and overall survival. Specific attention was paid to any clinical or laboratory evidence of cardiovascular toxicity, particularly thromboembolic events. This study was approved by the local institutional review board.

PSA responses and times to progression were used to assess efficacy. Since radiographic follow up was variable and not prospectively defined in this retrospective study, radiographic responses are not reported. A PSA response was defined as a PSA reduction of 50% or more from baseline, with a partial response defined as a decrease in PSA that did not reach the 50% threshold. The median time to progression (TTP) was calculated for each response group. Both PSA responses and progression were defined based on the PSA working group criteria [22]. According to these guidelines, progression was defined as a 50% PSA increase above the nadir, provided that the increase was at least 5 ng/ml, in patients who had a 50% PSA decline. In patients who experienced a PSA decrease that did not reach 50% or who did not have any response, progression was defined as a 25% increase over the nadir PSA level, again by at least 5 ng/ml. All PSA responses and progressions were confirmed by a second PSA level.

All 63 patients were included in the safety analysis. Five patients were excluded from the efficacy analysis; 4 had insufficient data (no follow-up appointment or DES use for less than 4 weeks) and 1 patient had a non-PSA secreting prostate carcinoma and progression was monitored with carcinoembryonic antigen (CEA) levels.

Five patients remained on DES at the end of the data collection period, 3/1/08 and were assessed by Kaplan-Meier survival analysis. Eight patients had an interruption in their DES treatment (drug holiday); in these instances, only the data pertaining to the first DES treatment period was included in the primary efficacy analysis.

Results

All of the patients in this study had advanced CRPC with progression of PSA-detected disease despite anti-androgen withdrawal. Sixty-one patients were treated with GnRH agonists and 2 had undergone bilateral surgical orchiectomy; patient characteristics are described in Table 1. Sixty-two patients were treated with an anti-androgen prior to the DES; for the remaining patient, his previous anti-androgen exposure was not clear and he is not considered in the efficacy analysis due to this missing data. The median number of previous medical treatments was 2 (average 2.6). The median baseline PSA upon initiation of DES was 25.5 ng/mL and the median Gleason sum score was 8. At the beginning of treatment, 30 patients had radiographic evidence of metastatic disease.

Efficacy

Of the 58 patients with sufficient data for efficacy assessment, we first assessed 49 with CRPC who were treated with DES in the pre-chemotherapy setting. For the entire chemotherapy naive cohort, the median TTP was 16.0 weeks (95% CI, 11.9, 24.1) [Figure 1]. A formal PSA response was observed in 19 of 49 patients (38.8%) [Table 2] and the median TTP was 30 weeks (95% CI, 21.9, 68.7) [Figure 2] for this group. An additional 16 patients (32.7%) had a partial response, a PSA decrease that did not reach 50% with a median TTP was 16.4 weeks (95% CI, 13.0, 37.6). Fourteen patients (28.6%) did not respond, their median TTP was 6.9 weeks (95% CI, 5.6, 12.9), essentially a continuation of their previous disease course. The best PSA response for each patient is displayed as a waterfall plot in Figure 3.

In addition to the treatments given in the pre-chemotherapy setting, 13 patients received DES after chemotherapy and 9 of these had sufficient data for efficacy analysis. Four patients were treated with a docetaxel-based regimen, 1 was treated with a Mitoxantrone-based regimen, 3 had trials of both, and 1 patient was treated with separate trials of Mitoxantrone, Docetaxel, and Carboplatin-based regimens. Among those 9 patients, 4 had no response, 3 had a greater than 50% reduction in PSA, and 2 patients experienced a partial response. The median TTP for these 9 patients was 11.9 weeks (95% CI, 6.7, NA) [Table 3].

Another subgroup of patients was defined as those re-treated with DES after a drug holiday. The initial DES treatment was stopped due to progression, an adverse event, a clinical judgment of non-efficacy, or patient non-compliance and subsequent progression, with an intervening period between the treatments of at least 1 month. Two patients had a third separate DES treatment course. The PSA responses during each treatment in these 8 patients are described in Table 4. Notably, 7 of 8 patients had a PSA response with a re-challenge of DES. Among the 7 patients who responded, 3 did not have a PSA response in their initial treatment period. Two patients had 3 separate DES treatments and experienced a PSA response during each treatment.

Adverse Events

Lower extremity deep venous thrombosis (DVT) developed in 2 of the 63 patients, which was confirmed by Doppler ultrasound and required full anticoagulation [Table 5]. All 63 patients were on ASA, 6 patients were previously on coumadin for other indications with continuation of this therapy during DES treatment, and 15 were started on a fixed dose of 2mg of coumadin for additional DVT prophylaxis (although this was not our practice at the end of the trial period). Both patients with DVTs recovered fully without further adverse events, one was re-started on DES in conjunction with 5mg of coumadin and remained on DES for another year without incident. Another patient with very rapidly progressive prostate cancer was treated with DES for 2 weeks and then quickly transitioned to docetaxel for advancing disease. Primary fibrinolysis syndrome was recognized at the time of the initiation of docetaxel in this patient, and was believed to be possibly related to the DES use. No other cardiovascular toxicities occurred among the remaining 60 patients.

