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Surgical Or Medical Castration: The Challenge In The Management Of Heart Failure Patients Undergoing Androgen Deprivation Therapy For Histopathologically Confirmed Prostate Cancer. A Single Centre Retrospective Study In Aba South Eastern Nigeria

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ABSTRACT
Prostate cancer is the most common male cancer in Nigeria with increasing morbidity and mortality. Over 98% of the cases are adenocarcinoma which is amenable to hormonal manipulation.
Androgen deprivation therapy (ADT) is useful in various stages of management.
This was a retrospective study spanning 8 years from January, 2015 to December, 2022 to evaluate the cardiovascular adverse effects found in men with both compensated and decompensated heart failure subjected to ADT.
Out of the 155 men who had ADT within the period, 45 (29.03%) developed cardiovascular adverse effects on treatment with ADT. These men were those who had heart failure prior to introduction of ADT.
38 of them (84.5%) had compensated heart failure prior to treatment and took 5 to 10 months to develop overt signs and symptoms of heart failure.
Only 7 (15.55%) had decompensated heart failure and took only 1 to 2 months to develop worse symptoms and signs.
The management of adenocarcinoma of the prostate with associated heart failure is a challenge.
Measures must be put in place for favourable outcome.
KEY WORDS: Prostate cancer, cardiovascular adverse effects, heart failure, androgen deprivation therapy and Aba.

I. INTRODUCTION

Androgen deprivation therapy is the mainstay of first line management of prostate cancer especially in the advanced setting.

Despite its usefulness in this regard, it is associated with cardiovascular adverse effects.

Testosterone is a sex hormone predominant in males but also occurs in lower concentration in females.

It has effects on the blood vessels of the cardiovascular systems and on the heart as well. It also has effects on the risk factors of cardiovascular disease.

Testosterone is an anabolic steroid hormone and is a major circulating androgen in males.

Androgen deficiency has shown to be a major risk factor in the development of several disorders such as:

- Obesity
- Metabolic syndrome
- Ischemic heart disease

Testosterone exerts cardio-protective effects such as:

- Anti-arrhythmic effects
- Reduced infarct size
- Enhanced vasodilatation
- Reduced Atherosclerosis
- Improved metabolic parameters

Men with coronary artery disease and congestive heart failure have been shown to have lower levels of testosterone compared to healthy men.

At high levels, testosterone is deleterious to the cardiovascular system by:

- Increasing cardiovascular diseases
- Causing myocardial infarction
- Stroke
- High blood pressure
- Blood clots
- Heart failure

Testosterone secretion is a function of the hypothalamic – pituitary-Leydic cell axis with elaboration of luteinizing hormone (LH) which stimulates the leydic cells to secrete testosterone.

Secreted testosterone circulates in the blood as:

- Free form

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- Bound rigidly to sex hormone binding globulin (SHBG) 60%.
- Bound loosely to albumin 40%

Both free testosterone and testosterone loosely bound to albumin can be described as free circulating bioavailable testosterone.

Bioavalable testosterone exerts its effects directly on the androgen receptors or may be metabolized to other forms such as:

- Dihydro testosterone through the enzymatic action of 5 alpha reductase.
- Estradiol (E2) through the enzymatic action of aromatase.

Oestrogen influences the lipoprotein profiles lowering LDL and increasing HDL.

Oestrogen has a definitive protective effect on the cardiovascular system.

In the cardiovascular system, oxidative stress is considered important in the pathogenesis of:

- Atherosclerosis
- Myocardial dysfunction
- Cardiac hypertrophy
- Heart failure
- Myocardial ischemia

Oestrogen plays a regulatory role in the cardiovascular system through its action on the oestrogen receptors.

Testosterone therefore exerts its effects either through its action on the androgen receptors or through its conversion to oestrogen which acts on the oestrogen receptors.

II. METHODOLOGY

This was a retrospective study spanning 8 years from January 2015 to December 2022. The case files of patients who were histopathologically confirmed cases of adenocarcinoma of the prostate and were managed by androgen deprivation therapy were retrieved and essential information obtained including age, investigations done, treatment modality instituted and adverse reactions observed throughout the duration of treatment and the management given.

INCLUSION CRITERIA

All men with histopathologically confirmed adenocarcinoma of the prostate within the study period who had androgen deprivation therapy as a modality of treatment and developed cardiovascular adverse effects.

EXCLUSION CRITERIA

All men with adenocarcinoma of the prostate who had ADT with adverse effects aside from cardiovascular effects were excluded.

III. RESULTS

Within a period of 8 years from January 2015 to December, 2022, 202 had histopathologically confirmed adenocarcinoma of the prostate.

