Original Article

COMPARISON OF CHANGES IN SERUM PROSTATE SPECIFIC ANTIGEN IN PROSTATE CANCER PATIENTS TREATED EITHER WITH FLUTAMIDE OR STILBOESTROL MONOTHERAPY.

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ABSTRACT

Prostate cancer is a disease of males. Though commoner in the elderly, cases are beginning to be reported in the younger population. It is the commonest cancer diagnosed in males. Risk factors include ageing, genetic/familial factors, racial predilection, increased fat diet, and hormonal imbalance. It is a slow-growing tumour but can be associated with severe morbidity. The commonest histologic type is adenocarcinoma (>95%). When detected early, cure may be possible. Prostate-specific antigen (PSA) is the major serum marker used to monitor progress of the disease and its' response to therapy. Several treatment modalities have been used in the management of prostate cancer. This includes watchful waiting, prostatectomy, radiotherapy, hormone therapy, and chemotherapy. These treatment options are not without devastating and sometimes life-threatening adverse effects; hence the choice of therapy depends on patient's age, stage of disease, other co-morbidities, and even patient's choice.

AIMS AND OBJECTIVE: This study aimed at establishing the variation in PSA among patients with advanced CaP treated either with Flutamide or Stilboestrol monotherapy in UCTH, Calabar. This helped in choosing an agent with better patient compliance, better therapeutic effect, minimal side-effects, and cost-effectiveness.

METHOD: All newly diagnosed prostate cancer patients in the Division of Urology, Department of Surgery, UCTH, Calabar that met certain inclusion criteria were treated either with Flutamide or Stilboestrol monotherapy over a period of one year. Patients enrolled into the study were shared into two equal groups based on certain considerations. Response to therapy was monitored by conducting a three-monthly PSA check and results from the groups compared.

RESULTS: Fifty patients were enrolled into the study. The mean age was 70.12±8.93, and age range was 51-93 years. The peak age range was 61-70 years constituting 40.0% of total number of patients. The decline in serum PSA caused by flutamide and stilboestrol during each quarter of the year was 8.0%, 12.0%, 12.0%, 4.0% and 28.0%, 4.0%, 28.0%, 4.0% respectively. Overall flutamide caused a 36.0% reduction and stilboestrol 64.0% reduction in serum PSA over the period. In all, stilboestrol caused a greater decline in serum PSA compared to flutamide, and this became statistically significant at 9 months (p=0.044) and one year (p=0.048) of therapy.

CONCLUSION: Patients who are on androgen deprivation therapy for CaP have their serum PSA reduced by either flutamide or stilboestrol monotherapy. However, over time, the PSA is more rapidly reduced by stilboestrol monotherapy compared to flutamide monotherapy.

KEYWORDS: Prostate Cancer, Flutamide, Stilboestrol, PSA.

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INTRODUCTION

The prostate gland is the male organ most commonly afflicted with either benign or malignant neoplasms[1]. Prostate cancer (CaP) is the most common cancer in men[2]. It is the second leading cause of cancer death for men in North America[1,3]. In Nigeria, it is the most commonly diagnosed cancer in men[4,5]. An estimated hospital prevalence of 127 per 100,000 was reported in 1997 in Lagos, Nigeria[6]. The incidence continues to increase with advancing age. Of all cancers, the prevalence of CaP increases the most rapidly with age[1]. The lifetime risk of a 50-year-old man for latent CaP (detected as an incidental finding at autopsy, not related to the cause of death) is 40%; for clinically apparent CaP, 9.5%; and for death from CaP, 2.9%[1]. Thus many prostate cancers are indolent and inconsequential to the patient while others are virulent, and if detected too late or left untreated, may result in a patient's death.

Various treatment modalities are used in the management of CaP. This include androgen deprivation therapy (ADT), corticosteroids, radiotherapy, chemotherapy, and surgery. Stilboestrol (also called diethylstilboestrol-DES) and flutamide are some agents that have been used mostly in treatment of advanced CaP. Though at physiologic levels oestrogens do not have direct effect on prostate cancer, exogenous oestrogens block the hypothalamic steroid receptor and inhibit the release of luteinizing hormone-releasing hormone (LHRH) leading to below castrate levels of testosterone. It also has cytotoxic effects on the tumour cells[7]. Diethylstilboestrol at 1-3mg/day reduces testosterone to castrate levels {0.7-1.7nmol/l (0.2-0.5ng/ml)}[7,8]. DES is associated with increased incidence of cardiovascular-related deaths. Risk of cardiovascular disease increase with age, weight >75kg and a history of cardiovascular disease[9]. Other side-effects include nausea, fluid retention, ankle oedema, hypertension, heart failure, thromboembolic disease, testicular atrophy, loss of libido,

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impotence, gynecomastia, and nipple pigmentation.

