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Research Paper

Review Of The Adverse Effects Of Androgen Deprivation Therapy In Men Treated For Advanced Prostate Cancer: A Single Centre Retrospective Study In Aba, South - Eastern Nigeria.

IBE U. IBE
CONSULTANT UROLOGIST,
DEPARTMENT OF SURGERY,
ABIA STATE UNIVERSITY TEACHING HOSPITAL ABA.
NIGERIA.

JOHN AUSTIN CHIKEZIE
COUSULTANT NEPHROLOGIST,
DEPARTMENT OF INTERNAL MEDICINE
ABIA STATE UNIVERSITY TEACHING HOSPTIAL ABA.
NIGERIA.

OBINNA CHIKEZIE
MEDICAL OFFICER
DEPARTMENT OF MEDICAL SERVICES
ABIA STATE MINISTRY OF HEALTH
UMUAHIA
ABIA STATE
NIGERIA.

ABSTRACT
Prostate cancer is most common non-skin cancer and the second most common cause of cancer death in U.S. men. In Nigeria, it is the most common cancer among men.
Androgen Deprivation Therapy specifically surgical and medical castration, constitutes the first line treatment for advanced disease especially in the metastatic setting.
It is also used as an adjuvant to local treatment of high risk disease.
The aim of this study was to retrospectively review the adverse effects in men managed by Androgen Deprivation Therapy over an 8 year period from January, 2015 to December, 2023.
In our study, we found out those patients experienced different adverse effects. Loss of libido was the most common seen in 138 of the 155 patients (89.03%) closely followed by erectile dysfunction – ED 130 cases (83.87%). Hot flushes were seen in 125 cases (80.64%).
The Flare phenomenon was seen in only 1 case (0.64%) who was referred from a different center. Our patients had adequate pre-treatments with anti-Androgens for 14 - 21 days before institution of medical castrations.
Sexually related adverse effects were the most common adverse effects seen in Aba. Cognitive decline and Depression were seen in men over 70 years of age who had Androgen Deprivation Therapy.

KEY WORDS
Advanced prostate cancer, Androgen Deprivation Therapy, adverse effects and Aba.

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I. INTRODUCTION

Androgen Deprivation Therapy (ADT) is effective for palliation in many patients with advanced prostate cancer. It also improves outcome for high risk patients treated with radiation therapy for localized disease. Patients with rising PSA levels after local treatment and in the absence of metastasis undergo ADT.

ADT is described as surgical castration when it involves testicular ablation and medical castration when it involves hypothalamic – pituitary – leydig axis suppression by drugs. It is the mainstay and first line of treatment of advanced prostate cancer.

In 1941, Huggins and Hodges first noted the beneficial effects of castration and injection of oestrogens in patients with prostate cancer.

Later, the basis of this treatment became clear with:

- Knowledge of the expression of androgen receptors in prostate cancer.
- The growth dependence on the androgen receptors.

Today ADT is used mainly in treating:

- Metastatic prostate cancer
- Treatment in cases of rising PSA after local treatment
- Used on adjuvant basis for men undergoing radiation treatment for high risk localized disease.
- Used on neo-adjuvant and adjuvant basis for men undergoing radiation therapy for locally advanced disease.

Most of the androgens, about 95% are generated through the hypothalamic- pituitary-leydig cell axis or pathway.

Only about 5 – 10% is generated by the adrenal glands.

The hypothalamus releases luteinizing hormone releasing hormone (LHRH) which interacts with the anterior pituitary receptors to release luteinizing hormone (LH).

LH is able to bind the leydig cells of the testes to promote testosterone production.

Once produced, testosterone diffuses into the blood to effector organs one of which is the prostate.

It enters prostate cells where it is converted into a more active form dihydrotestosterone (DHT) through the enzymatic action of 5 alpha reductase.

DHT in the cytosol binds to androgen receptor (AR) and this complex translocates into the nucleus.

In the nucleus, AR acts as a transcription factor binding to specific DNA which leads to expression of a variety of genes.