Out of this, 155 men (76.7%) had ADT at one stage in their management.

Out of the 155 men, 45 (29.03%) developed cardiovascular adverse effects on treatments.

Out of the 45 patients, 38 (84.5%) had compensated heart failure with no obvious clinical signs and symptoms but with only Electrocardiographic (ECG) changes.

These developed obvious clinical signs and symptoms within 5 to 10 months after exposure to ADT.

Only 7 patients (15.55%) had decompensated heart failure with obvious signs and symptoms prior to introduction of ADT. Their clinical state got worse only after 1 to 2 months on ADT.

TABLE 1 – SHOWING AGE GROUP/CHARACTERISTICS OF 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%**

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

S/N	AGE GROUP	NUMBER	PERCENTAGE
1.	40 – 50 years	2	1.29%
2.	51 – 60 years	15	9.67%
3.	61 – 70 years	51	32.90%
4.	71 – 80 years	60	38.70%
5.	81 – 90 years	24	15.48%
6.	91 – 100 years	3	1.94%
	TOTAL	**155**	**100%**

TABLE 3 – SHOWING AGE GROUP/CHARACTERISTICS OF CASES THAT HAD CARDIOVASCULAR ADVERSE EFFECTS UNDER ADT

S/N	AGE GROUP	NUMBER	PERCENTAGE
1.	40 – 50 years	NIL	NIL
2.	51 – 60 years	NIL	NIL
3.	61 – 70 years	10	22.2%
4.	71 – 80 years	33	73.3%
5.	81 – 90 years	2	4.44%
6.	91 – 100 years	NIL	NIL
	TOTAL	**45**	**100%**

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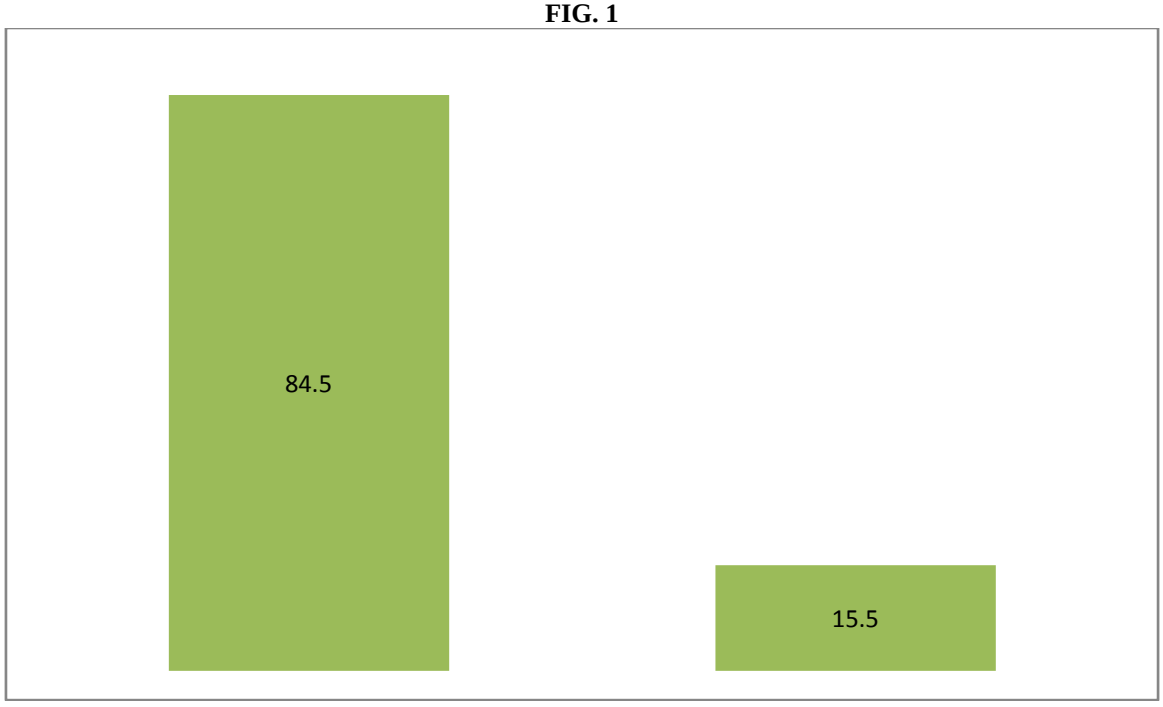
TABLE 4 – SHOWING STATE OF THE HEART AND TIME LAG BEFORE COMMENCEMENT AND EXACERBATION OF SYMPTOMS

