ORIGINAL ARTICLE

Impact of the Duration of Androgen Deprivation Therapy for Prostate Cancer on Cognition: a study using mini-mental state examination

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ABSTRACT

Aim: Recently, some data has emerged linking androgen deprivation therapy (ADT) for prostate cancer (PC) to cognitive impairment. The aim was to investigate the association of cognitive status in men treated for PC with the duration of ADT using the Mini-mental state examination (MMSE).
Methods: In this cross-sectional study, men receiving ADT for PC with luteinizing hormone releasing hormone agonists (LHRHa) (n=20) were assessed for cognitive function using MMSE.Based on the length of the received LHRHa treatment, recruited men were grouped into two; i. Early ADT group comprised of patients on LHRHa for 4 months or less (n=8) and ii. Late ADT group consisting of patients on LHRHa for more than 4 months (n=12).
Results: The mean overall MMSE score was 26.45 (Range 20-30). No correlation was found between MMSE scores and the duration of ADT (R= -0.12, p-value = 0.605).No difference was observed between MMSE scores in the early (n=8) versus late ADT (n=12) groups (mean MMSE score 26.87 vs. 26.16, p-value = 0.610).
Conclusion: No association was observed between cognitive function scores on MMSE and the duration of ADT. MMSE does not appear as a suitable tool for assessing cognitive function in men receiving ADT for PC. Clinically usable, convenient and sensitive neuropsychiatric instruments need to be developed for such assessments.
Keywords: Prostate cancer, Androgen deprivation therapy, Cognition, Mini-mental state examination

INTRODUCTION

Prostate cancer is a common life-threatening malignancy and a leading cause of cancer-related morbidity and mortality affecting men the world over[1,2]. Due to the androgen-responsive nature of (PC), one of the major treatment modalities for advanced PC is androgen deprivation therapy (ADT) which was initially achieved by bilateral orchiectomy (surgical castration) or oral estrogen administration (medical castration)[3,4]. The present-day mainstay of ADT for PC is luteinizing hormone releasing hormone agonists (LHRHa) which suppress serum testosterone by up to 95% and bring about an 80% decline in serum estradiol by altering the hypothalamic-pituitary-gonadal axis[5]. ADT-induced reduction in serum concentration of sex steroids to the development multiple adverse effects such as osteoporosis[6], sexual dysfunction[7], vasomotor disturbances[8] and cardio-metabolic derangements[9.10].

In addition to these established toxicities of ADT, some recent studies have also linked ADT to the development of cognitive pathology[11,12,13,14]. Sex steroids are known to influence cognitive physiology in multiple ways. Cognitive abilities differ between males and females[15], possibly due to the varying sex steroid levels and their receptor distribution in brain. Data from menopausal women suggest that women using hormone replacement therapy (HRT) have better cognitive skills compared with age-matched non-users[16,17]. Cognitive decline has higher prevalence in elderly men and testosterone replacement in older men has been shown to improve cognitive abilities[18,19]. However, the Current knowledge on deleterious effects of ADT on cognitive function is inconsistent as it has been generated using vastly differing and complex approaches which make clinical interpretation difficult[12,20]. The present study explored the effect of duration of ADT with LHRHa on cognitive status in PC patients using an established global cognitive assessment tool having a longstanding history of use in research and clinical practice.

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MATERIALS AND METHODS

A cross-sectional observational study design was employed for this study. Patients were recruited from the uro-oncology follow-up clinics of Imperial College Healthcare Trust, London, United Kingdom. Written informed consent was obtained before participants entered the study. Patients between the ages 55 to 85 years who were currently undergoing ADT for PC with LHRHa and could give written informed consent were included in the study.Patients with a known history of neuropsychiatric pathology, stroke, traumatic brain injury or neurodegenerative disorders and associated dementia or delirium were excluded. Patients clinically assessed as having cognitive impairment prior to starting ADT with LHRHa or with a history of receiving ADT with LHRHa prior to current treatment were also excluded. Based on the duration of received ADT, recruited patients (n=20) were grouped into two to expound any observed cognitive difference. Patients who had been receiving LHRHa for 4 months or less were included in the early ADT group (n=8) while those having LHRHa for more than 4 months were included in the late ADT group (n=12).