AR signaling is absolutely critical for normal prostate function and prostate cancer cells also require it for survival.

Almost all prostate cancers begin in an androgen dependent state where AR signaling is predominant for cancerous cell growth and proliferation.

When exposed to ADT, both normal and cancerous cells undergo apoptosis due to impaired AR signaling. However, overtime some cancer cells are able to manifest molecular and cellular transformational changes.

These mechanisms or changes enhance AR signaling during androgen deprivation and they include:

- AR gene amplification
- AR gene mutation
- Changes in AR – Co regulatory proteins
- Changes in expression of steroid-generating enzymes
- AR independent pathway.

All these lead to the development of tumors that are androgen independent.

II. METHODOLOGY

This was a retrospective study of men treated with androgen deprivation therapy who had histopathologically confirmed prostate cancer over an 8 year period from January 2015 to December 2023. These men were followed up within these years. Their case files were withdrawn and important information obtained including age, date of commencement of ADT, modality of ADT, adverse reactions following exposure and treatment offered.

INCLUSION CRITERIA

All men with histopathologically confirmed prostate cancer who had either surgical castration by Bilateral Total Orchidectomy or medical castration by LHRH analogues and anti-androgens (Androgen Receptor Blockers).

EXCLUSION CRITERIA

All men with histopathologically confirmed prostate cancer who were not managed with ADT were excluded from this study.

III. RESULTS

Patients were aged between 40 to 100 years, median age was 65 and mean age was 69.5 years (variance =6.9) + or_ 3SD.

The adverse effects of those treated with androgen deprivation was observed and recorded.

Among the adverse effects noted, patients suffered more than one adverse effect at a time.

The most common adverse effect was loss of libido with 138 cases (89.03%) while erectile dysfunction – ED had 130 cases (83.87%). Hot flushes followed with 125 cases (80.64%). Gynaecomastia occurred with psychological disturbance as men were distressed for looking like women with enlarged tender breasts. It occurred in 72 men (46.75%).

Cognitive decline and depression were seen only in elderly of over 70 years exposed to ADT. Cognitive decline occurred in 12 men (7.7%) and depression in 1 man (0.64%).

Cardiovascular adverse effects were seen in men with prior cardiac problems and their clinical condition got worse after exposure to ADT.

In this study, no case of genital (penis) shrinkage was seen.

TABLE 1 – AGE GROUP/RANGE CHARACTERISTICS OF ALL HISTOPATHOLOGICALLY CONFIRMED PROSTATE CANCERS (ADENOCARCINOMA)

S/N	AGE GROUP	NUMBER	PERCENTAGE
1.	40 – 50 years	3	1.5%
2.	51 – 60 years	16	7.9%
3.	61 – 70 years	74	36.7%
4.	71 – 80 years	78	38.6%
5.	81 – 90 years	28	13.9%
6.	91 – 100 years	3	1.5%
	TOTAL	202	100%

TABLE 2 – AGE GROUP/RANGE CHARACTERISTICS OF ALL HISTOPATHOLOGICALLY CONFIRMED PROSTATE CANCERS (ADENOCARCINOMA) MANAGED BY ADT

S/N	AGE GROUP	NUMBER	PERCENTAGE
7.	40 – 50 years	2	1.29%
8.	51 – 60 years	15	9.67%
9.	61 – 70 years	51	32.90%
10.	71 – 80 years	60	38.70%
11.	81 – 90 years	24	15.48%
12.	91 – 100 years	3	1.94%
	TOTAL	**155**	**100%**