The most common adverse event was gynecomastia which occurred in 37 patients (59%), usually in the first few months of treatment. Twenty had Grade III and 17 had Grade II gynecomastia. Of these 37 men, 17 underwent breast-tissue irradiation, which halted the progression and reduced pain. One patient was treated with Tamoxifen for gynecomastia. Multiple patients reported hypogonadal side effects (e.g. hot flashes and erectile dysfunction), but these are not reported here as the men were all medically or surgically castrate and accurate attribution of DES to these symptoms is not possible retrospectively. Finally, 2 patients developed a Grade I rash during treatment, 1 patient grade III mastitis, and 1 patient experienced Grade I fatigue.

Discussion

To our knowledge, this represents the largest series of low-dose, single-agent DES treatment in patients primarily treated with GnRH agonists and progressing after anti-androgen treatment and withdrawal – the modern working definition of CRPC. DES has significant activity in this setting with 72% of patients experiencing some degree of PSA reduction. The PSA response rate of 39% observed here is similar to that of several recent smaller studies of low-dose DES as a second-line hormonal therapy, which reported PSA responses in 23% and 43% of patients [7,8]. For this group of patients with a PSA response there was a clinically relevant median TTP of 30 weeks. A very recent article by Shamash et al found that a PSA decline >50% after 1 month of therapy with DES and dexamethasone was

prognostic for overall survival with this therapy, suggesting PSA response is a potential surrogate for clinically meaningful responses with DES treatment [9]. It is notable that 29% of patients did not respond to DES treatment and had a median TTP of 6.9 weeks. A possible explanation for the resistance to this therapy in some patients is the expression of increased levels of estrogen receptor- α in a subset of patients, which could promote tumor progression [19]. Low dose DES or other estrogen therapy may not be indicated for this group of patients. As further research is performed in this area, elucidating differences in receptor expression and active pathways in CRPC, a specific subgroup of patients who would most benefit from low dose DES could potentially be more readily identified.

Low-dose DES was safe and well tolerated. Less than 5% of the patients experienced thromboembolic events and there were no cardiovascular deaths on treatment. Two patients developed a DVT and were managed medically, remaining clinically stable and without further complications. The incidence of thromboembolic adverse events is similar to that observed in other smaller series (5–8%) of low-dose DES in the modern era [7,8]. Moreover, the baseline risk of thromboembolic events is increased in men with prostate cancer and further increased in men undergoing endocrine treatments [23]. We are unable to differentiate the relative risk of DES versus hypogonadism in this case series. Some investigators have administered low, fixed-dose warfarin in conjunction with DES to potentially mitigate the thrombotic event risk, particularly with higher doses of DES [24]. Based on recent studies demonstrating a lack of efficacy from low, fixed-dose warfarin in cancer patients with a central venous catheter, it has been our practice to use ASA, but not warfarin in average-risk patients on low-dose DES [25]. Gynecomastia, the most common adverse event associated with DES treatment, was observed in the majority of the patients. This side effect can be managed with external beam radiation to arrest the further progression of gynecomastia, and it may also be given prophylactically to prevent its development [26].

Two additional findings in this study merit special attention: The activity of DES in patients after progression on chemotherapy and in patients who had previously progressed on DES but were re-challenged after a drug holiday. Although both groups are too small to lead to firm conclusions, the results are hypothesis-generating and support other small reports of post-chemotherapy activity. Post-chemotherapy activity was very recently described in a study of 1 mg DES after docetaxel-based chemotherapy, with PSA decreases of 50% or more observed in 5 of the 20 subjects [27]. Another case report observed the efficacy of DES in 2 patients following docetaxel chemotherapy who had already progressed on DES prior to beginning chemotherapy [28]. These findings are significant as there are limited therapeutic options after docetaxel failure in prostate cancer. Mitoxantrone is approved for use in advanced prostate cancer but its activity in the post-docetaxel setting is modest with PSA responses of approximately 20% and it is associated with grade 3 or 4 toxicity in the majority of patients in this setting [29]. In comparison, low-dose DES may be an acceptable palliative therapeutic option. Additionally, PSA responses after a re-challenge of DES were observed in the majority of subjects and are noteworthy. We generally have used rechallenge in those not able or unwilling to undergo cytotoxic chemotherapy. The apparent activity observed here with DES retreatment was unexpected and suggests an additional setting in which DES may be active in prostate cancer.

