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Original Article

Experience with using Fosfestrol for Treating Metastatic Castrate-Resistant Prostate Cancer in Resource-Limited Setting

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Abstract

Background: Fosfestrol is a low-cost estrogen analog that is useful in the management of metastatic prostate cancer in resource-challenged settings. It acts by altering the pituitary axis, adrenal secretion, and 5-alpha reductase activity. **Patients and Methods:** The outcomes of metastatic castration-resistant prostate cancer patients treated with fosfestrol in our center between June 2012 and December 2015 were analyzed retrospectively. Fosfestrol was given orally at a dose of 120 mg thrice daily. Event was defined as the discontinuation of fosfestrol due to tumor progression or drug toxicity or death due to any cause. The event-free survival (EFS) and overall survival (OS) were calculated by the Kaplan–Meier method. **Results:** The analysis included 47 patients with a median age of 65 years. Initial Gleason score was available for 41 of 47 patients, of which 17% (7), 39% (16), and 44% (18) were low risk, intermediate risk, and high risk, respectively. The most common site of metastasis was bone (98%). Of 47 patients, 32 (68%) received fosfestrol as the second line of treatment after progression on complete androgen blockade, 14/47 (30%) received it as the third line, and 1/47 received it as the fourth line of treatment. The median prostate-specific antigen (PSA) value at the start of fosfestrol and the nadir PSA value were 43.7 ng/ml and 13.1 ng/ml, respectively. Ninety-one percent (n = 43) of patients had not been previously treated with chemotherapy (docetaxel). Response of PSA of >50% was observed in 55% (n = 26) of patients. The median EFS and median OS after the start of fosfestrol were 6.8 and 14.7 months, respectively, with a median follow-up of 10.9 months. Only two patients developed Grade 3 toxicity, both of whom had diarrhea. **Conclusions:** In resource-challenged settings, oral fosfestrol is an effective, cheap, and safe option for the management of metastatic prostate cancer progressing after first-line complete androgen blockade.

Keywords: *Castration-resistant prostate cancer, diethylstilbestrol diphosphate, fosfestrol, prostate-specific antigen, survival*

Introduction

Prostate cancer is the most common cancer in males.[1] Prostate cancer is androgen dependent, and therefore, suppression of androgens either by surgical castration or by GnRH agonists is the first line of therapy for metastatic prostate cancer. Recent evidence has shown that addition of chemotherapy upfront to androgen deprivation in high-risk patients with metastatic disease improves survival.[2] Invariably, most patients with metastatic prostatic cancer will progress while on androgen suppression and develop metastatic castration-resistant prostate cancer (mCRPC).[3] Survival of mCRPC has improved over the last decade with the advent of newer agents such as docetaxel, abiraterone, enzalutamide, and cabazitaxel.[4-8] However, majority of the newer antiandrogens and cabazitaxel are expensive and beyond the reach of the common people in resource-challenged settings. Estrogen therapy was an important component in the management of prostate cancer in the past; however, with the advent of newer drugs, its use has declined. Estrogen acts by inhibiting the production of adrenal androgens, increasing the testosterone-binding protein, thereby reducing the testosterone levels, and directly acting on Leydig cell steroidogenesis.[9] Estrogen receptors are also present in the stroma of prostate cancer which may negatively influence the growth of prostate cancer.[10] Fosfestrol also known as diethylstilbestrol diphosphate is an estrogen analog used in the management of metastatic prostate cancer. Fosfestrol can be administered as a high-dose intravenous infusion or a low-dose oral maintenance

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therapy. The high-dose infusion in comparison to oral low-dose fosfestrol has a rapid response rate, but results in serious toxicities such as deep venous thrombosis and ischemic heart disease.[11] There is a paucity of data on low-dose maintenance fosfestrol in metastatic prostate cancer. The present study was conducted to analyze the efficacy and safety of fosfestrol in metastatic prostate cancer patients undergoing treatment at our hospital.