TABLE 3 – SHOWING THE USE OF ADT IN DIFFERENT STAGES OF THE PROSTATE CANCER

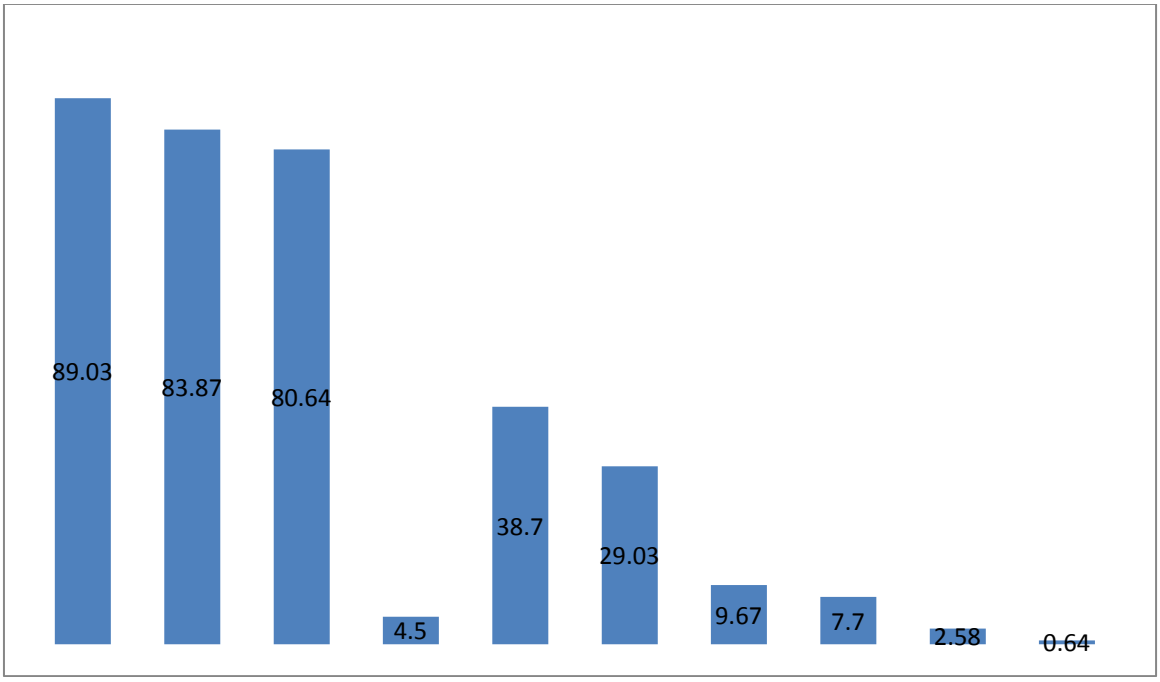
S/N	CLINICAL STAGE	TOTAL	B.T.O	LHRH ANALOGUES	ANDROGEN RECEPTOR BLOCKERS
1.	METASTATIC STAGE	120	80 66.6%	30 25%	10 8.37%
2.	LOCALLY ADVANCED STAGE	30	20 66.6%	10 33.3%	-
3.	ORGAN CONFINED STAGE	5	-	5	-
	TOTAL	**155**	**100**	**45**	**10**

TABLE 4 – SHOWING THE ADVERSE EFFECTS OF ADT

S/N	ADVERSE EFFECT	NUMBER	PERCENTAGE
1.	Loss of libido	138	89.03%
2.	Erectile dysfunction	130	83.87%
3.	Hot flushes	125	80.64%
4.	Gynaecomastia	72	46.45%

5.	Loss in muscle mass	60	38.70%
6.	Cardiovascular	45	29.03%
7.	Haematologic (Chronic Anaemia)	15	9.67%
8.	Cognitive decline	12	7.7%
9.	Depression	4	2.58%
10.	Flare Phenomenon	1	0.64%

FIG. 1



IV. DISUSSION

Androgen deprivation therapy is the first line of management in advanced prostate cancer when the pathologic sub-type is adenocarcinoma.

It is very useful but some troublesome reactions which may be long-lasting in surgical castration but may abate when medical castration is discontinued. The adverse effects of androgen deprivation therapy may be subdivided into:

- Immediate
- Acute
- Chronic

The immediate effect is the Flare phenomenon due to an excessive release of testosterone following medical castration particularly a luteinizing hormone releasing hormone analogues when there is minimal or no pre-medication with androgen receptor blockers. This Flare is absent in surgical castration.