With emerging data on the persistent activity of the androgen receptor in patients previously characterized as “androgen-independent”, the castrate-resistant state is becoming more difficult to precisely define. In 2010, CRPC is commonly described as disease progression (increasing PSA or radiographic progression) despite anti-androgen challenge and withdrawal in the setting of castration (e.g. testosterone < 50 ng/dL). It has been our practice to regularly use DES prior to declaring a patient “hormone refractory” and starting cytotoxic

chemotherapy. In this series, the PSA response rate to DES for these patients fitting a definition of “CRPC” is approximately 40%. In contrast, the PSA response rate to the widely utilized anti-androgen withdrawal maneuver was only 11% in one of the largest series of this approach, yet anti-androgen withdrawal remains an essential part of our working definition of CRPC [30]. Despite the clear activity and reported safety of low-dose DES, the use of DES is almost negligible in the U.S, although it is noted that DES is currently only generally available through compounding pharmacies, limiting its access in some localities [31]. While DES is an “old” treatment, its incorporation into the standard definition of CRPC and its general use before exposing patients to cytotoxic chemotherapy deserves renewed consideration. Additionally, with the emergence of several promising novel hormonal therapies for the treatment of prostate cancer, namely Abiraterone acetate and MDV3100, DES may have a role in conjunction with these agents or after failure of these agents [32,33]. It was announced at the European Society of Medical Oncology Congress in October of 2010 that Abiraterone Acetate plus placebo yielded a 4 month survival advantage over prednisone alone in prostate cancer patients previously treated with docetaxel chemotherapy. This finding emphasizes the ongoing importance of androgen receptor targeting, even in very advanced cases of prostate cancer.

Conclusions

In summary, low-dose DES is safe and effective in CRPC prior to the initiation of chemotherapy, with a PSA response rate of 39% and a DVT incidence of < 5% in this series. Importantly, PSA responses are observed in the post-chemotherapy setting, in which no clearly effective standard therapy currently exists. Additionally, the frequent responses observed in a small number of patients re-treated with DES after a drug holiday is hypothesis generating and merits further investigation. A therapeutic trial of DES should be considered before declaring a patient to be hormone refractory and initiating cytotoxic chemotherapy in appropriate patients.

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Figure 1. Kaplan-Meier estimate of the progression-free survival in pre-chemotherapy patients treated with DES, with the 95% confidence interval shown. '+' indicates censored observations.

Figure 2. Kaplan Meier estimates of the progression-free survival of PSA-responders versus PSA non-responders in the pre-chemotherapy setting. '+' indicates censored observations.

Figure 3.
The best PSA response to therapy for each subject, displayed as a waterfall plot.

Table 1

Patient Characteristics

Characteristics	No.
Total no. of patients	63
No. of patients analyzed for efficacy	58
PSA at start of treatment (ng/mL)	
Median	25.5
Range	0.15–1484
Median Gleason Score	8
Patients with radiographic evidence of metastatic disease	30
Age (years)	
Median	70
Range	56–84
Prior Local Therapy	
Radiation	36
Surgical Resection	32
Cryotherapy	7
Brachytherapy	3
No of previous medical treatments	
Median	2
Range	1–6
GnRH agonist	61
Surgical orchiectomy	2
Anti-Androgen	62
Taxotere-based chemotherapy	13
5 α Reductase Inhibitor	7
Silibinin (silybin-phytosome)	6
Ketoconazole	5
Mitoxantrone-based chemotherapy	5
Investigational Vaccine	4
Carboplatin-based chemotherapy	1
Samarium-153	1

Table 2

PSA Responses in the chemotherapy naïve setting

PSA response	No. of patients	Median time to progression
50% reduction from baseline	19/49 (38.8%)	30 weeks (95% CI, 21.9, 68.7)
<50% reduction from baseline	16/49 (32.7%)	16.4 weeks (95% CI, 13.0, 37.6)
No response	14/49 (28.6%)	6.9 weeks (95% CI, 5.6, 12.9)

Table 3

PSA Responses in the post-chemotherapy setting

PSA response	No. of patients	Time to progression
50% reduction from baseline	3/9 (33.3%)	14.6, 57.7, 62.5 weeks
<50% reduction from baseline	2/9 (22.2%)	10, 27.7 weeks
No response	4/9 (44.4%)	4.3, 4.7, 6.7, 11.9 weeks

Table 4

PSA Responses after DES re-challenge

1 st DES treatment 50% reduction	No. of patients	Length of treatment median (range)	2 nd DES treatment 50% reduction	No. of patients	Length of treatment median (range)	3 rd DES treatment 50% reduction	No. of patients	Length of treatment
Yes	4	62.6 weeks (44.1–92)	yes	4	50.4 weeks (17.1–126.7)	yes	2	28.3, 37 weeks
			no	0		no	0	
No	4	8 weeks (5.6–68.9)	yes	3	19.4 weeks (8.7–29)			
			no	1	29 weeks			

Table 5

Significant Adverse Events

Adverse Event	Number		
	Grade 1	Grade 2	Grade 3
Gynecomastia		17	20
Deep Vein Thrombosis			2
Mastitis			1
Primary Fibrinolysis Syndrome			1
Rash	2		
Fatigue	1		