Original Article

Factors associated with response to Androgen Deprivation Therapy in patients with Metastatic Prostate Cancer at the University Teaching Hospital Lusaka, Zambia

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ABSTRACT

Background: Prostate cancer in most cases is dependent on the presence of androgens (testosterone) produced either by the testis or adrenal gland. The major risk factors for development include aging, ethnicity and genetic predisposition. Organ confined prostate cancer is curable by surgery or radiotherapy while metastatic disease is treated by androgen deprivation therapy (ADT). ADT can be achieved medically (gonadotropin releasing hormone agonists or antagonists) or surgically (bilateral orchiectomy). A decrease in serum prostate specific antigen (PSA) is used as a marker of response to ADT. Metastatic prostate cancer has been found to be the most common cause of death in the urology department at the University Teaching Hospitals – Adult Hospital even after ADT, therefore, the aim of this study was to identify the pre-treatment factors that can be used to determine the response to ADT.

Methodology: This was a cross section study conducted at the University Teaching Hospitals-Adult Hospital and Cancer Diseases Hospital. It was carried out between December 2017 and September 2018. Patients with metastatic prostate cancer were recruited. Socio-demographic characteristics, clinical presentation and histopathological findings were elicited by detailed history and file review. PSA and Eastern Cooperative Oncology Group (ECOG) performance status score were obtained prior to ADT commencement. ADT was done and patients were scheduled for a three month post ADT review where PSA and ECOG performance status score were reobtained.

Results: 50 patients were recruited into the study. The total patient retention was 88% (n=44). The average age was 71. Majority, 89% (n=39) had some level of education; 98% (n=43) had lower urinary tract symptoms (LUTS); 11% (n=5) had paraplegia. 98% (n=43) had bone metastasis. Duration of symptoms at presentation was > 6 months in 75% (n=33) patients. ECOG score was above 1 in 75% (n=33). Initial PSA was above 100ng/ml in 75% (n=38). All patients had Gleason scores above 7. All patients had a drop in PSA after ADT. The average PSA percentage drop in men below 60 years was 80.5% whereas the average percentage drop in PSA with regards to other factors was 91.19%.

Conclusion: All patients had androgen dependant cancers. These patients also had high risk prostate cancer with initial PSA values above 100ng/ml and Gleason scores above 7. Of all the factors analysed, age below 60 years was found to be the only clinically significant factor associated with poor response to ADT.

INTRODUCTION

Prostate cancer is the most common cancer amongst males above the age of 40 in Zambia. The lifetime risk of being diagnosed with prostate cancer is

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approximately 1 in 4 in men of African origin. There are several major factors that influence that risk, most of which are non-modifiable. These include advancing age, ethnicity and genetics, being more common in the black race with the incidence beginning to rise after the age of 55 years. Androgen deprivation therapy (ADT) is considered to be the standard therapy for men with metastatic disease. It can be done surgically (bilateral orchiectomy) or medically by the administration of Gonadotropin Releasing Hormone /Luteinizing Hormone Releasing Hormone agonists or antagonists.

Studies have documented that African men present with a more advanced and lethal course of disease. Therefore, the first treatment option for these patients is androgen deprivation therapy. A study done recently in Mexico showed that age at commencement of androgen deprivation therapy can predict response, with older men having better response than younger men. Performance status is an important prognostic factor in androgen deprivation therapy as eluded by a Belgian study which showed that patients with better health status responded better to treatment. Poor response to androgen deprivation therapy has been associated with a high Gleason score according to a study done in Thailand and in a study done in Egypt, it was noted that patients with an initial PSA of less than 50ng/ml and a Gleason score less than 7 responded well to androgen deprivation therapy.

Patients with metastatic prostate cancer can be palliated with ADT for years, however, most of our Zambian patients are dying within a few months from after the start of therapy. This study was carried out to establish the factors associated with the varying outcomes in Zambian patients presenting with metastatic prostate cancer.

METHODS

This was an observational, prospective cohort study. The study was conducted in the Department of Surgery; Urology section at the University Teaching Hospitals - Adult Hospital and the Cancer Diseases Hospital, Lusaka. Patients with confirmed prostate cancer scheduled for androgen deprivation therapy (medical or surgical) by attending doctor were recruited into the study. A detailed history to collect demographics and clinical presentation was carried out. Eastern Cooperative Oncology Group (ECOG) performance status scale was then administered. File review to record histopathological findings was done. Pre-treatment PSA blood sample was collected and ADT was done. Patients were then scheduled for review 3 months post androgen deprivation therapy. At the 3 month review, another PSA blood sample was collected and ECOG performance status scale re-administered. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 22 software. Bias was avoided as all men with metastatic prostate cancer were recruited and sample size was calculated using open epi version 3.01. Chance was avoided by using a 95% confidence interval and P value of 0.05. Errors were minimised by using a double entry system, ranges and consistent checks. Chi square test and Pearson's Correlation Coefficient was used to determine the association between categorical variables and T-test was used to determine the association between continuous variables.