In our study, we had one case Flare phenomenon (0.64%) who was managed elsewhere but referred to us when symptoms got exacerbated. To avoid the Fare Phenomenon, patient is pre-treated with androgen receptor blockers for 14 to 21 days before commencement of LHRH analogues.

The acute adverse effects become manifest within a few weeks of commencement of ADT and they include:

- Loss of libido
- Erectile dysfunction (ED)
- Hot flushes

Loss of libido or sexual desire is difficult to manage. ED can be managed with phosphodiesterase inhibitors and intracavenosal suppositories and injections and both symptoms came to abate after withdrawal of medical castration.

Hot flushes are caused by inappropriate stimulation of the thermo-regulatory centers in the hypothalamus resulting in peripheral vasodilatation. Hot flushes lasts from a few seconds to up to 20 minutes with recurrences. Flushing of the skin, perspiration and chills in the upper part of the body are characteristic.

The withdrawal of or low level of testosterone disrupts the equilibrium of neuro-transmitters – Norepinephrine, serotonin and hormones including testosterone.
This disequilibrium dysregulates the homeostatic mechanism of the thermo-regulatory centers in the pre-optic zone of the hypothalamus.
The chronic adverse effects include:

- Musculo-skeletal effects.
- Haematological effects
- Cardiovascular effects
- Cognitive decline
- Depression
- Gynaecomastia

Gynaecomastia characterized by enlarged and tender breasts in males usually elicits psychological trauma to the patients. It is due to oestrogenic dominance over androgen and may be managed by androgen receptor blockers such as Tamoxifen.
Haematologic effect is characterized by chronic anaemia.
Anaemia in a prostate cancer patient may be due to:

- Loss of appetite and malnutrition
- Blood loss from intermittent haematuria
- Bone marrow suppression by metastatic deposits.
- Androgen deprivation therapy

Testosterone normally increases the production of erythrogenesis stimulating proteins and therefore ATD by reducing testosterone to castrate level may indirectly inhibit erythrogenesis causing anaemia.
Musculo-skeletal effects include:

- Loss in muscle mass due to low level testosterone which is an anabolic hormone.
- Osteoporosis due to decrease in bone density

Skeletal related effects arising from prostate cancer metastasis and/or ADT are managed using:

- Biophosphonates .
- Lifestyle modifications such as cessation of smoking, reduction of alcohol intake and the use of calcium supplements.

Cardiovascular morbidity and mortality may rise due to ablation of testosterone, a key nutrient of the heart,
In our study, we had these cases in patients who had cardiac problems prior to ADT. And in our practice, we chose medical castration over surgical castration as ADT is tailed off after palliative radiation therapy.
Cognitive decline and depression were seen in the elderly patients above 70 years. Testosterone is a key nutrient to the brain and the adverse neurological effect is due to low level of testosterone.

V. CONCLUSION

Sex related adverse effects of ADT were the most common in Aba followed by hot flushes.
Cardiovascular morbidity and mortality were found in men with prior cardiac problems.
Cognitive decline and depression were found in elderly patients exposed to ADT. Comprehensive Cardiac evaluation is necessary before choosing the modality of ADT.

REFERENCES

1. Stone P, Hardy J. Huddart R. etal
Fatigue in patients with prostate cancer receiving hormone therapy.
Eur J. Cancer 2000:36
1134 – 1141.

2. Higano C.
Management of bone lessions in men with prostate cancer.
J. Urol 2003: 170
559-564

3. Nima Sharif, James L. Gulley and William L. Dahurt.
Androgen Deprivation Therapy for prostate cancer.
Jama 2005: 294(2) 238 – 244.

4. Mark A. Perimutter and Herbert Lepor

Androgen Deprivation Therapy in treatment of advanced prostate cancer
Rev. Urol 2007, 9 (suppli)
S3 – S8

5. Chih-Pin Chuu, John M. Kolcontis, Liang Cheng Su
Androgen as therapy for Androgen Receptor Positive castration resistant prostate cancer.
Journal of Biomedical Sciences 18 Article No 63 (2011).