Flutamide is a pure anti-androgen that blocks the effects of androgen at the target organs and the brain. It initially increases the blood levels of testosterone, luteinizing hormone (LH), and oestradiol. Its administration can lead to painful gynecomastia, decreased libido and potency, nausea, vomiting, diarrhoea, and hepatitis-like syndrome[7]. This study is aimed at comparing PSA changes in prostate cancer patients treated either with stilboestrol or flutamide monotherapy.

PATIENTS AND METHODS

This was a prospective observational study that was carriedout over a period of one year from July 2016 to June 2017. Ethical approval was gotten from the Hospitals' Health Research Ethics Committee.

INCLUSION CRITERIA

1. All newly histologically diagnosed primary advanced prostate cancer patients in UCTH, Calabar.
2. All newly diagnosed primary localized prostate cancer patients who opted for/were placed on ADT for various reasons.
3. All of number one above placed either on flutamide or stilboestrol monotherapy
4. All of number one above not on any other form of therapy for BPH or CaP.

EXCLUSION CRITERIA

1. Prostate cancer (CaP) patients already on any treatment modality
2. CaP patients who were not treated with flutamide or stilboestrol monotherapy
3. CaP patients placed on more than one form of therapy
4. CaP patients whose histologic diagnosis was done outside UCTH
5. CaP patients whose therapy were changed during the course of the study
6. CaP patients with poor drug compliance were removed from the study
7. CaP patients who opted for non-hormonal treatment
8. Patients with secondaries from other sites to the prostate gland

An investigator-administered proforma was designed to record details of patient's personal and clinical data as well as findings from relevant investigations.

Every patient seen at the Urology clinic of UCTH with complaints of Lower Urinary Tract Symptoms (LUTS) relevant to CaP was 'clerked' and examined in accordance with the proforma for the study. A careful clinical examination with emphasis on digital rectal examination (DRE) was carried out on each patient. Patients received counselling on the possible pathology and the management options. Following DRE, patients with suspicious findings were requested to do serum PSA and trans-rectal ultrasound scan. Those whose scans showed heterogenous (hypoechoic or hyperechoic) echotexture, distorted prostate capsule, were counselled for prostate biopsy. For each candidate, about 6-12 prostate biopsy samples were collected into a container of Bouin's solution and sent with a well-filled histopathology request form to the Histopathology laboratory of UCTH for analysis. Patients whose histopathology reports were positive for primary prostate cancer and qualified for treatment had counselling for the various treatment options available. Those who chose hormonal therapy received further counselling for either flutamide or stilboestrol monotherapy. Those who weighed >75kg, and/or had cardiovascular/risk of cardiovascular diseases were placed on flutamide while those with paraparesis/paraplegia (being a sign of spinal deposits) were placed on stilboestrol. This was done until equal number of persons were recruited into each group. Flutamide was administered orally at 250mg 8-hourly and DES orally at 1mg daily for at least 32 weeks as was the protocol of the Urology Division. Patients were told of the possible side-effects of each medication, asked to adhere strictly to the prescription, and report any adverse event to the clinic. Patients were also told to present the medications being taken at each clinic visit and asked to describe how they were being taken to confirm adherence. They were asked to do a three monthly check on serum PSA for follow up of response to treatment as was the protocol of the Urology Division of UCTH, Calabar. Patients were given the requisite investigation form, stating the times of follow-up tests and visits. Where possible, they were contacted via phone calls to remind them of their follow-up visits. At each visit, each patient had his vital signs and relevant anthropometry checked, interviewed on drug compliance, side effects, and counselled on progress made before the next appointment was given.

The change in the PSA of those treated with flutamide only were then compared with those treated with stilboestrol only. All the participants in the study had adenocarcinoma.

STATISTICAL ANALYSIS

Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 20. Frequencies, percentages, means, and standard deviation were used to summarize the data. Relevant tests of significance such as the Chi-square (x^2) and T-test were conducted at a confidence limit of 95% and a P-value of <0.05. Data were presented in tables, charts, and figures.

RESULTS

Table 1: Socio-demographic characteristics f patients who received either Flutamide or Stilboestrol monotherapy for cancer of the prostate (N=50).

