ANDROGEN DEPRIVATION THERAPY AND CARDIOVASCULAR RISK IN PATIENTS WITH PROSTATE CANCER

Muhammad Yousaf Khan, Naeem Haider, Shahid Rasul, Ahsan Mahmood, Muhammad Sohaib Nadeem

Combined Military Hospital / National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: The objective of this study was to investigate the effects of androgen deprivation therapy (ADT) on risk of subsequent cardiovascular morbidity in men with prostate cancer.

Study Design: Quasi experimental study.

Place and Duration of Study: Department of oncology Combined Military Hospital Rawalpindi, from Sep 2014 to May 2015.

Patients and Methods: Thirty consecutive patients fulfilling inclusion criteria were enrolled. All patients were subjected to medical castration/ androgen deprivation therapy (ADT) with monthly 3.75 mg leuprorelin acetate intramuscular injection until castrate levels of testosterone (<50ng/dL) were achieved. We used Framingham's score for assessment of 10 years cardiovascular risk of individual patient before initiation and after completion of 6 months ADT. Serum lipid profile (fasting), systolic blood pressure, history of smoking, diabetes and antihypertensive medication were recorded. Proforma was designed to get clinical information. A *p*-value of <0.05 was considered significant. A paired-samples t-test was conducted to compare Framingham cardiovascular risk scores before initiation and after completion of 6 months ADT.

Results: We enrolled 30 men with high/intermediate risk localized prostate cancer. Mean age was 63.47 ± 7.32 years. All patients received 6 months ADT with monthly 3.75mg leuprorelin acetate intramuscular injection. There was a significant difference in Framingham cardiovascular risk scores before (mean ± sd; 20.95 ± 7.98) and after (mean ± sd; 25.72 ± 6.15) 6 months ADT; t (29) =−4.54, *p*<0.01, two-tailed. Hence ADT resulted in a significant increase (mean ± sd; 25.7 ± 6.15) in 10 years cardiovascular morbidity risk t (29) =−4.54, *p*<0.01, two-tailed. Subset analyses revealed significant increase in fasting serum total cholesterol, triglycerides and Low-density lipoprotein (LDL) levels after 6 months ADT (*p*<0.01, <0.01 and <0.01 respectively) however high density lipoprotein (HDL) remained un-changed (*p*=0.043) in comparison to pre-ADT values.

Conclusion: Androgen deprivation therapy results in significantly increased risk of cardiovascular morbidity in patients with prostate cancer however this relationship between ADT and risk of cardiovascular morbidity may be confounded by unmeasured variables like obesity, atherosclerosis and body mass index (BMI) variations.

Keywords: Androgen, Cardiovascular, Morbidity, Prostate cancer, Therapy.

INTRODUCTION

Prostate cancer is the 2nd most frequently diagnosed cancer and 6th leading cause of death from cancer in men worldwide[1]. Approximately 50% of men with prostate cancer die of non-cancer etiology with cardiovascular disease being the most common cause of death in these patients[2]. Radical prostatectomy and/or radiotherapy are the treatment modalities adopted for organ confined prostate cancer however androgen deprivation therapy (ADT) is the essential part of standard treatment for men with advanced prostate cancer[3]. Majority of Pakistani patients with prostate cancer present to clinics with advanced stage/metastatic disease at diagnosis as reported in the literature regarding Asian countries[4] hence majority of patients in our population are candidates for ADT at diagnosis. Role of androgens in growth stimulation of prostate gland and androgen dependence of prostate cancer was reported and established in 1941 by Charles Huggins and Clarence V. Hodges[5]. ADT has been incorporated as the primary treatment for advanced prostate cancer.

