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Research Aticle

Orchiectomy Versus Goserelin Each Plus Bicalutamide in Patients with Metastatic Adenocarcinoma of the Prostate: Adverse Events Highlighted

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Abstract

Background: Androgen deprivation therapy (ADT), palliation for advanced/metastatic prostate cancer can be medical or surgical. This study compares the results of goserelin injection to orchiectomy each in combination with bicalutamide in patients diagnosed with metastatic adenocarcinoma of the prostate highlighting the adverse events.

Methods: Ninety-six patients with histologically diagnosed adenocarcinoma of the prostate, were prospectively randomized into two arms. Medical arm patients had subcutaneous goserelin injection plus bicalutamide. Surgical arm patients had bilateral orchiectomy plus bicalutamide. A nadir serum prostate specific antigen (PSA) of 0.2ng/ml was chosen and response to treatment was by determining total serum PSA levels at 3 and 6 months. The student's t test, chi-squared test and Kaplan-Meier survival analysis were the instruments for statistical analysis.

Results: Follow up was between 6-30 months. There were 11 (23%) and 9 (19%) deaths in the surgical and medical arms respectively. At 6 months serum PSA levels of ≤ 0.2ng/ml was noted in 44 (92%) and 45 (94%) patients of the medical and surgical castrations respectively. Anemia, impotence, hot flushes were some of the adverse events noted in both groups during the study worse with medical castration.

Conclusion: There was no statistical difference between the oncological efficacy and survival of both arms of treatment but a statistical difference in the adverse events

Keywords: Metastatic adenocarcinoma; Goserelin; Orchiectomy; Bicalutamide

Introduction

Prostate cancer is one of the most fatal cancers and the second most common cancer in men worldwide [1]. African authors have reported that prostate cancer is the commonest genitourinary cancer [2-5] With an estimated 1.1 million new cases and over 300,000 deaths annually, majority of the patients in developed, resource abundant regions are diagnosed with localized and potentially curable disease while patients in developing and resource limited regions typically present with advanced disease and increased mortality [1,6,7]. Androgen deprivation therapy (ADT) based on the primary work of Huggins C and Hodges CV in 1941 is the main stay of treatment for advanced /metastatic prostate cancer [8-15]. ADT may be surgical by way of bilateral orchiectomy or medical by subcutaneous injection of luteinizing hormone releasing hormone (LHRH) agonist. The major circulating androgen is testosterone with 90% - 95% secreted by the testes and 5% - 10% of adrenal gland origin [14,16-19]. Antiandrogen can be combined with either medical or surgical castration to suppress androgens from both the testes and the adrenals termed maximal androgen blockade (MAB) [16,19]. About 80% - 90% of prostate cancers are androgen dependent at initial diagnosis [20]. Castration either medical or surgical effectively lowers serum testosterone levels by 90% - 95% [10,16,17,20], normalizes serum levels of prostate specific antigen (PSA) in 80% - 90% of patients [21,22]. Consequently, most prostate cancer cells die or go into a dormant phase lasting for a few months to up to 20years [18,23]. There are objective tumor responses in 80% - 90% of patients [15,20,21,24-27]. This study compares the clinical oncological efficacy and survival of goserelin plus bicalutamide to that of bilateral orchiectomy plus

bicalutamide in patients with histologically proven, previously untreated metastatic adenocarcinoma of the prostate. Maximal androgen blockade was adopted in both arms using bicalutamide to block the effects of adrenal androgens hence comparing the clinical effects of goserelin and orchiectomy. Furthermore, adverse events from either of the modalities of treatment were documented. To the best of my knowledge, this is the first time this kind of study is being carried out in Nigeria using maximal androgen blockade in both arms, hence the reason for the study.

Materials and Methods

This prospective study was carried out in two tertiary health institutions in south-east Nigeria. Clearance was got from the ethical committees of both institutions and informed written consent of individual patients got.

Inclusion criteria

a) Histologically diagnosed and previously untreated metastatic adenocarcinoma of the prostate

b) Total serum PSA of ≥20ng/ml

c) Adequate liver and renal functions

d) Hemoglobin of ≥10gm/dl

e) Platelet count of ≥90x109/l

f) Eastern Cooperative Oncology group performance status (ECOGps)≤3 [28].