Patients and Methods

We conducted a retrospective review of case records. All consecutive patients with metastatic prostate cancer treated with fosfestrol at our hospital between June 2012 and December 2015 were analyzed. Ethical clearance was not required as the study involved only retrospective analysis of case records. Our hospital is a charitable institution, and majority of our patients have financial constraints for treatment. The clinical features, laboratory data, treatment details, and outcomes were obtained from the patient records. Diagnosis of prostate cancer was confirmed by transrectal ultrasound-guided prostate biopsy and elevated serum prostate-specific antigen (PSA). All patients underwent bone scan; chest X-ray; ultrasound of abdomen and pelvis; and computed tomography scan of chest, abdomen, and pelvis for disease staging. Patients received fosfestrol after clinical, radiological, or PSA progression after first-line complete androgen blockade (orchiectomy or leuprolide with androgen receptor blocker bicalutamide) or beyond and with castrate levels of serum testosterone (50 ng/dL).

Fosfestrol (Honvan, Zydus Cadila, India) was prescribed at a standard dose of 120 mg three times a day continuously. The decision to start fosfestrol was based on physician and patient preference. Patients were followed up monthly with clinical assessment and PSA testing. Bone scan and other imaging were performed on follow-up, if clinically indicated. Fosfestrol was discontinued if patient had disease progression (clinical, radiological, or serial rise in PSA for 3 monthly visits) or Grade 3 or 4 toxicity. Biochemical relapse was defined as serial rise in PSA in 3 consecutive tests done a month apart in an asymptomatic patient. No absolute cutoff of PSA was taken to define biochemical relapse. Event in the study was defined as appearance of new lesions on imaging or biochemical relapse or Grade 3/4 toxicity or death. PSA normalization while on fosfestrol was defined as decline of PSA <4 ng/ml, which is the upper limit of normal for PSA in our laboratory. Patients were stratified based on Gleason score, PSA response from baseline, age at fosfestrol exposure, and prior chemotherapy exposure. Event-free survival (EFS) was calculated from the time of starting fosfestrol to the occurrence of an event. Overall survival (OS) was calculated from the time of starting fosfestrol to the date of last follow-up or death of the patient. Biochemical response to fosfestrol was defined as fall in serum PSA by >50% of the value at the start of fosfestrol.

The demographic data of patients were reported as descriptive statistics. Survival was calculated by the Kaplan–Meier analysis using the statistical software SPSS version 21 (SPSS Inc., IBM, Chicago, USA), and the factors were compared using log-rank test.

Results

The study included 47 patients with metastatic prostate cancer with a median age at diagnosis of 65 years (range: 42–82 years). Baseline characteristics are described in Table 1. The median age at the start of fosfestrol was 67 years (range: 46–85 years). The median PSA at the start of therapy of fosfestrol was 43.7 ng/ml (5 ng/ml–1860 ng/ml). Gleason score of more than 6 at diagnosis was present in 34/47 (80%) patients. The skeletal system was the only site of metastasis in 41/47 (87%) patients, 3/47 had lymph node and bone metastases, 2/47 had lung and bone metastases, and 1/47 had only nodal metastases before initiation of fosfestrol. The common comorbidities in the patients included diabetes mellitus and hypertension in 7, 3 had diabetes mellitus alone, 8 had hypertension only, 1 had hypertension and ischemic heart disease, and 2 had ischemic heart disease.

Orchidectomy was performed in 40/47 (85%) patients, and medical castration with leuprolide was prescribed to 7/47 (15%) patients as the first line of treatment. All patients received antiandrogen bicalutamide along with surgical or medical castration for complete androgen blockade. Patients who received leuprolide continued it after progression on complete androgen blockade. Bicalutamide withdrawal was tried for patients progressing on complete androgen blockade before proceeding to the second line of treatment.

Of 47 patients, 32 (68%) received fosfestrol as the second line of treatment, 14/47 (30%) received it as the third line, and 1/47 received it as the fourth line of treatment. Only 4/47 (8%) patients had received docetaxel and 1 patient had received abiraterone before exposure to fosfestrol. Indications for starting fosfestrol included asymptomatic PSA rise in 24/47 (51%) patients or clinical symptoms with rise in PSA in 23/47 (49%) patients. All 23 symptomatic patients had progression of bone metastasis, and in addition, 1 patient each had new nodal and lung metastasis, respectively, before initiation of fosfestrol. Only 10/36 (27%) patients who had progression/intolerance to fosfestrol received further lines of treatment. All the 46 patients with skeletal metastases received monthly zoledronic acid for a total duration of 2 years; none the patients received denosumab.