RESULTS

The study recruited 50 patients, however, six patients did not complete the entire follow up due to the following reasons; five patients died before their three month follow up review, and one patient was lost to follow up. Therefore, 44 patients completed the study fully and data was analysed accordingly.

The age ranged from 56 to 89 years, with an average age of 71 years. 89% (n= 39) had some level of education while 11% had no education, 98% (n=43) presented with lower urinary tract symptoms (LUTS). In addition to LUTS, 11% (n=5) also had paraplegia. Bone metastases were found in 98% (n=43). 75% (n=33) presented after 6 months duration of symptoms. Pre treatment ECOG performance status was 2 and above in 75% (n=33) of patients, whereas initial PSA was above 100 ng/ml in 75% (n=33) of patients. 77% (n=34) had high risk Gleason scores (Gleason score > 7) and 23% (n=10) had intermediate risk Gleason scores

(Gleason score = 7), no patients had low risk Gleason scores (Gleason < 7). Thirty-nine patients had surgical castration while five had medical castration.

Table 1: Demographic Characteristics of Patients versus Average Percentage Drop in PSA

Demographic Characteristics of Patients	Number of Patients	Percent (%)	Average PSA Percent Drop (%)	p-value
Patient's Age Group				
51-60	4	9	80.5	0.522
61-70	18	41	89.8	
71-80	14	32	95.4	
81-90	8	18	96.2	
Educational Status				
No Education	5	11	91.6	0.509
Primary School	17	39	95.8	
Secondary School	10	23	91.3	
Tertiary School	12	27	86.8	
Total	**44**	**100**		

Table 2: Clinical Presentation of Patients versus Average PSA Percentage Drop After Three Months of ADT

Clinical Presentation	Number of Patients	Percent (%)	Average PSA Percentage Drop (%)	p-value
Lower Urinary Tract Infections				
Yes	43	98	91.8	0.429
No	1	2	95.8	
Acute Urinary Retention				
Yes	23	52	92.9	0.303
No	21	48	90.9	
Paraplegia				
Yes	5	11	96.1	0.297
No	39	89	86.8	
Duration of symptoms (months)				
<6	11	25	90.5	0.528
6-12	29	66	88.4	

Table 3: Investigations versus Average PSA Percentage Drop

Investigations	Number of Patients	Percent (%)	Average PSA Percentage Drop (%)	p-value
Initial PSA (ng/ml)				
<100	11	25	91	0.246
100 - 500	19	43	89.4	
501 - 1000	6	14	96.6	
>1000	8	18	95.6	
Initial Performance Status				
0	1	2	93.2	0.401
1	10	23	81.7	
2	20	46	95.5	
3	8	18	95.3	
4	5	11	96.1	
Total	**44**	**100**		

Table 4: Histopathological Characteristics versus Average PSA Percentage Drop

Histopathologica Characteristics	Number of Patients	Percent (%)	Average PSA Percent Drop (%)	p-value
Gleason Grade				
Low Risk (< 7)	0	0	0	0.108
Intermediate Risk (7)	10	23	95.3	
High Risk (<7)	34	77	90.9	

Average percentage drop in PSA from baseline based on other factors was 91.19% whereas in men below 60 years was 80.5%. All P- values had no statistical significance.

DISCUSSION

Androgen deprivation therapy has been the mainstay for the management of metastatic prostate cancer since the 1940s. In this study, 88% (n=39)

underwent surgical castration and all patients had androgen dependant cancers as seen by their drop in PSA after ADT. These patients were also noted to have had high risk cancers with the majority having initial PSA values above 100ng / ml and Gleason scores above 7. The results revealed that metastatic prostate cancer is a disease of older men (mean age 71 years) and it was noted that as the patients age increased, so did the average PSA percentage drop (Table 1). This meant that the oldest group of patients (aged 81 to 90 years) responded best to ADT than the younger age groups.

