**Title:** Pattern of presentation and management castration resistant prostate cancer in tertiary Hospital of Northwestern Nigeria: 7-year Review

Running title: Castrate Resistant Prostate Cancer in a Nigerian Hospital

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**Pattern of presentation and management castration resistant prostate cancer in tertiary Hospital of Northwestern Nigeria: 7-year Review**

**Background:**

Prostate cancer is the second commonest malignancy and commonest cause of mortality worldwide(1). Prostate cancer is the commonest cancer in men in Africa (2). The mortality is due to progression to castration resistance and metastasis.

The objective of is study was to review pattern and management of castration resistant prostate cancer (CRPC) in our hospital.

**Methods**

This is a retrospective study of patients managed for castration resistant prostate cancer in our hospital from January 2013 to December, 2019. Data was collected from the case notes via a proforma and was analyzed using SPSS version 25.0. Results were reported percentages, mean ±SD

**Results:**

There were 20 patients with CRPC within the study period with Mean age of 66.2 ± 7.4 and a range of 53-78 years. Bilateral total orchidectomy was done in 16 patients (80%) while subcutaneous Zoladex 10.8 mg, 3-monthly depot was given to 4 patients as a form of androgen deprivation therapy (ADT). The mean PSA value at the commencement of ADT was 44.06 ± 37.3 ng/ml. The PSA nadir and PSA doubling time (PSADT) were 20.63 ± 25.85 ng/ml and 8.71 ± 10.75 months. The mean duration to development of CRPC and follow up were 16.9 ± 13.3 months and 7.93 ± 8.5 months respectively. Metastatic CRPC was diagnosed in 16 patients (80%) and Non-metastatic CRPC in 4 patients (20%). Maximal androgen blockade (MAB) and medical adrenalectomy were used for all the patients. Four (4) patients (20%) with progressive disease required use of abiraterone as second line agent and 1 patient on medical castration had BTO with good response. Analgesia, alendronate, and radiotherapy were given to 18 patients, 15 patients and 1 patient respectively. There was clinical biochemical improvement in 15 patients (75%) and mortality in 5 patients (25%).

**Conclusion:** Castration resistant prostate cancer present predominantly as metastatic disease in our environment. There was good response initially to maximal androgen blockade and medical adrenalectomy. Abiraterone is very effective in subsequent resistance but it’s use is limited by the cost. Surgical castration may be effective in patients that progress on medical castration. There was high PSA nadir, short PSADT, short duration for development of CRPC and erratic follow up.

**Keywords:** castration resistant prostate cancer, PSA nadir, PSADT, ADT, castration, ketoconazole, bicalutamide, abiraterone

**Introduction:**

Prostate cancer is the second commonest malignancy and commonest cause of mortality worldwide(1). Prostate cancer is the commonest cancer in men in Africa (2). The mortality is due to progression to castration resistance and metastasis.

Castration resistant prostate cancer (CRPC) is defined as evidence of biochemical, clinical or radiological progression of disease despite androgen deprivation therapy with castrate level of testosterone(2).

The mechanism and timing of castration resistance is variable and subject of debate (1). After the initial response to ADT, patients with prostate cancer (CAP) developed CRPC within 5 years with an average duration of 18- 24 months (3). Most of CRPC patients developed metastatic disease 2 years after the diagnosis(4). There are two models that explained the mechanism of castration resistance, the adaptation and clonal selection models(5). The adaptation model postulate that the androgen receptors are homogenous in their androgen response, castration resistance developed by genetic and epigenetic changes which convert the tumour cells to androgen independent cells. The clonal selection model postulates that androgen receptors are heterogenous in their response to androgens and there is preexisting minority clone of castration resistant cells which is selected after elimination of androgen sensitive cells by ADT. Several studies proved presence of androgen receptors in CRPC(3). Several theories that try to explain the development of CRPC include hypersensitivity, promiscuity and outlaw, which androgen receptor dependent(3). The androgen independent include bypass and lucker cell theories. The androgen receptors (AR) may be amplified or mutated, which increase their sensitivity to even small amount of androgens(3). The AR may be promiscuous to other ligands such as corticosteroid or even anti-androgens. Growth factors such as Insulin like growth factor-1, epidermal growth factor, interleukin-6, protein kinases A and C can increase the transcriptional activity of AR in the absence of androgens(3). The receptors may also be by-passed by alternative survival pathway such Bcl-2 (1). In Lucker cell model, small subset of androgen resistant cells are selected by ADT(1).

Ninety (90%) of patients with CRPC have spinal metastasis at diagnosis(6). The median survival of patients with CRPC is 1- year.(7) Management of CRPC is multidisciplinary involving urologist, clinical oncologist, radiation oncologist, pain management specialist and palliative care team(1) among others.