Correspondence: Dr Muhammad Yousaf Khan, Registrar Oncology Department Combined Military Hospital Rawalpindi Pakistan (*Email: drusaf909@yahoo.com)*

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Aim of ADT was to achieve castrate levels of serum testosterone i.e. <50ng/mL[6]. Castrate levels of serum testosterone can be achieved either by medical castration i.e. via the gonadotropin releasing hormone (GnRH) analogues/antagonists therapy or by surgical castration via bilateral orchiectomy[6]. Medical and surgical castration is equally effective in terms of overall survival, progression-related outcomes, and time to treatment failure.

Several long term devastating outcomes of ADT have been documented in the form of increase in BMI and body fat mass, decline in lean body mass, impaired sexual functions, bone density loss and muscle weakness[7]. Studies have also been done to evaluate risk of cardiovascular morbidity and diabetes in men undergoing ADT[8]. In addition several studies have also been done to evaluate impact of ADT on fasting serum lipoprotein profile and reported arterial stiffness and hyperinsulinemia as adverse outcomes of ADT. Arterial stiffness and hyperinsulinemia are established risk factors for cardiovascular mortality exactly as adverse lipid profile and smoking. These side effects of ADT have been often overlooked at the time of decision making for treatment of prostate cancer.

Keeping in view the highly significant number of prostate cancer patients developing cardiovascular morbidity and mortality, this study analyzed the effect of ADT on patient's risk of subsequent cardiovascular morbidity depicted as Framingham Cardiovascular risk score. This study will not only highlighted the importance of regular monitoring of cardiovascular risk factors in patients with prostate cancer on ADT, it will also emphasized on making cardiovascular risk assessment as an essential factor at the time decision making for treatment of prostate cancer. This has particular importance in our setting owing to majority of patients presenting with advanced stage disease.

PATIENTS AND METHODS

This quasi experimental study was carried out on 30 indoor and outdoor patients reporting to oncology department CMH Rawalpindi from September 2014 to May 2015. Thirty men with histologically proven adenocarcinoma of prostate risk group (intermediate/high), age 50-75 years and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤3 were included. Patients with history of hypo-gonadism, diabetes mellitus, dyslipidemia, taking lipid lowering drugs, past or present history of concomitant second primary and those who had received previous ADT were excluded from the study. Sample size of 40 was calculated using WHO sample size calculator. Non-probability consecutive sampling technique was adopted. After enrollment and registration, patients were subjected to following diagnostic work-up: physical and radiological examinations (chest x-ray and computed tomography (CT)/magnetic resonance (MR) scan of abdomen and pelvis), serum prostate specific antigen (PSA) and serum Testosterone levels. ECOG PS was documented. Disease staging was done according to the 7th edition American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM)[9].

Cardiovascular risk was assessed on Framingham risk score calculator[10] at baseline before initiation of ADT and after completion of 6 months ADT. ADT was prescribed and administered at the oncology department, CMH Rawalpindi with monthly 3.75mg leuprorelin acetate intramuscular injection for consecutive 6 months. Castrate levels of serum testosterone (<50 ng/dL) were achieved in all patients. Eight parameters including history of smoking, diabetes mellitus, antihypertensive medication, age, gender, fasting serum total cholesterol, fasting serum HDL and systolic blood pressure were recorded and used for calculation of 10 years risk of cardiovascular morbidity (Framingham Risk Score).

All clinical information, Framingham scores and statistical data were recorded on proforma designed for the purpose. After completion of 6 months ADT, all patients were again subjected to history, examination and 10 years cardiovascular morbidity risk assessment using 8 parameters

including history of smoking, diabetes mellitus, antihypertensive medication, age, gender, fasting serum total cholesterol, fasting serum HDL and systolic blood pressure for calculation of 10 years risk of cardiovascular morbidity (Framingham Risk Score). Post-ADT Framingham risk scores were compared with pre-ADT Framingham risk scores in order to determine impact of ADT on risk of cardiovascular morbidity. Data analysis were computer based with use of SPSS version 19. Mean and standard deviation were calculated for numerical variables like age. Frequency and percentages were computed for categorical variables like risk groups. A paired samples t-test was conducted to compare Framingham cardiovascular risk scores before initiation and after completion of 6 months ADT. A *p*-value of <0.05 were considered statistically significant.