Cognitive assessment was done using the Mini-Mental State Examination (MMSE)which is a short clinical screening tool (11 items, maximum score 30) that tests cognitive areas including orientation, registration, attention, calculation, recall, and language[21]. MMSE is a validated cognitive screening instrument utilized extensively both in clinical practice and research[22]. For MMSE testing, it was ensured that each participant was wearing his routine hearing and/or visual aid if any, as testing required adequate hearing and vision. The study was conducted as part of a research project which received ethical approval

from the Queen Square Research Ethics Committee (REC), London (Ref 13/LO/0731).

Data were analysed using SPSS version 23.0. Demographic data were presented as range, mean and frequency. Mean±Standard Deviation (SD) was calculated for normally distributed quantitative variables. Pearson's correlation was applied to observe correlation between the study parameters. Independent sample t-test was applied to observe group mean differences. A p-value of <0.05 was considered statistically significant.

RESULTS

The age range of study participants (n=20) was 57-85 years with a mean of 72.1 years.The mean duration of ADT with LHRHa for all the study participants was 5.67 months with a range of 1-11 months. The mean MMSE score for all the study participants was 26.45 with a range of 20-30. No correlation was found between the MMSE scores and the duration of ADT (R= -0.12, p-value = 0.605) (Figure 1). On grouping the patients by duration of ADT as specified in the methods section, no difference was observed between the MMSE scores in the early (n=8) and late ADT (n=12) groups (mean MMSE score 26.87 vs. 26.16, p-value = 0.610) (Table 1, Fig. 2). The mean duration of treatment in early ADT group was 2.56 months while in the late ADT group, it was 7.75 months. Both the groups were matched for age (Table 1).