Exclusion criteria

a) Cancers at other sites

b) Significant cardiovascular disease

c) Other cancers of the prostate

Detailed history was taken from all the patients emphasizing on symptoms of metastasis like bone pains, pathological fractures, chest pain. Co-morbid pathology like diabetes mellitus, hypertension, dyslipidemia was sought. Physical examination for pallor jaundice, paraplegia, pedal oedema, scrotal/penile lymphedema was done. ECOGps of each patient was noted. Hepatomegaly and pelvic masses were sought. Digital rectal examination (DRE) was done to ascertain the nodularity and obliteration of median sulcus of the prostate. Laboratory investigations included hemoglobin, platelet count, serum electrolyte, urea and creatinine, calcium, total serum PSA, lipid profiles, fasting blood sugar. Abdomino pelvic/Transrectal ultrasonography (US), plain x-rays of the chest and spine, computerized tomographic scan (CT Scan), isotopic bone scan were utilized to detect metastasis. Either digital guided or ultrasound guided trans rectal needle biopsy of the prostate was done to confirm adenocarcinoma and determine the Gleason score. The patients were openly randomized into two modalities of treatment. There were two arms of (48 patients each), medical castration (MC) and surgical castration (SC). The MC group had subcutaneous injection of 3.6mg of goserelin in 39(84.8%) patients every four weeks or 10.8mg in 7(15.2%) patients every three months. Bicalutamide, 50mg daily was commenced a week before onset of goserelin injection. The SC group had total bilateral orchiectomy plus bicalutamide 50mg daily. Either 4mg of zolendronic acid every three weeks or 70mg alendronate tablet weekly was used to minimize bone mineral density (BMD) loss. A nadir serum PSA level of 0.2ng/ml was chosen, and treatment was continued until there was evidence of disease progression such as rising PSA, deteriorating ECOGps, bone pains, cord compression. Response to treatment was determined by assaying total serum PSA in three and six months after commencement of treatment, change in ECOGps. Adverse/toxic events following treatment in each group were documented.

Statistical Analysis

SPSS version 16.0, Chicago SPSS Inc was used to analyze the data. The student's t test, chi-square test and Kaplan-Meier survival analysis were the instruments for statistical analysis. p values ≤ 0.05 were considered statistically significant.

Results

Between January 2016 and January 2018, 96 patients were enrolled into the study comprising of two groups of 48 patients each. The median follows up was 20 months. (Range 6-30 months). There were 9 (18.6%) and 11(22.9%) deaths in the MC and SC groups respectively. Age range for MC was 45-80 years, mean of 68.0 years. Age range for SC was 53-79 years, mean of 67.8years. (p = 0.302) The sites of metastasis in the MC and SC groups included the bone (75% vs 67%), lymph nodes (21% vs 27%), liver (4% vs 2%) and scalp (2% vs 1%) respectively. (p = 0.870) The median Gleason score for MC and SC were 6 (range 4 - 10) and 7 (range 5 - 10) respectively (p = 0.49). Twenty-three (47.9%) patients in the MC group and 25 (52.1%) in the SC group had Gleason scores >7. The ECOGps of patients at presentation for MC and SC were 0 (4.2% vs 4.2%), 1 (43.8% vs 54.2%), 2 (45.8% vs 37.5%), 3 (6.2% vs 4.2%) respectively (p = 0.013). At 30 months follow up, ECOGps for MC and SC changed to 0 (54.1% vs 50.0%), 1 (27.1% vs 27.1%), 5 (18.8% vs 22.9%) respectively (p = 0.073; Table 1). Baseline total and mean serum PSA for MC group were 2595.54ng/ml and 54.10ng/ml. For the SC group, total serum and mean PSA values were 2851.5ng/ml and 59.29ng/ml (p = 0.256). Three months while on treatment, total and mean PSA for MC and SC groups were 221.26ng/ml, 4.61ng/ml and 181.95ng/ml, 3.78ng/ml respectively (p = 0.223). There were serum nadir PSA levels (≤ 0.2ng/ml) in 36 (75%) patients for MC and 39 (81.3%) patients for SC. At six months, total and mean serum PSA for MC and SC were 99.74ng/ml, 2.08±4.8ng/ml and 88.67ng/ml, 1.85±1.84ng/ml respectively. Serum PSA nadir levels (≤0.2ng/ml) was seen in 44 (92%) patients for MC and 45 (94%) patients for SC (p = 0.403; Table 2). Eleven (22.9%) patients and 14 (29.29%) patients during follow up had relapses in the MC and SC groups respectively. Mean progressive free survival (PFS) for MC was 14.0±4.55 months (95% confidence interval [CI] 9-23 months). Mean PFS for SC was 14.4±4.61 months (95% CI, 9.5-24 months). No statistical difference between the two groups (p = 0.883; Table 2, Figure 1). Survival rates for MC at 24 and 30 months were 85.4% and 83.3% respectively, mean