RESULTS

Mean age was 63.47 ± 7.32 years. Out of these (n=30) 19 patients (63.3%) presented with high risk while 9 patients (36.6%) with intermediate risk prostate cancer. Pre-ADT Framingham cardiovascular risk scores were compared with post-ADT score to determine impact of 6 months ADT on 10 years cardiovascular risk of patients. There was a significant difference in the scores before (mean ± sd; 20.95 ± 7.98) and after (mean ± sd; 25.72 ± 6.15) ADT; $p<0.01$. Hence ADT resulted in a significant increase (mean ± sd; 25.7 ± 6.15) in 10 years cardiovascular morbidity risk $p<0.01$. Subset analyses revealed significant increase in fasting serum total cholesterol, triglycerides and LDL levels after 6 months ADT ($p<0.01$, <0.01 and <0.01 respectively) however HDL remained un-changed ($p=0.43$). Detailed analysis revealed a significant difference in the serum total cholesterol before (mean ± sd; 5.00 ± 0.04) and after (mean ± sd; 5.87 ± 0.04) 6 months ADT; $p<0.01$. Similarly significant difference was noted in serum LDL before (mean ± sd; 2.93 ± 0.02) and after (mean ± sd; 3.80 ± 0.05) 6 months ADT; $p<0.01$. A significant difference was also noted in serum triglycerides before (mean ± sd; 0.98 ± 0.04) and after (mean ± sd; 1.23 ± 0.04) 6 months ADT; $p<0.01$. However no significant difference was there in serum HDL before (mean ± sd; 1.07 ± 0.01) and after (mean ± sd; 1.05 ± 0.01) 6 months ADT; $p>0.05$.

DISCUSSION

Given the highly significant number of prostate cancer patients developing cardio-vascular morbidity, the benefits of ADT have to be carefully weighed against its devastating outcomes as adverse effects. This is particularly important when a diagnosis of prostate cancer does not alter the life expectancy[11]. This study analyzed effect of ADT on patient's risk of subsequent cardiovascular morbidity depicted as Framingham Cardiovascular risk score. This study has not only highlighted the importance of regular monitoring of cardiovascular risk factors in patients with prostate cancer on ADT[12], it has also emphasized on making cardiovascular risk assessment as an essential factor at the time decision making for treatment of prostate cancer however there are very few studies focusing specifically on added cardiovascular secondary to ADT[13].

Wilcox et al conducted TROG 96.01 trial recruiting 802 men with locally advanced prostate cancer and randomized them to radiotherapy either alone or with 3 or 6 months of neo-adjuvant ADT. They used competing risk methodology to derive the cumulative incidence of fatal cardiac events. At 10 years, they reported the cumulative incidence of fatal cardiac events for the radiation therapy alone arm to be 7.54%[14] compared to a non-statistically significant decreased incidence of 6.44% in the 6 month ADT arm ($p=0.65$). Results of our study differ in regards that ADT resulted in a significant increase (mean ± sd; 25.7 ± 6.15) in 10 years cardiovascular morbidity risk. This difference can possibly be attributed to the dichotomous duration of ADT and unmeasured variables like obesity, atherosclerosis and BMI variations.

Concluded that androgen deprivation therapy may be associated with a greater incidence of diabetes and cardiovascular disease

owing to adverse effects of ADT i.e. decreases lean body mass, increases fat mass, decreases insulin sensitivity, and increased levels of serum LDL, HDL and triglycerides.