Overall, a proportion of 74.0% of patients belonged to the 61 to 80 years age group. In the flutamide group, this 61-80 year age group accounted for 72.0% compared with a slightly higher proportion of 76.0% in the stilboestrol group. The difference by age between the two arms was not statistically significant (p=0.323).

Variables	Flutamide group Frequency (100%)	Stilboestrol group Frequency (100%)	Total Freq.(100%)	Chi square test	p-value
Age group(years)					
51-60	5(20.0)	2(8.0)	7(14.0)	4.673	0.323
61-70	12(48.0)	8(32.0)	20(40.0)		
71-80	6(24.0)	11(44.0)	17(34.0)		
81-90	1(4.0)	3(12.0)	4(8.0)		
[illegible]	1(4.0)	1(4.0)	2(4.0)		
[illegible]	67.76±8.66	72.48±9.74	70.12±8.93	1.918*	0.061
Marital status					
Married	25(100.0)	25(100.0)	50(100.0)		
Level of education					
Primary	2(8.0)	5(20.0)	7(14.0)	1.906	0.409
Secondary	8(32.0)	9(36.0)	17(34.0)		
Tertiary	15(60.0)	11(44.0)	26(52.0)		
Tribe					
Efik	8(32.0)	8(32.0)	16(32.0)	2.889	0.717
Annang	3(12.0)	6(24.0)	9(18.0)		
Ibibio	2(8.0)	1(4.0)	3(6.0)		
Ekoi	7(28.0)	7(28.0)	14(28.0)		
Igbo	5(20.0)	3(12.0)	8(16.0)		
Religion					
Christianity	24(96.0)	25(100.0)	49(98.0)	1.407	0.236
Traditional	1(4.0)	0(0.0)	1(2.0)		

*=T-test statistic

Figure 1: Comparison Of Pre-Treatment PSAs Among CaP Patients Treated Either With Flutamide Or Stilboestrol Monotherapy.

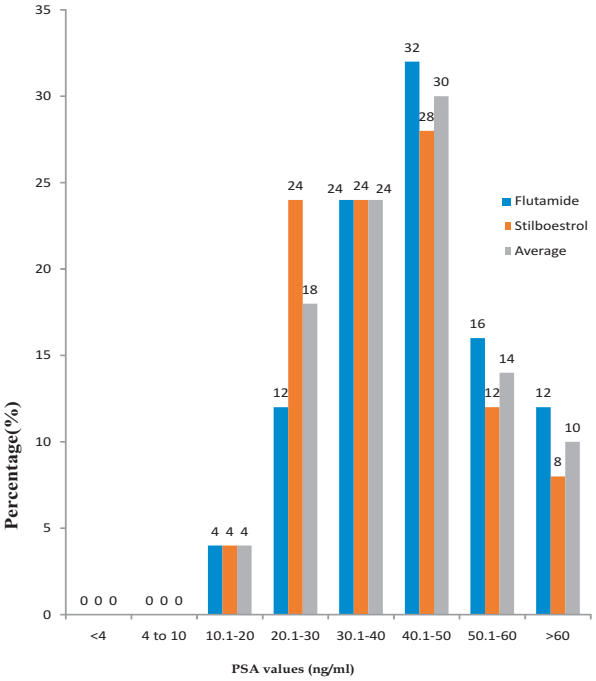

Figure 2: Complications Of Treatment With Either Flutamide Or Stilboestrol Monotherapy.

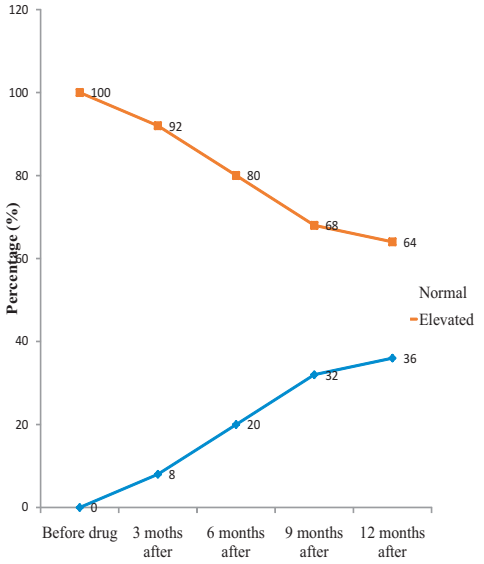

Figure 4: Proportion of CaP patients with normal or elevated serum PSA at different intervals relative to stilboestrol administration