survival was 23.05 months (95% CI, 17.5 - 28.6 months). Survival rates for SC at 24 and 30 months were 81.3% 77.1% respectively. Mean survival was 22.75 months (95% CI, 16.5 - 29 months). No statistical difference in survival rate (p = 0.836). The median overall survival was not reached in either of the two groups during the study (Table 2, Figure 2). A total of 94 adverse events were noted in the MC arm and 79 in the SC arm in this series (p < 0.001; Table 3). Some of the adverse events observed were anemia, new onset fasting hyperglycemic episodes, (mean 152.25mg/dl, range136 - 163mg/dl) in 4(4.3%) patients, impotence, pathological fractures in 2(2.1%) patients, (left hip and third lumber vertebra) and others.

Table 1: Clinicopathological characteristics of 98 patients in the two groups.

	Medical Castration (MC) N = 48	Surgical Castration (SC) N = 48	P Value
Age (years) mean	68.0 (45-80)	67.8 (53-79)	0.302
Site of Metastasis			
Bone	36(75%)	32(67%)	
Lymph Notes	10(21%)	13(27%)	0.870
Liver	2(4%)	1(2%)	
Scalp	1(2%)	2(4%)	
Gleason Score			
4-5	7(14.6%)	9(18.8%)	
6-7	18(37.5%)	14(29.1%)	0.49
>7	23(47.9%)	25(52.1%)	
Total	48(100%)	48(100%)	
Median	6(4-10)	7(5-10)	
ECOGps			
At Presentation			
0	2(4.2%)	2(4.2%)	
1	21(43.8%)	26(54.2%)	0.013
2	22(45.8%)	18(37.5%)	
3	3(6.2%)	2(4.2%)	
At 30 months Follow Up			
0	26(54.1%)	24(50%)	
1	13(27.1%)	13(27.1%)	0.073
5	9(18.8%)	11(22.9%)	

Table 2: Response to treatment (Changes in Serum PSA, Relapses and Survival).

Base Line PSA (ng/ml)	MC N = 48	SC N = 48	P Value
Total	2595.54	2851.5	
Mean	54.10 (20.23-170)	59.2 (20.48-136.40)	0.256
At 3months of Treatment			
Total	221.26	189.5	
Mean	4.61 (0.03-24.7)	3.78 (0.07-21.4)	0.256
No with PSA ≤ 0.2ng/ml	36(75%)	39(81.3%)	
At 6months of Treatment			
Total	99.74	88.67	
Mean	2.08 (0.01-7.19)	1.85 (0.01-9.42)	0.05
No with PSA ≤ 0.2ng/ml	44(91.7%)	45(93.8%)	
Progression Free Survival (PFS)			
No. of Patients	11 (22.9%)	14(29.2%)	
Mean (Months)	14.0	14.4	0.883
Survival Rate			
Mean (Months)	23.05	22.75	0.836

Table 3: Adverse Events Following Treatment.

MC N = 48			SC N = 48		P Value
Nature of Adverse Event	Frequency	%	Frequency	%	
Anaemia	17	18.0	9	11.4	
Hot Flushes	23	24.5	21	26.6	
Tumor Flare	1	1.1	-	-	
Gynecomastia	2	2.1	1	1.3	0.001
Impotence	45	47.9	48	60.8	
New Onset Fasting Hyperglycemic Episodes	4	4.3	-	-	
Pathological Fracture	2	2.1	-	-	
Total	94	100	79	100	