Saigal et al reterospectivly analysed the effects of ADT in a population-based registry. They measured subsequent cardiovascular risk in newly diagnosed prostate cancer patients who had undergone ADT. They reported a 20%[15] higher risk of serious cardiovascular morbidity compared with similar men who did not receive ADT. Although the results of this study are similar to ours, there are significant differences in design of study and method of cardiovascular risk assessment. We followed the patients prospectively incorporating 8 parameters including history of smoking/ diabetes/ antihypertensive medication, age, gender, fasting serum total cholesterol, fasting serum HDL and systolic blood pressure for calculation of subsequent 10 years risk of cardiovascular morbidity (Framingham Risk Score). We found significantly (p<0.01) increased risk of subsequent 10 years cardiovascular morbidity in patients receiving 6 months ADT. This increased risk of cardiovascular morbidity in these patients was explained by subset analyses showing significant increase in fasting serum total cholesterol, triglycerides and LDL levels after 6 months ADT (p<0.01, <0.01 and <0.01 respectively). Here interplay of the vast spectrum of unmeasured variables like obesity, atherosclerosis, diet, BMI and lifestyle variations associated with cardiovascular morbidity and mortality could not be ruled out. However the fact that benefits of ADT have to be carefully weighed against its adverse effects is emphasized given the highly significant number of prostate cancer patients developing cardiovascular morbidity. This is particularly important at the time of decision making when a diagnosis of prostate cancer does not alter the life expectancy of patient.

CONCLUSION

Androgen deprivation therapy results in significantly increased risk of cardiovascular morbidity in patients with prostate cancer however this relationship between ADT and risk of cardiovascular morbidity may be confounded by unmeasured variables like obesity, atherosclerosis and body mass index (BMI) variations.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics: 2011. CA Cancer J Clin 2011; 61(2): 69–90.
2. Braga-Basaria M, Muller DC, Carducci MA, Dobs AS, Basaria S. Lipoprotein profile in men with prostate cancer undergoing androgen deprivation therapy. International J Impotence Res 2006. p. 494–8.
3. Mohler JL, Armstrong AJ, Bahnson RR, Boston B, Busby JE, D'Amico AV, et al. Prostate cancer, version 3. 2012: Featured updates to the NCCN guidelines. JNCCN 2012. p. 1081–7.
4. Cullen J, Elsamanoudi S, Brassell S, Chen Y, Colombo M, Srivastava A, et al. The burden of prostate cancer in Asian nations. J Carcinogenesis 2012. 7.
5. Shastri BR, Yaturu S. Metabolic complications and increased cardiovascular risks as a result of androgen deprivation therapy in men with prostate Cancer. Prostate Cancer 2011. 1–9.
6. Novara G, Galfano A, Secco S, Ficarra V, Artibani W. Impact of surgical and medical castration on serum testosterone level in prostate cancer patients. Urologia Internationalis 2009. p. 249–55.
7. Schwandt A, Garcia JA. Complications of androgen deprivation therapy in prostate cancer. Curr Opin Urol 2009; 19(3): 322–6.
8. Grossmann M, Zajac JD. Management of side effects of androgen deprivation therapy. Endocrinol and Metab Clin of North Am 2011. p. 655–71.
9. Paras C, Hussain MM, Rosenson RS. Emerging drugs for hyperlipidemia. Expert Opin Emerg Drugs. 2010; 15(3): 433–51.
10. Egner JR. AJCC Cancer Staging Manual. JAMA: J Am Med Ass 2010. 1726.
11. Grossmann M, Zajac JD. Androgen deprivation therapy in men with prostate cancer: How should the side effects be monitored and treated? Clin Endocrinol (Oxf) 2011; 74(3): 289–93.
12. 16.Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol 2013; 189(1 Suppl): S34–42; discussion S43–4.
13. Punnen S, Cooperberg MR, Sadetsky N, Carroll PR. Androgen deprivation therapy and cardiovascular risk. J Clin Oncol 2011; 29(26): 3510–6.
14. Wilcox C, Kautto A, Steigler A, Denham JW. Androgen deprivation therapy for prostate cancer does not increase cardiovascular mortality in the long term. Oncology 2012. p. 56–8.
15. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007; 110(7): 1493–500.