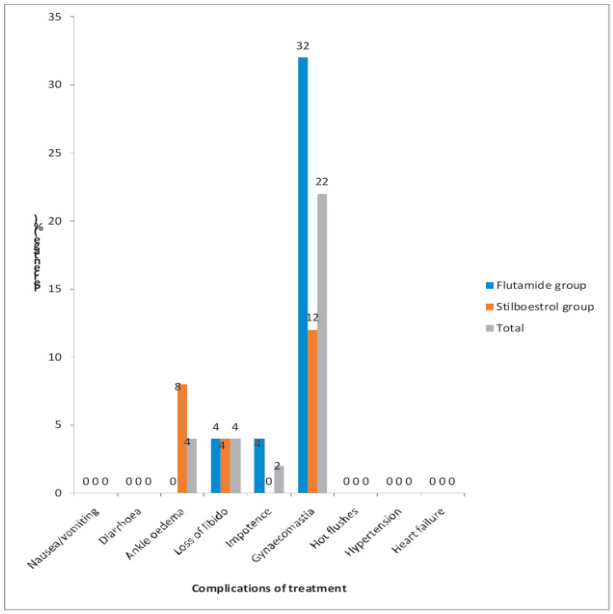

Figure 3: Proportion of CaP patients with normal and elevated serum PSA at different intervals relative to flutamide administration

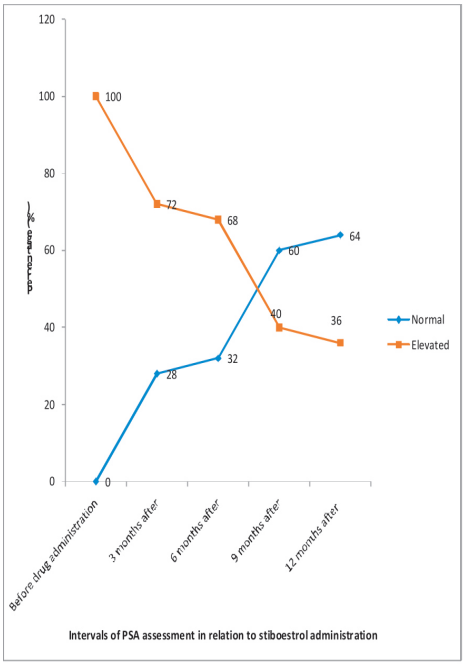

Figure 5: Comparison Of Percentage Of CaP Patients Who Attained Normal Serum PSA Values Following Treatment With Either Flutamide Or Stilboestrol Monotherapy. (p<0.05; from 9 months and above).

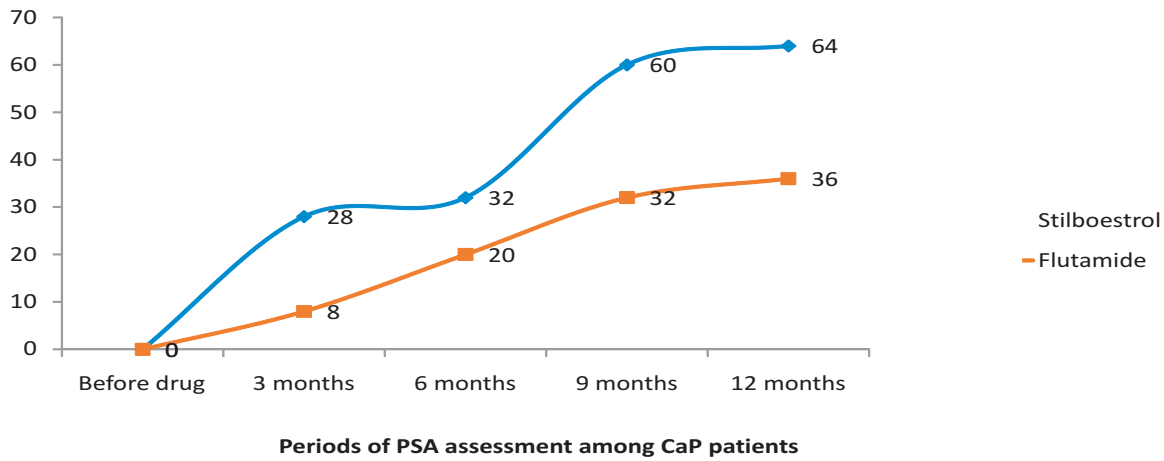

Table 2: Comparison Between Serum PSA Among Cap Patients Treated With Either Flutamide Or Stilboesterol Monotherapy Over A Period Of One Year (N=50)