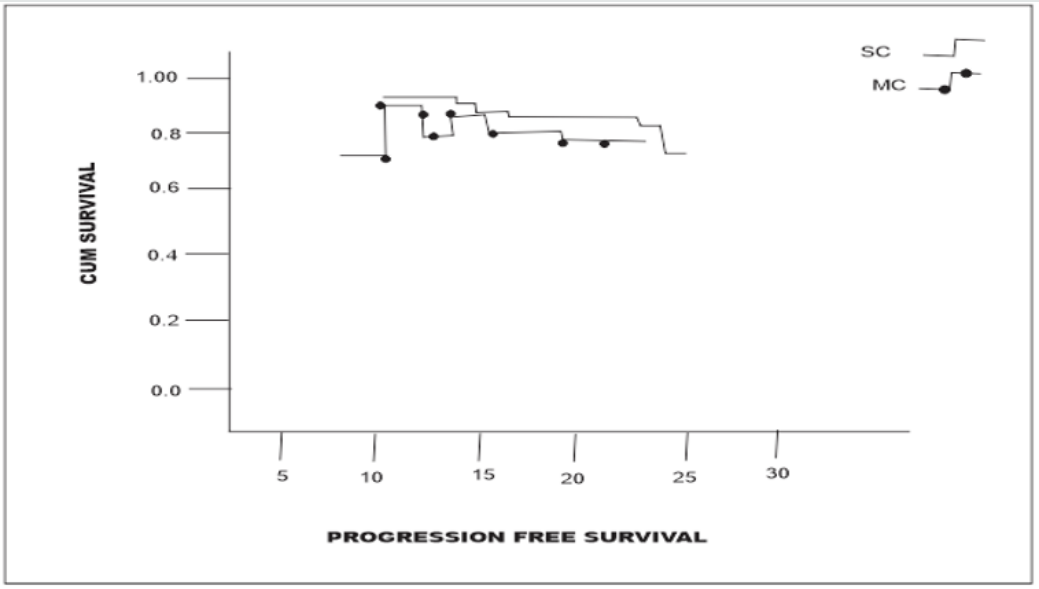

Figure 1: Kaplan-Meier curves for progression free survival in MC and SC arms of treatment.

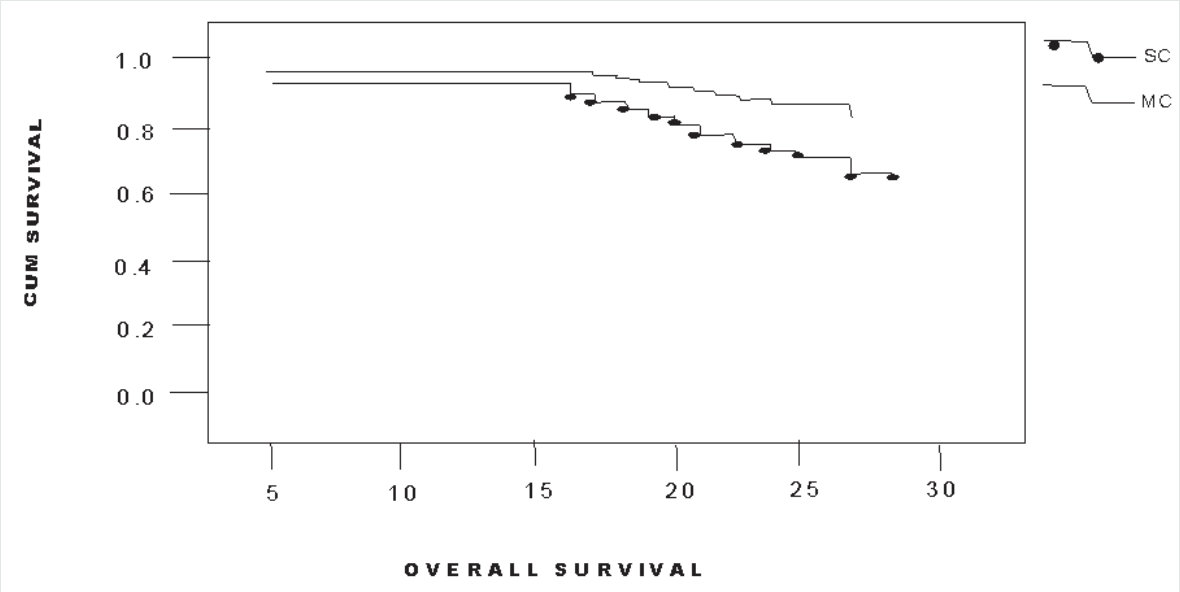

Figure 2: Kaplan-Meier curves for overall survival in MC and SC arms of treatment.