The disease is divided in to non-metastatic CRPC (NMCRPC) and metastatic CRPC (mCRPC)(4). The use of maximal androgen blockade, systemic corticosteroid therapy and second line hormonal agents, chemotherapy with docetaxel and carbazitaxel produced various improvement in the disease symptoms and prostate specific antigen (PSA) elevation(1)(7). Targeted immunotherapy with immune check point inhibitors and prostate cancer vaccines are promising(1). Various hormonal manipulations suffix in NMCRPC while chemotherapy with docetaxel and carbazitaxel as first and second line agents are tried in metastatic disease with good results(4)(6). Some studies have shown benefits of chemotherapy pre second line hormonal agents. Hormonal agents have more acceptable and tolerable side effects(3). The use of anti-androgen bicalutamide to effect MAB post ADT initially or antiandrogen withdrawal for those already on MAB suffix(1)(8). For those that progress, medical adrenalectomy with ketoconazole and prednisolone may produce appreciable response(1). The use of enzalutamide, abiraterone have revolutionalised the treatment of CRPC and can be used pre or post chemotherapy(6). Other important treatments are bone targeting agents such bisphosphonates, danusumab, radiopharmaceuticals and pain management(1). SPARTAN, ARAMIS and PROSPER trials have proved efficacy of Enzalutamide, apalutamide and darolutamide(9)(10). Selecting treatment for mCRPC is difficult due to inability to hormonise finding of different studies on mCRPC unlike NMCRPC(1).

There are limited studies in Africa on CRPC(8) and none in my environment. We review cases of castration resistant disease in our institution within the last 7 years.

**Methodology:**

This is a retrospective study of patients managed for castration resistant prostate cancer in our hospital from January 2013 to December, 2019. Data was collected from the case notes via a proforma. Information retrieved include biodata, presentation, clinical features, radiological findings, and laboratory investigation findings, diagnosis, treatments, drugs, follow up and outcome. The laboratory investigations include PSA, Haemogram, urine microscopy, serum testosterone, urea and creatinine. Data was analyzed using SPSS version 25.0. Results were reported percentages, mean ±SD

**Results:**

There were 20 patients with CRPC within the study period with Mean age of 66.2 ± 7.4 and a range of 53- 78 years. The median age was 70 years.

The most common presentations were lower urinary tract symptoms (LUTS) and low back pain in 20 patients and 12patients respectively. Other modes of presentation are shown in Table 1 below.

**Table 1: Presentations of patients with CRPC**

|  |  |  |
| --- | --- | --- |
| Presentation | Number of patients | Percentage (%) |
| LUTS  acute urinary retention  chronic urinary retention  Low back pain  Inability to walk  Urinary tract infection  uremia  Weight loss  Anorexia  Anemia | **20**  4  1  **12**  **9**  **6**  **3**  **3**  **2**  **2** | 1**00**  20  5  **60**  **45**  **30**  **15**  **15**  **10**  **10** |

The baseline clinical, radiological, histological findings and classification of castration resistant prostate cancer are shown in table 2 below.

**Table 2: Baseline clinical, biochemical and histological characteristic of the patients with CRPC**

|  |  |  |
| --- | --- | --- |
| Parameters | Number of patients  N=20 | Percentage (%) |
| DRE- normal  abnormal  TRUS – normal  - abnormal  PSA- normal range  > 10 ng/ ml  HISTOLOGY  Adenocarcinoma  Gleason score  ≤ 7 (3+4)  >7 (4+3)  CRPC  NMCRPC  mCRPC | 6  14  6  14  1  19  20    8  1 2  4  16 | 30  70  30  70  5  95  100  40  60  16  84 |

The mean PSA nadir was high and there was short PSADT and short mean time to development, of CRPC as shown in table 3 below.

**Table 3: Prostate Specific Antigen Kinetics**

|  |  |  |
| --- | --- | --- |
| Parameter | Mean PSA kinetic | Range values |
| Pretreatment PSA  PSAN nadir  PSADT  tNadir  ADT- CRPC duration | 44.06 ± 37.3  20.63 ± 25.85  8.71 ± 10.75  7.93 ± 8.5 months  16.9 ± 13.3 months | 3- 126.43 ng/ml  0.26- 95.7 ng/ml  1-31 months  3-36 months  3-47 months |

The commonest first treatment offered was maximal androgen blockade and medical adrenalectomy using ketoconazole which is non-specific antiandrogen. Other treatments are shown in Table 4 below.

**Table 4: Treatment of Patients with Castration Resistant Prostate Cancer**

|  |  |  |
| --- | --- | --- |
| Treatment | Number of patients | Percentage (%) |
| Primary treatment  BTO  medical castration  CRPC  BTO1  MAB: BTO+ bicalutamide  ketoconazole  Abiraterone  chemotherapy – paclitaxel  Bisphosphonate- Alendronate  Analgesia  radiotherapy | 16  4  1  20  20  4  0  15  18  1 | 80  20  5  100  100  40  0  60  90  5 |

Analgesia- Opioids paracetamol Non-steroidal Anti-inflammatory drugs

There was biochemical and clinical improvement in 15 patients (75%) and 5 patients (25%) died of MCRPC. The average duration of follow up was 22.6 ± 14.8 with a range of 6-60 months.