Decline in PSA after initiation of fosfestrol therapy was observed in 33/47 (70%) patients, and a decline of more than 50% was observed in 26/47 (55%) patients. Normalization of PSA (<4 ng/ml) was seen in 13/47 (28%)

Table 1: Baseline characteristics and treatment details

Characteristics	*n* (%)
Age at start of fosfestrol (*n*=47) (years)	
<65	15 (32)
≥65	32 (68)
Gleason strata (*n*=41)	
Low (<7)	7 (17)
Intermediate (7)	16 (39)
High (>7)	18 (44)
PSA at start of fosfestrol (*n*=47)	
<20	13 (28)
≥20	34 (72)
Metastasis (*n*=47)	
Skeletal only	41 (87)
Skeletal with extraskeletal	5 (11)
Extraskeletal only	1 (2)
Line of fosfestrol (*n*=47)	
Second	32 (68)
Third	14 (32)
Fourth	1
Reason for start of fosfestrol (*n*=47)	
Biochemical progression	24 (51)
Biochemical and clinical progression	23 (49)
Therapy before fosfestrol (*n*=47)	
Orchidectomy	40 (85)
Leuprolide	7 (15)
Bicalutamide	47 (100)
Flutamide	10 (21)
Ketoconazole	2 (4)
Docetaxel	4 (8)
Abiraterone	1 (2)
Therapy postfosfestrol progression* (*n*=36)	
None	26
Docetaxel	6
Enzalutamide	1
Abiraterone	5
Ketoconazole	4
PSA response >50% from baseline	
Yes	26/47 (55)
No	21/47 (45)
Any PSA response	
Yes	33/47 (70)
No	14/47 (30)

*Few patients received >1 line of therapy. PSA – Prostate-specific antigen

patients. The overall response rate (ORR) to fosfestrol, which includes complete response (normalization of PSA) and partial response (decline in PSA by 50%), was 55%. Disease-related symptoms were present in 23/47 (49%) patients at the start of fosfestrol, and among them, 14/23 (61%) patients had symptom relief.

The median follow-up period after the start of fosfestrol was 12.9 months (range: 0.2–47 months). The median EFS was 6.8 months [Figure 1]. The median EFS of PSA responders was 12.3 months compared to 1.8 months in nonresponders (P = 0.01) [Figure 2]. The median OS after the start of fosfestrol was 14.7 months [Figure 3]. The median OS after the start of fosfestrol for PSA responders was 20.8 months compared to 4.8 months in nonresponders (P = 0.01) [Figure 4]. There was no significant difference in EFS and OS according to the site of metastases (visceral vs. skeletal), primary modality of treatment (orchidectomy vs. leuprolide), and indication for starting fosfestrol (asymptomatic PSA rise vs. clinical or radiological progression) [Table 2]. On univariate analysis, only factor which was predictive of EFS and OS was PSA response [Table 2].

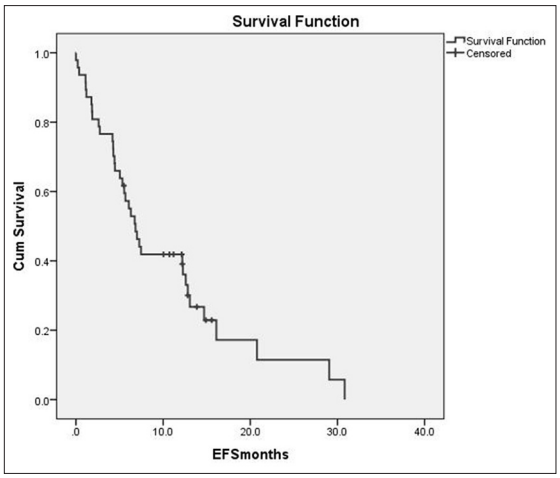

Figure 1: Event-free survival of all the patients

Toxicity was recorded in five patients. Three patients had Grade 2 toxicity (elevated liver enzyme, diarrhea, and somnolence), of them two patients required dose reductions. Grade 3 toxicity was seen in two patients both of whom had diarrhea and required discontinuation of fosfestrol.