Discussion

Bicalutamide at a dose of 50mg daily was given to each patient in the two groups. About 500ug/day of testosterone secretion is of adrenal origin. Furthermore, 40% of prostatic dihydroxy testosterone is of adrenal origin [19,29]. The bicalutamide is to block the effect of adrenal testosterone. Furthermore, the tumor flare symptoms occasioned by the initial surge of testosterone from goserelin injection is averted [12,17,30,31]. Bone was the commonest metastatic site in this series. This has been noted in other studies [12,32-34]. Disseminated tumor cells (DTCs) from prostate cancer has predilection for the bone. They take advantage of the normal marrow physiology and survive far away from the primary tumor. The complex interaction between the DTCs and hematopoietic stem cells of the marrow vascular niche favors early bone colonization, proliferation and eventual metastatic mass [35,36]. There was a statistical difference in the ECOGPs of both groups pre therapy ($p = 0.013$). At 30 months follow up, the ECOGPs for both groups were similar ($p = 0.073$; Table 1). It was observed that the 20 deaths encountered during follow up had Gleason score of >7. This implies that irrespective of the modality of ADT, high Gleason score (>7) indicates poor prognosis and high mortality. This has been noted by other researchers that the Gleason score and the presence of metastasis were the strongest predictor of prostate cancer specific mortality in patients with high PSA levels at presentation [37,38]. Response to treatment in this study was by monitoring the changes to levels of serum PSA. Serum PSA is widely used for monitoring response to treatment and disease progression in metastatic prostate cancer [33,39-44]. Furthermore, it is useful in monitoring the rate of decline of PSA which may be of prognostic value [41,45,46]. The mean time to hormonal resistance in this series for MC and SC was 14.0±4.55 and 14.4±4.61 months respectively ($p = 0.883$). There was no statistical difference. Purushothaman et al. in their comparison of leuprolide to bilateral orchiectomy, the mean time to hormonal resistance were 20.78 and 19.71 months respectively ($p>0.05$) showing no significant difference between the study groups [12]. Furthermore, Aslan et al comparing bilateral sub capsular orchiectomy plus antiandrogen to LHRH agonist plus antiandrogen found mean time to hormonal resistance as 26.48 and 27.3 months respectively with no statistical difference ($p > 0.05$) [47]. In our study, the mean survival of MC and SC groups were 23.05 and 22.75 months respectively ($p = 0.836$). Purushothaman et al. got overall survival time of 45 months for medical castration and 41 months for surgical castration ($p>0.05$) [12]. Aslan et al. found average survival time for orchiectomy plus antiandrogen and LHRH agonist plus anti androgen to be 45.25 and 34.35 months respectively ($p > 0.05$) [47]. There were more adverse events noted during the study in the MC than the SC group ($p<0.001$; Table 3). Anemia was noted in both groups but more in the MC ($p<0.001$). Androgen stimulates erythropoetin release, increased bone marrow activity and increase iron uptake by red blood cells [48,49]. ADT will suppress those functions leading to anemia. Normocytic and normochromic anemia is a common side effect of patients on ADT [49,50]. Furthermore, Vargas et al noted a greater decrease in the hemoglobin levels of the group exposed to LHRH agonist [51]. A new onset fasting hyperglycaemic episode was noted in four (4.10%) patients in the MC group. Studies have confirmed the link of ADT and diabetes mellitus [50-55]. There is a decrease in number of skeletal muscles fibres during ADT therapy leading to reduction in peripheral glucose uptake by muscle tissues. Hypogonadism increases adipose tissues, a known risk factor for insulin resistance [51]. There is a greater reduction in androgen of adrenal origin in those subjected to LHRH agonist. In a study comparing the serum levels of dehydroeoiandrosterone (DHEA) in patients on ADT by means of bilateral orchiectomy versus LHRH agonist, there was a statistically significant reduction in DHEA levels in the LHRH agonist group [56]. Also found was a direct relationship between the decrease in DHEA levels and poorer insulin mediated glucose uptake in healthy men subjected to LHRH agonist [57]. There is thus, decreased insulin sensitivity in patients subjected to LHRH agonist [51]. This explains the new onset hyperglycaemic episodes in four of our patients subjected to goserelin. Two (2.1%) patients on goserelin had pathological fractures (left hip and third lumber vertebra). Patients on ADT with prostate cancer are predisposed to loss of bone mineral density (BMD) and fracture [50,58,59]. Both the cortical and trabecular bones are affected [60-63]. A direct relationship has been established between the number of doses of LHRH agonist given and the risk of fractures [50,58,62,63]. The findings of Sun et al indicate LHRH agonist was associated with significant higher rate of fractures and other complications compared to surgical castration [64]. There are reports of psychological stress in patients following loss of testicles from surgical castration for advanced prostate cancer [24,62,64]. No case of psychological stress was encountered in the patients in the SC arm in this series. Ibrahim et al in their series found no psychological stress following orchiectomy in any of their patients [65]. A major challenge in this study was recruiting patients for the MC arm due to high cost of goserelin. This is in contrast to what obtains in the developed world where more patients opt for LHRH agonists [41,64,66,67].

Conclusion

This study shows that there is no statistical difference in the oncological clinical efficacy of medical and surgical castrations. However, there is significant statistical difference in the adverse events noted in the MC and SC groups worse in MC. There were higher incidences of anemia, new onset diabetes mellitus, and bone fractures. These risks should be explained to the patients before treatment. A multi-disciplinary approach involving urologist and other specialist clinicians is advocated for patients on ADT. The goal here is to prevent and ameliorate the discomfort from these adverse events thus availing the patients a better quality of life.

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