6. Petros Sountoulides and Thomas Rountos
Adverse effects of Androgen Deprivation Therapy for prostate cancer prevention and management.
International scholarly research notices. Review Article Vol. 2013.
Article ID 240108.

7. Lepor H.
Optimizing the role of hormonal therapy in the management of prostate cancer.
Rev. Urol 2005: 7 S1 – S2.

8. Kumar R. J., Barqawi A. and Crawford E.D.
Adverse events associated with hormonal therapy for prostate cancer.
Rev. Urol 2005 7 S37 – S43.

9. Perylak DP, Tangen CM , Hussain MH etal.
Doxitaxel and extramustine compared with mitoxantrone and prednisolone in advanced refractory prostate cancer.
N. Engl J Med 2004: 351; 1513 – 1520.

10. Yoanna S. Pumpalora, Adarsh Ramakrishnam, Shauli Minkowitz Sean Doherty, Elvira Singh, Audrey Pentz, Wenccng Carl Chen Alfred, Neugut, Timothy Rebbeck and Maureen Joffe.
Predictions of overall survival among black South African men treated with Androgen Deprivation Therapy for metastatic prostate cancer.
Journal of clinical oncology. Vol. 40 16 2022.

11. Pollack etal
Androgen Ablation in addition to Radiation therapy for prostate cancer: Is there true benefit?
Semin Radiat Oncol 1998 April.

12. Carrie etal
Salvage Radiotherapy with or without short term hormone therapy for rising prostate specific antigen concentration after radical prostatectomy.
Lancet Oncol 2016.

13. Zagars GK etal
Conventional external beam radiation therapy alone or with androgen ablation for clinical stage III (T3 NX/NO, MO) Adenocarcinoma of the prostate.
Int. J. Radiat Oncol Bio Phys 1999.

14. Tiguert R. etal
Neoadjuvant hormone therapy before salvage radiotherapy for an increasing post radical prostatectomy serum prostate specific antigen level.
J. Urol 2003 PMID 12853796.

15. Ghadjar P. etal
Use of androgen deprivation and salvage radiation therapy for patients with prostate cancer and biochemical recurrences after prostatectomy
Strahlenther Oncol 2018 PMID 29383406.

16. Sylvester J. etal
The role of androgen ablation in patients with biochemical or local failure after definitive radiation therapy.
A survey of practice patterns of urologists and radiation oncologists in the United States.

Urology 2001 PMID 11502452.

17. Abayomi K. Arogundade, Ademola A. Popoola, Abdulwahab A. Ajape, Olajide O. Abiola and Sikiru A. Biliaminu.
Surgical androgen deprivation therapy in advance prostate cancer in patients of African descent: comparison of biochemical efficacy of bilateral total and sub-capsular orchiectomy.
African Open Access Vol. 23 No 1(2023).

18. Iya Eze Bassey etal
Impact of androgen deprivation on oxidative stress and anti-oxidant status in Nigerian patients with prostate cancer undergoing androgen deprivation therapy.
JCO Globe Oncol 2020 Oct.

19. Donovan K. A. etal
Effects of androgen deprivation therapy on sexual function and bother in men with prostate cancer. A controlled comparison.
Psychooncology 2018 PMID 28557112.

20. Okon Ekwere Essien, Iya Eze Bassey, Rebecca Ntaku Gali, Alphonsus Ekpe Udoh, Uwem Okon Akpan and Enakirehi E. Glen.
Cardiovascular disease risk factors: how relevant African men with prostate cancer receiving androgen deprivation therapy.
Journal of global oncology Vol. 3 Nov. 1, 2015.

21. April P. Carson, Daniel L. Howard, William R. Carpenter, Yhenneko J. Taylor, Sharon Peacock, Anna P. Schenek.
Trends and racial differences in the use of androgen deprivation therapy for metastatic prostate cancer.
Journal of pain and symptom management
Volume 39 issue 5, May 2010.
Pages 872 – 881.