Discussion

The use of low-dose fosfestrol has slowly decreased in metastatic prostate cancer after the advent of chemotherapy and other newer hormonal agents such as abiraterone and enzalutamide. We observed that 70% of patients had a decline in PSA with fosfestrol and the ORR to fosfestrol was 55%. The ORR in mCRPC with docetaxel was 45%, mitoxantrone 32%, and abiraterone 62%.[4,12] The ORR of fosfestrol is comparable to other agents used in mCRPC. Fosfestrol can be given as high-dose intravenous infusion or a low-dose oral maintenance therapy. Studies have shown that high-dose intravenous fosfestrol is associated with increased risk of cardiac toxicities and thromboembolic events, but the response rates are not increased in comparison to low-dose oral fosfestrol.[11,13-15] There were no Grade 4 toxicities in our study, and only two patients discontinued treatment due to Grade 3 diarrhea. Surprisingly, there were no documented cardiac or thromboembolic events in our study; this contrasts with reports from data from other

Table 2: Univariate analysis for event-free survival and overall survival after starting fosfestrol

Factors (*n*)	Median EFS (months)	*P**	Median OS (months)	*P**
Overall (47)	6.8		14.7	
Age at start of fosfestrol (years)				
<65 (15)	6	0.5	20.8	0.32
≥65 (32)	7		13.5	
Gleason strata (*n*=41)				
Low risk (7)	7.2	0.59	14.7	0.28
Intermediate risk (16)	6.3		9.6	
High risk (18)	6		20.8	
PSA decline >50% (*n*=47)				
Yes (26)	12.6	0.009	29	0.01
No (21)	5		9.2	
PSA decline - any (*n*=47)				
Yes (33)	12.3	<0.0001	20.8	0.01
No (14)	1.8		4.8	
First-line treatment (*n*=47)				
Orchidectomy (40)	7	0.61	17.3	0.4
Leuprolide (7)	6		29	
Indication for starting fosfestrol (*n*=47)				
Clinical symptoms (23)	7.2	0.81	12.7	0.66
Biochemical progression (24)	6.3		17.3	
Metastasis (*n*=47)				
Skeletal (41)	7	0.4	14.7	0.49
Skeletal + visceral (6)	2.6		29	

*Log-rank test. EFS – Event-free survival; OS – Overall survival; PSA – Prostate-specific antigen