**Discussion:**

Prostate cancer is the second most common malignancy and commonest cause of mortality worldwide(2). The mortality is usually to progression to CRPC(4). In the western world there are many patients with NMCRPC who benefited most from the new hormonal agents(1). In Africa most of our patients have mCRPC(8) though many respond to new agents like abiraterone and enzalutamide but are limited by cost and the availability.

National Comprehensive Cancer Network (NCCN)(11) defined CRPC as prostate cancer that progress clinically, radiographically or biochemically despite castrate level of testosterone (< 50 ng/dl). American Association of Urology (12) defined CRPC as rising PSA despite surgical or medical castration (serum testosterone < 50ng/dl) with or without radiographic evidence or metastasis or prior docetaxel therapy. Also rising PSA > 2 ng/ml above nadir (at least 25% rise above nadir). The NCCN and AUA are easily adaptable in our setting. All our patients had evidence of progression well above nadir with castrate level of testosterone. Most of our patients (84%) presented with metastatic disease and 60% has high grade disease as reported by a previous studies(8),(13).

The median age of 70 years in this study is comparable similar 70 years reported by Bello JO et al (8) but the mean age of 66. 2 years is lower than 67.5 years and 68.4years reported by Ofoha et al (14) and Ajape AA et al (13) respectively.

Our patients present with features of advanced disease, uremia and urinary tract infection which common in African population. In the study by Bello JO et al (8)the symptoms presented by the patients were LUTS (83.3%), bothersome pains (79. 2%), anaemia (45.8%), cord compression (33.3%), pathological fracture (4. 2%). The rate of LUTS in their study was lower that the finding in the present study (100%). But pain (60%), anaemia (10%) were lower in the present study. We did not record any cord compression neither the authors of the previous study reported on UTI and uremia.

The mean pre-treatment PSA of patients in this study was 44.06 ng/ ml which is higher than 42 ng/ml reported by Bello JO et al.(8) There were 60% high grade tumour [( ≥ Gleason score of 7, (4+3)] in the present study which was lower than 72.9% reported by Bello et al.(8) Surgical and medical castration were done for 80% and 20% of our patients which is comparable to the finding of 83.3% and 16.7% respectively by the previous study. There was high PSA nadir of 20.6 ng/ml as compared to 5.7 ng/ml reported by Bello JO et al.(8) High PSA nadir, short PSADT (8.7months), time to nadir (7.9 months) and time interval for castration resistance (16.9months) are associated with early progression to metastasis and mortality which was not prominent in this study. This might be affected by the variable tumour behavior and level patient’s retention in the study which is low in our setting.

Patients who did not reach undetectable nadir PSA are at risk of progression to castration resistance within 4 months(3). None of our patients reached undetectable nadir. The mean nadir was 20.63 ± 25.85 and yet the average progression in our study was 8 months. This might be due to different tumour behavior in western world and Africa. But prostate is known to be more aggressive in blacks more especially African Americans(2).

In a study in Asia(3), PSA nadir of 1.1 ng/ml at 6 months is the most sensitive predictor of progression at 24 months. The median survival was 75 months for patients achieving PSA nadir 0.2 ng/ml as compared to 13 months for nadir of 4 ng/ml which is lower than the nadir of 20.63 ng/ml recorded in this study.

All the patients received MAB, Ketoconazole, and 4 received abiraterone which is contrary to the finding by Bello JO et al (8) where 20 patients received docetaxel and one patient each had abiraterone and enzalutamide. None of our patient received enzalutamide and docetaxel. Many of our patients (90%) received analgesia and alendronate (60%) which is higher than what was reported by the similar study, where less than 25% received those agents(8). Radiotherapy was given to one patient and none was reported by the previous studies.

Use of bone targeting agents such bisphosphonates, danusumab, radiopharmaceuticals and pain management(1) are integral part of bone metastatic disease. Alendronate, various pain management using opioids, non-steroidal anti-inflammatory drugs and radiotherapy have been use in our patients. We have no experience in the use of danosumab and radiopharmaceticals as they are not available in our environment.

A recent study suggests increase survival and decrease bone metastasis for early docetaxel therapy before commencement of second generation of antiandrogens such as abiraterone and enzalutamide (7). We have not used docetaxel for any of our patients

The mortality rate of our patients was 25% at an average follow of 22 months is lower than 58.3% mortality reported by Bello JO et al (8)at an average follow up of 8 months. Our patients average follows up of 22 suggest better survival than 11month median overall survival reported by the previous study. This is lower than average survival in western world of 27 months(1)(8).

**Conclusion:**

Castration resistant prostate cancer present predominantly as metastatic disease in our environment. There was good response initially to maximal androgen blockade and medical adrenalectomy. Abiraterone is very effective in subsequent resistance but it’s use is limited by the cost. Surgical castration may be effective in patients that progress on medical castration. There was high pre-ADT PSA, PSA nadir, short PSADT, short duration for development of CRPC and erratic follow up. The average duration for development of CRPC was 17months

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**Authors contribution:**

Muhammad AS- conception, design, data acquisition, data analysis, data interpretation, writing of the manuscript, review for critical contents

Mungadi IA- Concept/ design, review

**Accessibility of data**- data is available with the corresponding whenever requested.

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