PSA category at different intervals:	Drug administered				
	Flutamide (n=25)	Stilboesterol (n=25)	Total (N=50)	Chi square test	p-value
Before drug administration					
Normal	0(0.0)	0(0.0)	0(0.0)	--	--
Elevated	25(50.0)	25(50.0)	50(100.0)		
3 months after drug administration					
Normal	2(22.2)	7(77.8)	9(100.0)		0.138
Elevated	23(56.1)	18(43.9)	41(100.0)		
6 months after drug administration					
Normal	5(38.5)	8(61.5)	13(100.0)	0.936	0.333
Elevated	20(54.1)	17(45.9)	37(100.0)		
9 months after drug administration					
Normal	8(34.8)	15(65.2)	23(100.0)	3.945	0.044*
Elevated	17(63.0)	10(37.0)	27(100.0)		
12 months after drug administration					
Normal	9(36.0)	16(64.0)	25(100.0)	3.920	0.048*
Elevated	16(64.0)	9(36.0)	25(100.0)		

Fisher's Exact** implies some (2 cells) had expected count less than 5;
*=Statistically significant

DISCUSSION

Over the years, either pure anti-androgens (flutamide/bicalutamide)[10] or stilboestrol monotherapy has been used in the treatment of advanced primary carcinoma of the prostate[11]. However, no comparison has been made as regards the efficacy of one over the other. This study was aimed at bringing to lime-light such differences in their efficacy if any.

In a study carriedout earlier in UCTH, Calabar by *Ekwere et al.* (2002), a mean age of 66.6±9.8 years was obtained[12]. Another study carried out in UCTH (2003), Calabar gave a mean age of 66.9±10.1 years[13]. *Ojewola et al.*had in a similar study done in Lagos reported a mean age of 66.9±10.7 with a peak of 61-70 years[14]. These correlate strongly with our findings in this study, thus re-affirming the knowledge that CaP is commoner in the older age group.

The commonest LUTS was urinary frequency (50.0%) followed by nocturia (42.0%). This correlates with a study by *Glasser et al.* who had reported that storage symptoms were commoner than voiding symptoms[15].

Gynaecomastia (22.0%) was the commonest complication of treatment among patients who participated in this study. This was, however, commoner among the flutamide group (32.0%) compared to the stilboestrol group (12.0%). *Ekwere PD* had reported same as an important adverse reaction following high dose stilboestrol (15mg three times per day) use in prostate cancer patients[16].

There was no significant difference in the pre-treatment PSAs among the two groups.

Denis et al. had reported a 90.0% decline in serum PSA following androgen withdrawal therapy[17]. This is in keeping with studies by *Smith et al.*and *Serrate et al.* who reported 43.0% and >50.0% decline respectively in serum PSA of CaP patients treated with DES[18, 19]. *Domenico et al.*had also reported $\geq$ 50.0% reduction of total PSA in 26.0% to 66.0% of patients with CRPC[8].

From the study, either flutamide or stilboestrol monotherapy were noted to cause a reduction in the serum PSA of CaP patients with flutamide causing a lower reduction (36.0%) compared with stilboestrol that caused 64.0% reduction over the period. Up to 6 months, the difference in percentage changes between the serum PSA

among the 2 groups was not statistically significant (p>0.05). After 9 months (with those having normal levels of PSA increasing), the percentage changes remained higher in the stilboestrol group when compared with the arm that received flutamide (60.0 % versus 32.0%), and the difference became statistically significant (p<0.05). Similarly, after 12 months, more of those that received stilboestrol compared with those who received flutamide had normal PSA values (64.0% versus 36.0%). Again, the difference in percentage change was statistically significant (p<0.05).

Over the period of this study (at each measurement), it was also noted that the total percentage reduction of serum PSA among those that were on stilboestrol was consistently higher compared to those that were placed on flutamide. This difference, however, was not statistically significant until after 9 months of therapy and beyond (p=0.044 at 9 months and p= 0.048 at 12 months).

Thus, there is a statistically significant difference in the change in the serum PSA of CaP patients treated either with flutamide or stilboestrol monotherapy over time.

Some limitations of this study include poor drug compliance by some patients, paucity of funds to procure medications and do relevant follow-up investigations, poor compliance with clinic appointments and change of therapy during the course of treatment due maybe to development of resistance

CONCLUSION

This study has shown that either flutamide or stilboestrol monotherapy can cause a decline in the serum PSA of CaP patients. The percentage decline, however, vary among the two drugs; being higher among the stilbesterol group. However, this change became statistically significant after 9 months and 12 months of therapy.

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