All patients had a drop in PSA from their initial PSA value regardless of the various factors. The PSA values returned to normal (<4ng/ml) in 30% (n=13) and 81% (n=36) had a PSA percentage drop of more than 90% from their baseline. Of note in the 13 patients that attained PSA values of less than 4ng/ml post ADT, was that they had a duration of symptoms of less than 12 months and no paraplegia. In addition, the patients had a Gleason score of 7 (ISUP grade 2). It has been established by prior studies that normalisation of PSA or reduction by more than 90% by three months post ADT is prognostic of prolonged progression free interval. In this study, patients with initial PSA values above 500ng/ml responded better than those with PSA values less than 500ng/ml. Therefore, since the average PSA drop was more than 90% for both groups, initial PSA cannot be used as an independent prognostic factor. This correlated with the findings of Varenhorst, who concluded that initial PSA cannot be used as a prognostic indicator for response to ADT. However, this was in contradiction with a study done by Glass, in which initial PSA less than 65ng/ml was found to be a good prognostic marker.

All the recruited patients presented with metastasis as their first presentation of prostate cancer and had an average age of 71 years. This was consistent with findings from some regions such as Mexico, whereas in other regions such as USA, the presentation was roughly 5 years earlier possibly due to routine prostate cancer screening. This study showed that men above the age of 60 years responded better to ADT. These findings correlated with another similar study that reported that the age at commencement of ADT can predict response, with older men (aged above 65 years) having better response than younger men.

Fifty percent of patients had attained at least secondary school level of education, thus lack of education could not be attributed to the late presentation in the majority (75%) of patients who presented after 6 months duration of symptoms. Men diagnosed with early prostate cancer usually do not have symptoms, but late stage disease is often associated with symptoms. This study showed that most (98%) of the patients had experienced lower urinary tract symptoms and about half of the patients also reported having acute urine retention. Only five patients had suffered from paraplegia. This showed that majority of patients who presented with metastatic prostate cancer seek medical attention as a result of urinary symptoms. The majority, 75% (33) of patients presented to the hospital late, after 6 months of symptoms, by this time metastases had already set in and curative treatment was not possible. It has been reported in previous studies that due to the natural course of the disease as well as the impact of social issues on African men, these patients may face a greater health burden than their Caucasian counterparts once they have been diagnosed. Therefore, when a diagnosis is made early in the African population it likely to improve the overall outcomes of the disease.

The association between symptoms and average PSA percentage drop was inversely related because some patients without symptoms showed better outcome after treatment compared to those that had symptoms. However, due to the negligible differences in response to ADT, clinical presentation cannot be used as a predictor of response to androgen deprivation. Patients with longer duration of symptoms (more than 12 months) showed better treatment outcomes than those with shorter duration of symptoms (less than 12 months). However, the reasons for these results could not be explained.

ECOG performance status assessment revealed that majority of patients had an initial performance status of grade 2 (in bed <50% of the time, capable of self-care, unable to carry out any work activities) and above, with only 10 patients having grade 1 performance status and one having a performance status of 0. This shows that majority of patients at the time of diagnosis are quite ill and restricted from carrying out their normal activity. There was a significant difference between performance statuses before treatment to that after 3 months of ADT (p-value <0.001). Although the majority of patients maintained the same performance status after treatment, there was some improvement in the performance status as the PSA reduced.

Hynes reported that African men tend to present with high grade prostate cancer[8], this was also the case in this study which revealed that 34 patients (77%) had high risk Gleason scores (above 7) and no patient had a low risk Gleason score (less than 7). However, regardless of the Gleason scores, all patients had an average PSA drop of greater than 90% (Table 4). In contrast, a similar study reported that poor response to ADT can be associated with a high Gleason score.

There were several limitations to this study. Firstly, there was no standard imaging protocol for detection of metastasis implemented. Time from diagnosis to ADT was not taken into account and lastly, serum testosterone post ADT was not routinely checked or monitored.

From the findings of this study, it is recommended that patients aged below 60 years should be commenced on ADT with additional treatment such chemotherapy to improve their overall survival.

CONCLUSION

This study revealed that all of the patients presenting to The University Teaching Hospital – Adult Hospital and Cancer Diseases Hospital with prostate cancer have androgen dependant cancers which agrees with the first treatment option of ADT. The majority of patients have high risk prostate cancer with initial PSA values above 100ng/ml and Gleason scores above 7. The study showed that of all the factors analysed, age below 60 years was found to be the only independent factor associated with poor response to ADT, though not statistically significant it was found to be clinically significant.

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