S/N	STATE OF THE HEART AND CARDIOVASCULAR SYSTEM	FEATURES	TIME LAG BEFORE COMMENCEMENT & EXACERBATION OF SYMPTOMS	NUMBER	PERCENTAGE
1.	Compensated heart failure	Only ECG changes – LT ventricular and LT Atrial enlargement	5 – 10 months	38	84.5%
2.	Decompensated heart failure	Leg swellings, shortness of breath, cough, hypertension	1 -2 months	7	15.5%
	TOTAL			45	100%

FIG. 1



IV. DISCUSSION

Prostate cancer is the most common male cancer in Nigeria with increasing morbidity and mortality. Most of the cases present at an advanced stage. Androgen deprivation therapy is the first line of treatment for advanced disease.

ADT is achieved surgically through bilateral total orchidectomy known as surgical castration or medically through medical castration.

Medical castration can be achieved through:

- LHRH agonists
- LHRH antagonists

- Androgen receptor blockers described as anti-androgens

As useful and important as ADT is, it is associated with adverse cardiovascular effects.
In our study, we found out that these effects were:

- Worse when patients already had latent cardiac challenges prior to ADT.
- Worse when patients were in the advanced Age group.
- Surgical castration because of its permanent nature had worse prognosis.
- That early institution of palliative radiotherapy and continuing with anti-androgen monotherapy gave better outcomes.

O' Farrel etal, in their work on risk and timing of cardiovascular disease after androgen ablation therapy in men with prostate cancer in 2015 reported interesting findings using data on filled drug prescriptions in the Swedish National Registers.
They investigated the risk of cardiovascular disease in a cohort of 41,362 men with prostate cancer who received ADT either as primary treatment or as a result of primary progression.
10,656 received monotherapy with anti-androgens while 26,959 received LHRH Agonists and 3,747 had bilateral total orchidectomy. They observed that the risk of cardiovascular disease was increased by 21% for LHRH Agonists and 16% for orchidectomy.
Men receiving monotherapy with anti-androgens had a decreased risk of cardiovascular disease.
Irrespective of the modality of ADT, men with a previous history of 2 or more cardiovascular events particularly if the last one occurred within a year were at a high risk of cardiovascular disease within the first 6 months of ADT.
This was totally in agreement with other findings. Men with prior cardiovascular events were at greater risk after ADT.
Even without prior cardiovascular events, men undergoing orchidectomy or LHRH Agonists were at an increased risk of cardiovascular disease compared to anti-androgen monotherapy.

Three important findings emerged from this O'Farrel's study:

1. Men with a significant cardiovascular disease history especially if they experience a recent event were at a higher risk of cardiovascular disease within months of starting ADT suggesting that these are more susceptible to the development of cardiovascular complications. These are in agreement to previous data reporting development of incident cardiovascular disease within 1 to 4 months of starting ADT.
2. Both bilateral total orchidectomy and LHRH Agonists were associated with an increased risk of cardiovascular disease. This implicates directly androgen deficiency] as the cause of the cardiovascular disease.
3. Men undergoing monotherapy with anti-androgens were at 13% lower risk for incident cardiovascular disease than comparison population, suggesting that endogenous Estradiol levels might have protective effects.

Surgical castration and LHRH Agonists reduce testosterone and Estradiol. LHRH Antagonists have relatively less cardiovascular adverse effects compared to LHRH Agonists.

Anti-androgens increase both testosterone and Estradiol and therefore the cardiovascular disease risk in patients undergoing anti-androgen monotherapy may be reduced.

The high level of receptor displaced testosterone is converted to estradiol by aromatization.

The beneficial effects of oestrogen (estradiol) to the heart is made manifest.

Because of oestrogen, pre-menopausal women have a lower incidence of hypertension, atherosclerosis, myocardial infarction, ventricular hypertrophy, heart failure and myocardial ischemia than age-matched men.
This advantage may disappear after onset of menopause.

V. CONCLUSION

Surgical castration, because of its permanent ablation of androgen is not a favourable modality of ADT in men with underlying cardiovascular events.

Cardiovascular toxicity is more pronounced in men with prior cardiovascular events subjected to ADT and also in men with advanced age.

Early institution of LHRH Agonists and Antagonists and withdrawal after palliative radiation therapy and continuing with anti-androgens may be recommended in severe cases.
A fairly good evaluation of patients including ECG should be instituted in men before commencement of ADT.

REFERENCES

[1]. Carolyn M. Webb and Peter Collins. The role of testosterone in the treatment of cardiovascular disease.
[2]. Eur. Cardiol 2017 Dec 12 (2) 83-87.