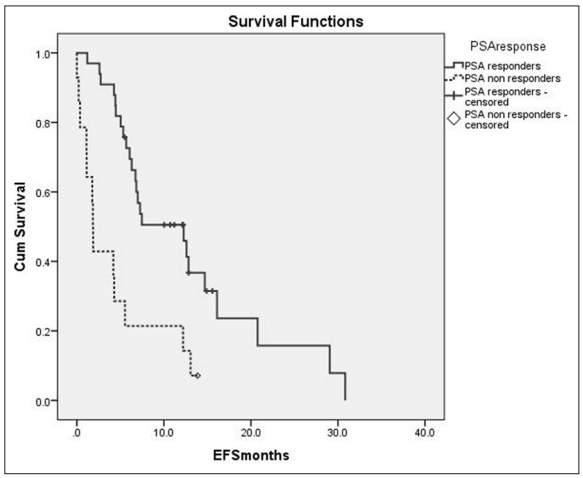

Figure 2: Event-free survival based on prostate-specific antigen response

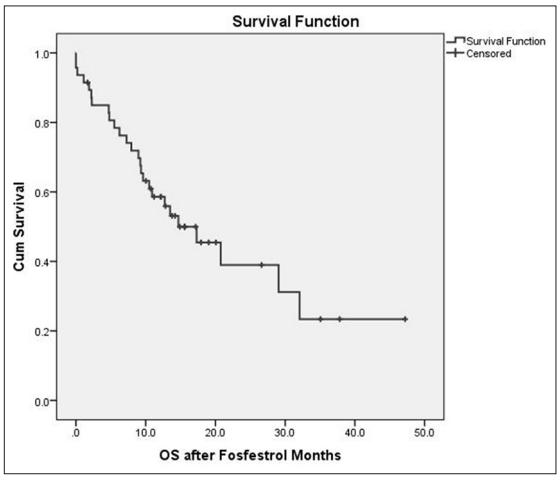

Figure 3: Overall survival after the start of fosfestrol of all the patients

authors [Table 3]. Genetic variation in susceptibility to fosfestrol-induced thromboembolism could be a factor for the above observation. There is a higher prevalence of hereditary thrombophilias such as factor V Leiden, protein C deficiency, and protein S deficiency in Caucasian population compared to the Indian population.[16,17] On univariate analysis, the only factor that predicted EFS and OS was the PSA response.

The monthly cost of fosfestrol treatment in India is approximately 2500 rupees. Drugs such as docetaxel (10,000 Rs/month), abiraterone (25,000 Rs/month), cabazitaxel (30,000 Rs/month), and enzalutamide (200,000 Rs/month) are beyond the reach of majority of patients with prostate cancer in resource-challenged settings. Our study shows that fosfestrol is an effective drug for providing symptom relief and prolonging survival in metastatic prostate cancer patients in resource-challenged settings. Limitations of our study include its retrospective nature, small sample size, and inability to capture all toxicities. Randomized controlled trials comparing fosfestrol to newer agents are required to ascertain its benefit and cost-effectiveness.

Table 3: Comparison of similar fosfestrol data series with our study

	Orlando *et al.*[15]	Williams and Whelan[13]	Droz *et al.*[11]	Grise *et al.*[14]	Our study
Number of patients	38	21	16	32	47
Median age	70	-	67	-	67
Dose of fosfestrol	100 mg oral thrice daily continuous - low dose	1100 mg iv for 5 days daily repeated once in 4 weeks - high dose	Varied from 3 g to 4.5 g/day for 5 days followed by 300 mg/day oral repeated once in 4 weeks - high dose followed by maintenance	1.2 g - 3 g/day for 10 days followed by maintenance - high dose followed by maintenance	120 mg thrice daily continuous - low dose
CR rate (%)	21	-	-	-	28
PR rate (%)	58	-	-	-	28
ORR rate (%)	79	39	44	40	55
Median start PSA (ng/ml)	120	-	-	-	43.7
Median survival after fosfestrol (months)	12	20 (mean)	5	8	14.7
Median survival in responders (months)	13	-	8	19.6	20.8
Median survival in nonresponders (months)	7	-	4	4.2	4.8
Major toxicity	DVT - 8%	DVT - 10%	Pulmonary embolism - 6%	-	GI - 6%
	GI - 19%		MI - 6%		Transaminitis - 2%
	Transaminitis - 2%		Treatment related mortality - 18%		

DVT – Deep vein thrombosis; GI – Gastrointestinal; iv – Intravenously; ORR – Objective response rate; PR – Partial response; CR – Complete response; PSA – Prostate-specific antigen

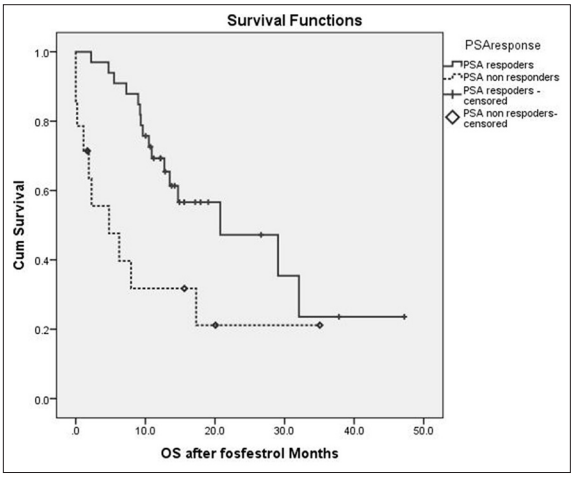

Figure 4: Overall survival after the start of fosfestrol based on prostate-specific antigen response

Conclusions

In resource-challenged settings, oral fosfestrol is an effective, cheap, and safe option for the management of metastatic castration prostate cancer progressing after first-line complete androgen blockade.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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