Fig. 1. Scatter plot of MMSE scores and duration of ADT

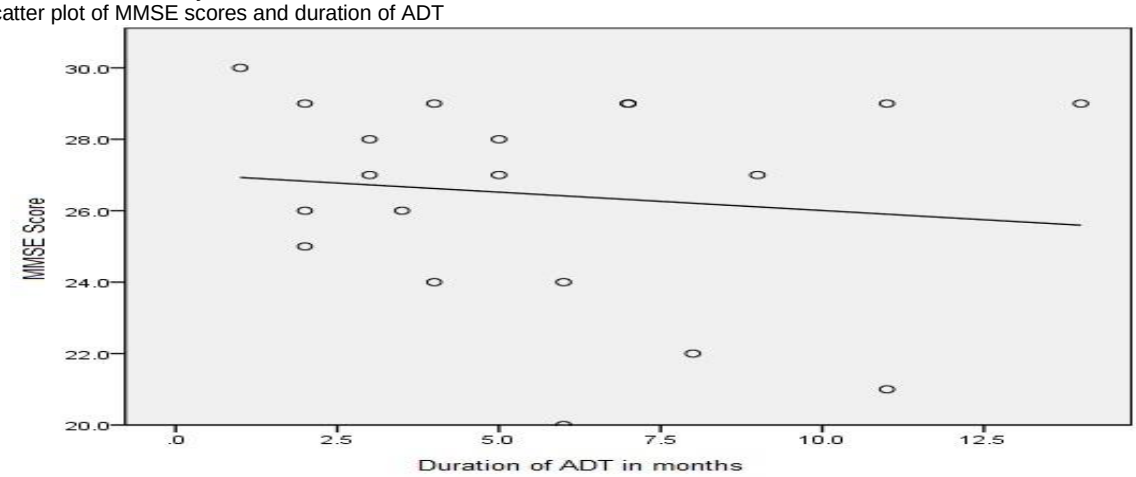

Fig. 2; Mean MMSE scores in early and late ADT groups

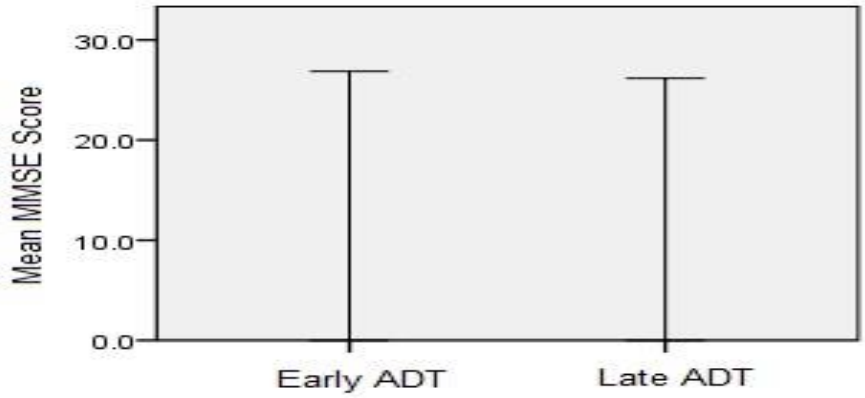

Table 1. Comparison of MMSE scores in early and late ADT groups

Variable	Early ADT (n=8) Mean±SD	Late ADT (n=12) Mean±SD	p-value
MMSE score	26.87 ± 2.03	26.16 ± 3.45	0.610
Age (years)	74.87 ± 4.79	70.25 ± 9.40	0.218

DISCUSSION

This current study explored the association between cognitive function and duration of treatment in patients with PC undergoing ADT with LHRHa. We employed the widely utilized MMSE as an instrument for assessing cognitive status[21]. MMSE has been used over the last four decades in multiple research and clinical settings[23-27]. Our results did not show any association of cognitive function with the length of LHRHa treatment. Our findings are not consistent with results from some studies published previously which reported ADT with LHRHa to be associated with early development of cognitive impairment[6,7,10,11]. Most of those studies used complex neuropsychological testing to demonstrate impaired performance on specific cognitive domains unlike our study which only assessed global cognition.

Furthermore, all the men in the present study had been on LHRHa treatment for less than 1 year which may not be long enough to produce cognitive deficits. A previous longitudinal study by Alibhai et al. did not report

cognitive impairment in men receiving ADT for one year despite using a comprehensive neuropsychological test battery examining distinct cognitive domains[28]. Besides, the existing literature also seems to suggest that not all patients on LHRHa exhibit cognitive side-effects to a similar extent. A meta-analysis conducted previously by Nelson et al. suggested that only half of the patients on ADT develop cognitive decline after 6 to 9 months of therapy[20]. Beer et al. showed cognitive domains including processing speed and long term verbal memory to be affected in PC patients on continuous ADT as compared to healthy controls. However, the mean duration of ADT in their study was much longer (~6 years) than the current study and results were not stratified for the type of ADT which included LHRHa or orchiectomy or a combination of either with an anti-androgen[29].

A limitation of the study is its cross-sectional design which does not provide information about the cognitive changes over time from baseline. The statistical power of the study is also limited by the small sample size. Additionally, it lacks control groups of demographically matched healthy men as well as patients with PC not receiving ADT, inclusion of whom would have enabled effective comparisons. Moreover, MMSE is a screening test for assessing global cognitive status and may lack sensitivity to pick subliminal cognitive decline in specific domains[22].

CONCLUSION

Considering the health-economic burden of any potential cognitive disability due to ADT with LHRHa, it is imperative that clinically convenient neurocognitive screening mechanisms should be developed for early detection and rehabilitation of affected individuals.Adequately designed future studies on the cognitive effects of ADT are warranted to precisely gauge cognitive pathology in settings of altered sex hormones and help establish changes in clinical practice having beneficial impact on the overall quality of life of PC survivors.

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