[3]. Wanpitak Pongkan, Siriporn C. Chattipakorn, Nipon Chatti Pakorn Roles of testosterone replacement in cardiac ischemia reperfusion injury Journal of cardiovascular pharmacology and therapeutics Jan. 2016
[4]. Reyman Mesbah, Oskul, William J. Frech, Michael J. Herring, Guy S. Meyeda, Steven Burste.Testosterone and the cardiovascular system. A comprehensive review of the clinical literature. Journal of the American Heart Association 2013:2 cooo2
[5]. Sean O'Farrel etal Risk and timing of cardiovascular disease after androgen deprivation therapy in men with prostate cancer J clin oncology 2015
[6]. Hargun Kaur, Geoff H. Werstuck The effect of testosterone on cardiovascular disease and cardiovascular risk factors in men. A review of clinical and preclinical data. CJC Open volume 3 issue 10 October 2021 pages 1238 – 1248.
[7]. Payner etal Androgen deficiency in the aging male. A guide to diagnosis and testosterone replacement therapy Can J. Urol 2007 PMID 1816948 Review
[8]. Narvarrol Penalvel M. etal Testosterone replacement therapy in difficult patients with chronic heart failure. A randomized double blind controlled pilot study. J. Cardiovasc Pharmacol Ther. 2018 PMID 29929385
[9]. Diaconu, Rodica, Donoiu, Iong, Mirea, Oana, Balseanu Tudor Adrian. Testosterone cardiomyopathics and heart failure. A narrative review, Asian Journal of Andrology 23 (4) P 348 – 358 July August, 2021.
[10]. Shehzad Basarca Cardiovascular diseases associated with androgen deprivation therapy. Time to give it due respect. Journal of clinical oncology vol 33 No 11 2014.
[11]. A.A. Knowlton and A.R Lee Estrogen and the cardiovascular system Pharmacol Ther 2012 July 135(1) 54-70
[12]. Du Xiang, Yang Liu, Shujun Zhou, Encheng Zhou and Yanfeng Wang Protective effect of Estrogen on cardiovascular diseases mediated oxidative stress Hindawi review article Vol. 2021, Article ID 5523516
[13]. Julia Boland ,William Choi, Maximilliam Lee and Jianling Lin Cardiovascular Toxicity of Androgen Deprivation therapy.Curr cardio Rep 2021 23(8), 109 July
[14]. James Fradin, Felix J. Kim, Grace L Lu-Yao, Eugene Storozynsky, William K. KellyReview of the cardiovascular Risk of Androgen Deprivation Therapy and the influence of race in men with prostate cancer.Cancers (Besel) April – 2023 15(8) 2316
[15]. Shabbir MH Alibahai, Minh Duong –Hua, Rinku, Sutradhal, Neil E Fleshner, Parpraig Warde, Angela M. Cheung and Lawrence F. Paszat Impact of Androgen deprivation therapy on cardiovascular diseases and diabetes.Journal and clinical oncology Vol. 27 Nov. 21 2009.
[16]. Michae J. Herring, Peyman Meshbah Oskui, Sharon L. Hale and Robbert A. Kloner Testosterone and the cardiovascular system; A comprehensive review of the basic sciences literature Journal of the American Heart Association (JAHA) 10 July 2013
[17]. Michael G. Kirby, Geoffrey Hackett, Sudarshan Rama Chandran Testosterone and the Heart European Cardiology Review 2019; 14(2) 103-10
[18]. Youquan Li, Whee Szeong, Jeffrey Kit, Loong Tuan, Cardiovascular Toxicities of Androgen Deprivation Therapy in Asian men with localized prostate cancer after curative radiotherapy; based observational study.Cardio-oncology 8 Article Number 4 (2022)
[19]. Jiun- Ruey Hu, Meredith S. Duncan Alicia A. Morgans, Jonathan D. Brown, Wouter C. Meijers, Mathew S. Freiberg, Joe Elie Salem, Joshua A Beckman, Javid J. Mosleh.Cardiovascular effect of Androgen deprivation therapy in prostate cancer.Contemporary Meta Analysis ATV Baha 119: 313046 2020: 40:e55-e64.
[20]. Azariyas A. Challa, Adam Christopher Calaway, Avirup Gusta Cardiovascular Toxicities of Androgen Deprivation Therapy Cardio – Oncology April 2021, volume 22 Article Number 47
[21]. Jeffrey Shikai Chan, Danish Litaf Satti, Temporal trends in cardiovascular burden among patients with prostate cancer receiving androgen deprivation therapy. A population based cohort study.British Journal of cancer 128, 2253- 2260 2023